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VOLUME II

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SCIENCE, SUSTAINABILITY, AND TECHNOLOGY: *Contemporary Research and Applications*

SCIENCE, SUSTAINABILITY, AND TECHNOLOGY: CONTEMPORARY RESEARCH AND APPLICATIONS

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We extend our sincere appreciation to the authors, reviewers, and contributors whose scholarly efforts have made this volume possible. It is our hope that this book will inspire further inquiry, foster collaboration across disciplines, and contribute to ongoing conversations on building a more sustainable and technologically progressive future.

Editors
Science, Sustainability, and Technology: Contemporary Research and Applications (Volume II)

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CHAPTER ONE

Mediterranean Diet and Healthy Food Related to Brain Health

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Abstract

Originating in the traditional cuisines of Mediterranean-bordering countries, the Mediterranean diet has achieved worldwide renown due to its extensive array of health benefits, principally concerning cognitive function and brain health. The diet emphasizes whole, minimally processed foods including a diverse array of fruits, vegetables, whole grains, legumes, nuts, and fats sourced primarily from olive oil. It recommends regular but moderate intake of fish and poultry, while discouraging red meat and processed food products. A growing body of epidemiological evidence indicates a significant inverse association between adherence to the Mediterranean dietary pattern and the incidence of age-related cognitive, including Alzheimer's disease dementia. The diet's rich nutrient profile, including antioxidants, omega-3 fatty acids, and anti-inflammatory compounds, primary determinant in promoting brain health by combating oxidative stress and inflammation, thereby supporting cognitive function and preserving brain structure as individuals age. As the global population continues to age, understanding the impact of dietary patterns on cognitive health becomes increasingly important. The aim of this study is to explore the mechanisms behind the Mediterranean diet's benefits on cognitive health, assess its practical applications, and review the growing body of research linking this dietary pattern to improved cognitive outcomes. By focusing on the Mediterranean diet, can implement actionable phases toward enhancing the brain health and overall well-being, making it a compelling area of study for researchers and health professionals alike.

Keywords: Antioxidants, Brain health, Cognitive function, Mediterranean diet, Neurodegenerative diseases

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Introduction

The Mediterranean diet, deeply embedded within customary dietary patterns of the diverse cultures contiguous with the of sea Mediterranean, has emerged as a model of healthy eating, widely acclaimed for its broad spectrum of health benefits, particularly in the realms of cardiovascular health and longevity (Fu et al., 2022). This diet originated from the dietary patterns of regions such as Spain, Greece, and Italy in the mid-20th century, when chronic disease rates were among the lowest and life expectancy was among the highest globally, despite limited access to modern healthcare (Sofi et al., 2020). This eating pattern transcends a mere diet, representing a holistic approach that emphasizes plant-derived foods, beneficial fats, and lean protein sources. The pattern is defined by a high intake of phytonutrient-rich plant foods, including fruits, vegetables, legumes, and whole grains, supplemented with nuts and olive oil. Animal products are largely limited to moderate fish and poultry, with strict minimization of red meat and sugar-sweetened items. This dietary regimen is high in essential nutrients, including a wide array of antioxidants, omega-3 fatty acids, and vitamins, together, these believed to contribute to its protective effects against various chronic conditions, notably cognitive decline and neurodegenerative diseases (Table 1) (Sofi et al., 2020).

Table 1. Nutritional Components of the Mediterranean Diet

Component	Sources	Health Benefits	References
Fruits	Berries, citrus fruits, apples	Rich in antioxidants; may reduce oxidative stress	Yeung et al. (2020).
Vegetables	Leafy greens, tomatoes, peppers	High in vitamins and minerals; anti-inflammatory	Sofi et al. (2020).
Whole Grains	Whole wheat bread, brown rice	Provides fiber; supports gut health	Aune et al. (2020).
Legumes	Lentils, chickpeas, beans	High in protein and fiber; may improve cognition	Semba et al. (2021).
Nuts and Seeds	Walnuts, almonds, flaxseeds	Source of healthy fats; omega-3 fatty acids	Wilson et al. (2020).

Olive Oil	Extra virgin olive oil	Rich in monounsaturated fats; supports heart health	Gaforio (2019).
Fish and Seafood	Salmon, sardines, mackerel	High in omega-3 fatty acids; beneficial for brain health	Kosti et al. (2022).
Moderate Dairy	Yogurt, cheese	Source of probiotics; supports gut and brain health	Dahiya and Nigam, (2022)
Herbs and Spices	Basil, oregano, garlic	Anti-inflammatory properties; enhances flavor without added salt	Dahiya and Nigam, (2022)

Longitudinal evidence demonstrates, systematic reviews confirmed the profound connection between adherences to the Mediterranean diet and enhanced cerebral role, most notably within aging populations. A thorough evaluation and meta-analysis, for example, demonstrated that individuals compliance with this nutritional regimen exhibit a notably slower rate of rational debility and a significantly reduced risk of developing Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) (Fu et al., 2022). It is believed that these cognitive enhancements stem from the diet's capacity to diminish inflammation and oxidative damage, both of which are central mechanisms involved in the onset and progression of neurodegenerative illnesses. (Martínez-Lapiscina et al., 2013). Specific nutrients are a hallmark component of the Mediterranean dietary pattern like vitamin E and certain fatty acids that are linked to neuroprotective effects further suggesting that this dietary pattern may play a critical impact on sustaining brain function and extending longevity (Martínez-Lapiscina et al., 2013).

Moreover, the Mediterranean diet's well-established positive impact on cardiovascular health lends further support to its role in cognitive preservation. Research has consistently shown that the same factors that promote heart health including enhanced blood circulation and lower incidence of vascular inflammation also pay to maintaining cognitive function, as cardiovascular diseases are known to exacerbate cognitive decline (Moore and Jefferson, (2021). This close interplay between heart and brain health underscores the holistic benefits of the Mediterranean diet, illustrating how a single dietary approach can exert extensive impact on both physical and cognitive well-being (Moore and Jefferson, (2021).

Despite the accumulating evidence supporting the Mediterranean diet's role in brain health, the relationship between this dietary pattern and cognitive preservation has only recently gained significant traction in the scientific community. There is a pressing need for further studies to replicate these findings across various demographic groups and geographical regions to establish the Mediterranean diet as a universally applicable as a neuroprotective intervention (Gregory et al., 2023). As research in this field keeps advancing, evidence consistently demonstrates dietary choices are fundamental to maintaining cognitive role also preventing the onset of neurodegenerative ailments, positioning the Mediterranean diet as a particularly promising area for continued exploration and intervention (Martínez-Lapiscina et al., 2013).

Ultimately, the Mediterranean diet represents a multifaceted and enduring strategy to nutrition that not only promotes overall health but also holds significant promise for enhancing cognitive resilience, particularly in aging populations. By integrating this dietary pattern into daily life, individuals may adopt a practical and effective strategy for supporting brain health and mitigating the risks associated with cognitive decline. This systematic review evaluates to comprehensively synthesize the existing literature regarding the association between the Mediterranean diet and brain health, elucidating the potential mechanisms underlying its neuroprotective effects, and offering insights into the directions future research might take to further validate and expand upon these findings. The Mediterranean diet is extensively praised for its variety and nutrient-rich components, which is a critical determinant of delivering its myriad therapeutic effects, particularly in enhancing cognitive function and overall well-being. Originating from the customary eating patterns of Mediterranean-bordering countries, this nutritional regimen emphasizes minimally processed foods. These foods not only contribute to the diet’s rich nutrient profile but also align with a lifestyle that supports healthy aging and the prevention of non-communicable diseases.

- **Key Nutritional Elements in the Mediterranean Diet**

Fruits and Vegetables: Fruits and Vegetable intake represents a core component of the Mediterranean dietary regime, offering a broad spectrum of essential micronutrients and bioactive compounds. This nutritional approach advocates for substantial diversity within plant food consumption, with a particular focus on those that are fresh, seasonal, and locally sourced. Notable vegetable components comprise

tomatoes, leafy greens (e.g., spinach, kale), and bell peppers, alongside fruits like berries, oranges, and grapes, are integral to this diet. These nutrients are fundamental for preserving general well-being and also contribute significantly to lowering the likelihood of long-term health conditions, especially those connected to cognitive impairment. The antioxidants and phytochemicals found in these fruits and vegetables, such as lycopene in tomatoes and flavonoids in berries, demonstrate protective effects against cellular oxidation and inflammatory processes, which are key contributors to the aging process and cognitive deterioration (Sofi et al., 2020; Lutski et al., 2020).

Cereals: Characteristic cereal sources within the Mediterranean diet comprise quinoa, barley, brown rice, and whole wheat products. These grains are consumed in their unrefined form, preserving their natural fibre content, vitamins, and minerals. Whole grains' high fibre content supports digestive function, aids in blood glucose regulation, and reduces cardiovascular risk factors. Moreover, their low glycaemic index signifies a slow and steady release of energy, it is associated with a reduced incidence of type 2 diabetes mellitus (T2DM), and related cardiometabolic disorders. Epidemiological studies consistently link whole-grain consumption with reduced risk of ischemic heart disease, stroke, and gastrointestinal cancers, further underlining their importance in the Mediterranean diet (Aune et al., 2020).

Healthy Fats: The Mediterranean dietary pattern is characterized by its lipid profile, predominantly featuring monounsaturated fatty acids (MUFAs) from extra virgin olive oil as the principal fat source. This oil is notably rich in phenolic compounds and MUFAs, particularly oleic acid, which demonstrate well-established hypocholesterolemic effects and anti-inflammatory properties through the modulation of pro-inflammatory pathways. The regimen additionally incorporates nuts and seeds including almonds, walnuts, and flaxseeds which provide polyunsaturated fatty acids (PUFAs), plant-based proteins, and essential micronutrients including α-tocopherol (vitamin E) and magnesium. These lipid sources contribute to cardiovascular risk reduction and support neurological function by maintaining neuronal membrane fluidity and providing neuroprotective effects against oxidative stress. (Semba et al., 2021; Estruch et al., 2018).

Fish and Seafood: Fish and seafood are recommended as a primary source of protein in the Mediterranean diet, particularly fatty fish such as salmon, sardines, mackerel, and trout. Piscine sources provide significant quantities of long-chain omega-3

polyunsaturated fatty acids, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which demonstrate neuroprotective properties. These essential lipids modulate inflammatory pathways, reduce serum triglyceride concentrations, and attenuate cardiovascular disease risk. DHA constitutes a fundamental structural component of neuronal membranes and supports synaptic plasticity. Epidemiological evidence associates regular marine fat consumption with decreased incidence of Alzheimer's disease and vascular dementia, suggesting their critical function in maintaining cognitive integrity during aging (Kosti et al., 2022; Koyama et al., 2012).

Legumes: Legumes, including beans, lentils, and chickpeas, comprise core components of the traditional Mediterranean diet, offering a rich source of plant-based protein and dietary fibre. These bioactive food components promote cardiovascular function through hypocholesterolemic effects and the maintenance of normative blood pressure parameters. The fibre in legumes also aids in digestion and this dietary pattern enhances gastrointestinal microbial diversity and function, factors now established as critical determinants of systemic homeostasis and pathogenesis. Habitual legume intake has been associated with a lower risk of chronic conditions like cardio disorders, diabetes, and certain cancers. Additionally, the protein and iron content in legumes make them an excellent meat alternative, contributing to the diet's sustainability and health benefits (Semba et al., 2021; Gardener et al., 2015).

Moderate Dairy and Wine: Dairy products in the Mediterranean diet are consumed in moderation, with a focus on yogurt and cheese. These dairy products are often fermented, providing probiotics that support gut health and contribute to a balanced digestive system. The combination of calcium and vitamin D in dairy products contributes to bone mineral density maintenance and osteoporosis risk reduction. The Mediterranean dietary pattern incorporates moderate wine consumption, primarily red varieties, typically consumed with meals. Red wine is rich in polyphenols, especially resveratrol, and these polyphenolic compounds demonstrate cardio-protective properties through enhanced endothelial function and attenuated oxidative damage. When consumed in moderation, red wine has been linked to a lower risk of heart disease and may contribute to the overall cardioprotective effects of the Mediterranean diet (Loughrey et al., 2017; Berendsen et al., 2018).

The synergistic interaction of various bioactive constituents within the Mediterranean nutritional regimen contributes to its positive health outcomes. This

eating pattern, characterized by a high intake of unprocessed, nutrient-dense foods, demonstrates neuroprotective effects while providing a viable and palatable framework for sustained well-being.

❖ Neuroprotective Effects of the Mediterranean Dietary Pattern

Evidence demonstrates that high adherence to the Mediterranean dietary pattern correlates with attenuated rates of cognitive deterioration in older adult cohorts. A systematic review and meta-analysis confirmed that strict compliance with this nutritional regimen is associated with a significantly lower incidence of Mild Cognitive Impairment (MCI) and Alzheimer's disease dementia (Fu et al., 2022). The neuroprotective properties associated with the Mediterranean dietary pattern are attributed to its high-density nutritional composition, particularly its enrichment with long-chain omega-3 polyunsaturated fatty acids from marine sources and polyphenolic compounds from plant-based foods (Loughrey et al., 2017). The mechanisms underlying these benefits may involve the diet's ability to reduce inflammation and oxidative stress, both of which are critical factors in cognitive decline. The human brain demonstrates particular vulnerability to oxidative injury owing to its elevated metabolic rate, high oxygen utilization, and substantial lipid content, greatly benefits from a diet that supplies antioxidants and anti-inflammatory compounds. Epidemiological evidence establishes a significant association between adherence to the Mediterranean dietary pattern and reduced dementia incidence, with proposed mechanisms including enhanced cerebrovascular function, reduced oxidative stress, and decreased neuro-inflammation (Koyama et al., 2012). The incorporation of unsaturated lipids, particularly monounsaturated fatty acids from olive oil and polyunsaturated fatty acids from nuts, demonstrates neuroprotective benefits through multiple pathways: improved endothelial function, enhanced synaptic plasticity, and reduced arterial compliance (Estruch et al., 2018).

Moreover, the cardio-protective effects of this dietary pattern contribute significantly to cognitive preservation, given the established relationship between cardiovascular pathology and cerebral deterioration. The brain's intricate network of blood vessels requires optimal cardiovascular health to ensure adequate blood flow and oxygen supply, which are vital for maintaining cognitive function. A recent study found that dietary patterns resembling the Mediterranean diet were associated with better cognitive outcomes and a lower risk of cognitive impairment (Psaltopoulou et al., 2020). This suggests that the Mediterranean diet may help prevent vascular-related

cognitive impairments, such as those caused by stroke or small vessel disease, by maintaining healthy blood vessels and reducing the risk of atherosclerosis.

In conclusion, the Mediterranean dietary pattern represents a viable nutritional intervention for supporting neurological function and attenuating age-related cognitive deterioration. The regimen's diverse portfolio of bioactive compounds and anti-inflammatory effects establish it as an effective strategy for maintaining cerebral health in geriatric populations. Its capacity to preserve cerebrovascular integrity, mitigate oxidative damage, and provide critical neuroprotective nutrients further substantiates its position as a fundamental component of cognitive preservation.

- **Specific Aspects of the Mediterranean Diet and Cognitive Function**

While the Mediterranean diet as a whole has shown promising results in maintaining cognitive function, certain aspects of the diet have been studied more extensively for their direct impact on brain health.

Fish and Omega-3 Fatty Acids: The intake of marine-derived foods, especially varieties abundant in long-chain omega-3 polyunsaturated fatty acids, demonstrates significant correlation with enhanced neurocognitive function and decreased incidence of age-related cognitive impairment. Omega-3 fatty acids, such as docosahexaenoic acid (DHA), are integral components of neuronal membranes, playing a crucial role in maintaining membrane fluidity, facilitating neurotransmission, and reducing neuroinflammation. Investigation demonstrated that elderly participants A prospective cohort study demonstrated that elderly subjects consuming marine sources at least weekly exhibited significantly reduced dementia incidence compared to those with lower consumption frequency (Kalmijn et al., 1997). Furthermore, omega-3 polyunsaturated fatty acids demonstrate enhanced synaptic plasticity critical for memory formation and learning processes, while simultaneously inhibiting beta-amyloid aggregation, a characteristic pathological feature of Alzheimer's disease neuropathology (Kosti et al., 2022).

Olive Oil and Monounsaturated Fats: Another aspect of the Mediterranean diet that has garnered significant attention is the role of olive oil, particularly extra virgin olive oil. This fundamental component of the Mediterranean dietary pattern contains elevated concentrations of monounsaturated fatty acids (MUFAs) and bioactive phenolic compounds, such as polyphenols, which may contribute to its

neuroprotective effects. MUFAs are known to improve blood lipid profiles, reduce inflammation, and improve insulin signaling pathways, collectively supporting neurological integrity. Spanish epidemiological research established that elevated olive oil intake correlated with superior cognitive performance and reduced incidence of mild cognitive impairment (Guasch-Ferré et al., 2020). The antioxidant properties of polyphenols in olive oil also help shield neuronal cells from oxidative injury, consequently maintaining cognitive capacity and lowering susceptibility to neurodegenerative pathologies (Martínez-González et al., 2017).

Plant-Based Foods and Cognitive Health: The Mediterranean dietary regimen's foundation in phytonutrient-dense botanicals specifically fresh fruits, vegetables, and unprocessed cereals constitutes a fundamental pathway for its observed neuroprotective effects through multiple biochemical mechanisms. These foods contain high concentrations of essential micronutrients., minerals, and dietary fibre, along with potent antioxidants like vitamin C, vitamin E, and polyphenols, demonstrate anti-inflammatory properties and protect against oxidative stress in the brain. The substantial dietary fibre component additionally promotes gastrointestinal microbial diversity, with growing evidence establishing gut microbiota composition as a significant modulator of neurological function via the gut-brain axis. Epidemiological research indicates that increased consumption of fruits and vegetables correlates with reduced incidence of age-related cognitive impairment in elderly populations, underscoring the neuroprotective significance of plant-based nutritional sources in maintaining cognitive integrity during aging (Kang et al., 2005).

In addition, whole grains in the Mediterranean diet, such as quinoa, barley, and whole wheat, facilitate gradual glycemic modulation, ensuring sustained cerebral metabolic substrate availability. This stable energy supply helps maintain cognitive performance, particularly in tasks that require sustained mental effort. The synergistic effect of low-glycaemic index carbohydrates and high fibre intake ensures that blood sugar levels remain stable, reducing the risk of insulin resistance, which has been associated with cognitive decline and an increased risk of Alzheimer's disease (Sofi et al., 2020).

In summary, the Mediterranean dietary pattern, through its prioritization of micronutrient-rich foods and beneficial lipids, represents a multifaceted nutritional strategy for sustaining neurological function. Through the integration of specific nutritional components including long-chain omega-3 polyunsaturated fatty acids

from marine sources, monounsaturated fatty acids from olive oil, and diverse phytonutrient-rich plant foods, this dietary regimen sustains neurological integrity via multiple complementary biological pathways. These include reducing inflammation and oxidative stress, enhancing vascular health, and providing essential nutrients that promote cognitive resilience. As research continues to evolve, the Mediterranean diet remains a powerful tool in the prevention and management of cognitive decline, offering a practical and enjoyable way to support brain health throughout life.

- **Impact of the Mediterranean Diet on Brain Health**

The Mediterranean dietary pattern has attracted significant scientific interest for its potential neuroprotective properties, particularly regarding cognitive performance and neurodegenerative pathology. This nutritional regimen, characterized by high consumption of plant-based foods, unrefined cereals, unsaturated lipids, and lean protein sources, demonstrates an inverse association with cognitive deterioration and Alzheimer's disease pathology.

❖ **Studies Linking Diet to Cognitive Function**

Substantial epidemiological evidence confirms a significant positive correlation between adherence to the Mediterranean dietary pattern and enhanced cognitive performance across multiple domains. A recent systematic review and meta-analysis demonstrated that elevated adherence to this nutritional regimen correlated with substantially diminished incidence rates of Mild Cognitive Impairment (MCI) and Alzheimer's disease dementia (Fu et al., 2022). The diet's emphasis on nutrient-dense foods, particularly omega-3 fatty acids from fish and antioxidants from fruits and vegetables, plays a crucial role in its neuroprotective effects (Lutski et al., 2020). For instance, a study published in Nature Aging highlighted that specific nutrients, including vitamin E and fatty acids, are linked to slower brain aging and better cognitive performance (Martínez-Lapiscina et al., 2013). This is particularly significant as cognitive decline is often associated with aging, and dietary interventions may offer a non-pharmacological approach to mitigate these effects.

❖ **Effects on Aging and Neurodegenerative Diseases**

The Mediterranean diet's impact on aging and neurodegenerative diseases is supported by various observational studies. Evidence demonstrates that compliance with this dietary pattern correlates with larger hippocampal volumes and preserved

brain structures, which are vital for memory and learning (Koyama et al., 2012). The hippocampus is particularly sensitive to dietary influences, and its health is crucial for cognitive functions such as spatial navigation and memory consolidation. Furthermore, the Mediterranean dietary pattern demonstrates neuroprotective effects through the attenuation of neuro-inflammation and oxidative damage, both recognized as primary pathological mechanisms in cognitive deterioration (Martínez-González et al., 2017).

A study focusing on Hispanic and Latino adults found that increased was positively associated to enhance cognition and decreased cognitive decline (JAMA Network Open, 2021). This suggests that the benefits of the Mediterranean diet may extend across diverse populations, emphasizing its universal applicability. Additionally, the diet's protective effects may stem from its ability to lower the prevalence of vascular comorbidities, which are known risk factors for cognitive impairment (Berendsen et al., 2018). Cardiovascular health is closely tied to brain health, as conditions such as hypertension and diabetes can adversely affect cognitive function.

- **Mechanisms of Action**

The mechanisms through which the Mediterranean diet influences brain health involve several interrelated factors. The elevated concentrations of antioxidant compounds present in fruits and vegetables mitigate oxidative stress, a pathological state capable of inducing neuronal injury and cognitive deterioration. Long-chain omega-3 polyunsaturated fatty acids, particularly abundant in fatty fish species, maintain neuronal membrane fluidity and facilitate adult neurogenesis (Wilson et al., 2020). Additionally, the anti-inflammatory characteristics of olive oil polyphenols and nut-derived bioactive components may attenuate neuro-inflammatory processes implicated in neurodegenerative disease progression.

In conclusion, the Mediterranean diet presents a promising dietary strategy for enhancing cognitive health and mitigating the risks associated with cognitive decline and neurodegenerative diseases. Its rich array of beneficial nutrients, combined with its anti-inflammatory properties, underscores its value in promoting brain health in aging populations. As research continues to evolve, the Mediterranean diet may serve as a cornerstone for public health recommendations aimed at preserving cognitive function and improving quality of life in older adults.

- **Mechanisms behind the Benefits**

The Mediterranean diet is not only celebrated for its contributions to overall health but also for its specific benefits to brain health. The mechanisms behind these benefits are multifaceted, involving the roles of antioxidants, healthy fats, and their influence on inflammation and oxidative stress.

❖ Role of Antioxidants and Healthy Fats

The Mediterranean dietary pattern demonstrates elevated concentrations of endogenous antioxidants, predominantly sourced from botanical produce, seeds, and unrefined cereals. These bioactive compounds comprising ascorbic acid, tocopherols, flavonoid derivatives, and phenolic constituents function as critical mediators in cerebral protection against oxidative damage, a pathophysiological state defined by disrupted redox homeostasis through reactive oxygen species accumulation. This oxidative impairment represents a well-established mechanistic contributor to neurodegenerative pathogenesis, particularly Alzheimer's dementia (Martínez-González et al., 2017; Petersson & Philippou, 2016). Empirical investigation confirms that elevated consumption of antioxidant-dense nutrients correlates positively with enhanced cognitive metrics and reduced progression to cognitive impairment (Lutski et al., 2020).

Beneficial lipid constituents, specifically monounsaturated fatty acids from oleaceous sources and long-chain omega-3 polyunsaturated fatty acids from piscine origins, constitute fundamental components of this nutritional framework. These lipid species maintain neuronal structural integrity through membrane stabilization and facilitate hippocampal neurogenesis. The n-3 fatty acid series demonstrates particular efficacy in modulating inflammatory cascades while enhancing synaptic plasticity fundamental processes underlying memory consolidation and cognitive processing (Bredesen et al., 2020; Fu et al., 2022). The concerted interaction between these neuroprotective lipids and redox-regulating compounds collectively strengthens neural resistance to senescence-associated cognitive deterioration.

❖ Influence on Inflammation and Oxidative Stress

The Mediterranean dietary regimen demonstrates significant efficacy in attenuating inflammatory pathways and oxidative damage, two principal mechanistic drivers of cognitive deterioration. Chronic inflammation is linked to various neurodegenerative diseases, and dietary patterns that emphasize anti-inflammatory foods can help

mitigate this risk. Evidence demonstrates that compliance with the Mediterranean dietary pattern correlates with reduced concentrations of systemic inflammatory biomarkers, including C-reactive protein (CRP) (Fu et al., 2022; Wengreen et al., 2013). Additionally, the dietary pattern's prioritization of unrefined, minimally processed foods promotes gastrointestinal microbial diversity and function, which is increasingly recognized for its role in brain health. A balanced gastrointestinal microbiota generates short-chain fatty acids (SCFAs) demonstrating anti-inflammatory characteristics and neuroprotective benefits (Martínez-González et al., 2017). The Mediterranean diet fosters a diverse gut microbiome, which may enhance cognitive function and protect against neurodegenerative diseases (Fu et al., 2022).

In summary, the Mediterranean diet's protective effects on brain health can be attributed to its rich content of antioxidants and healthy fats, as well as its ability to reduce inflammation and oxidative stress. These interconnected biological pathways collectively enhance neurocognitive performance and reduce susceptibility to neurodegenerative pathologies, establishing the Mediterranean dietary pattern as an effective nutritional intervention for supporting neurological integrity across the lifespan.

❖ **Practical Applications of the Mediterranean Diet**

Implementing the Mediterranean diet into daily life can be a rewarding endeavor that promotes both physical and cognitive health. This nutritional regimen prioritizes unrefined foods and promotes behavioral patterns incorporating social engagement and regular exercise. The following evidence-based implementation strategies facilitate effective adoption of the Mediterranean dietary pattern.

❖ **How to Implement the Mediterranean Diet**

- **Focus on Whole Foods:** Initiate dietary modification by emphasizing unprocessed foods including fresh produce, whole-grain cereals, pulses, tree nuts, and oilseeds. Aim for a colorful variety, as different colors often indicate different nutrients. Incorporate fresh, seasonal produce into your meals, and consider shopping at local farmers' markets to find high-quality ingredients (Wengreen et al., 2013).
- **Healthy Fats:** Replace saturated fats with healthy fats, primarily from extra virgin olive oil, which should be used as the main cooking fat. Incorporate fatty fish species, including salmon and sardines, with a minimum biweekly consumption frequency to ensure adequate intake

of long-chain omega-3 polyunsaturated fatty acids, which demonstrate essential neuroprotective properties (Estruch et al., 2018).

- **Meal Planning:** Structure nutritional intake according to the Mediterranean diet framework, which prioritizes abundant plant-derived components, moderate piscine and avian sources, and minimal red meat and refined carbohydrates. The following exemplifies a potential weekly nutritional schedule:
- **Breakfast:** Hellenic-style fermented dairy with acacia honey and poly-berry composition.
- **Lunch:** Andean pseudocereal preparation incorporating garbanzo legumes, solanaceous fruits, cucurbitaceous vegetables, and oleaceous emulsion.
- **Dinner:** Thermally-processed salmonid with roasted plant-based accompaniments and unrefined cereal supplementation.
- **Snacks:** Fresh fruit, nuts, or olives.
- **Social Aspects:** Embrace the social tradition of sharing meals with family and friends. Eating together not only enhances the enjoyment of food but also fosters a sense of community and well-being (Powers, 2022).
- **Cultural Adaptation:** Consider how to culturally adapt the Mediterranean diet to fit your local food environment and personal preferences. This may involve substituting local ingredients while maintaining the core principles of the diet, such as prioritizing plant-based foods and healthy fats (Powers, 2022).

❖ **Food Choices**

When making food choices, prioritize seasonal and local options. Integrate diverse pulse varieties, whole grains, and nuts into your diet. For dairy, choose low-fat options like yogurt and cheese, and limit red meat to occasional servings. Red wine can be enjoyed in moderation, ideally with meals, as it may offer cardiovascular benefits (Powers, 2022).

In summary, implementation of the Mediterranean dietary pattern represents an adaptable and gratifying nutritional strategy associated with substantial health improvements. Through emphasis on unprocessed foods, beneficial lipids, and

communal eating practices, individuals can establish a sustainable nutritional regimen that supports both extended health span and preserved cognitive function.

Conclusion

The Mediterranean dietary pattern has been established as a significant nutritional framework associated with multiple favorable health outcomes, particularly regarding neurological protection and reduced neurodegenerative disease risk. Characterized by abundant consumption of plant-based foods, unrefined cereals, unsaturated lipids, and lean protein sources, this regimen demonstrates substantial benefits for both physiological homeostasis and cerebral function preservation throughout the aging process.

Accumulating empirical evidence establishes a significant correlation between compliance with the Mediterranean dietary pattern and attenuated rates of neurocognitive deterioration, along with diminished incidence rates of prodromal cognitive disorders including Mild Cognitive Impairment (MCI) and Alzheimer's disease dementia pathologies (Fu et al., 2022). Primary neuroprotective mechanisms involve the regimen's high-density provision of radical-scavenging phytochemicals and unsaturated lipids, which collectively mitigate oxidative damage and neuroinflammatory cascades established pathological contributors to cognitive deterioration (Martínez-González et al., 2017; Lutski et al., 2020). Furthermore, the dietary framework's foundation in unrefined comestibles enhances cardiometabolic parameters, demonstrating strong cerebrovascular interconnectivity through hemodynamic and endothelial pathways (Berendsen et al., 2018). Overall, the evidence supports the Mediterranean diet as a sustainable and effective strategy for enhancing cognitive health and promoting longevity.

Future Directions for Research

Nevertheless, while extant findings remain promising, additional investigation is required to elucidate the precise molecular pathways and long-term neurological outcomes associated with this dietary pattern. Future studies should focus on longitudinal designs to explore the long-term effects of adhering to this dietary pattern on cognitive function across diverse populations. Additionally, research should investigate the specific constituents of the Mediterranean dietary regimen

that contribute most significantly to cognitive health, such as the roles of individual nutrients, food combinations, and their interactions with genetic factors.

Moreover, there is a need for studies that examine the mechanisms through which the Mediterranean diet influences brain health, particularly regarding gut-brain interactions and the role of the microbiome in mediating the diet's effects. Understanding these mechanisms could lead to more targeted dietary interventions for preventing cognitive decline.

Finally, as the Mediterranean diet is culturally adaptable, future research should explore how to effectively implement and promote this dietary pattern in various cultural contexts, ensuring that it remains accessible and relevant to diverse populations around the world.

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CHAPTER TWO

Cafestol and Kahweol Diterpenoids From Coffee Bean to Molecular Targets in Human Health and Disease

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Abstract

The coffee contains a variety of bioactive substances, including alkaloids such as caffeine and trigonellin, phenolic acids, diterpenes such as cafestol, lignans, and flavonoids. Two diterpenoids, cafestol and kahweol, play a role in raising cholesterol, but only caffeine in coffee has pharmacological effects. The amount of cafestol and kahweol in coffee depends on the brewing method. The greatest amount of these substances is released when they come into contact with boiling water. The soluble dietary fiber content of brewed coffee is also important. Scientists announced today the identification of a compound that benefits human health. Researchers say this information could one day help them develop new drugs to better prevent and treat diseases.

Keywords: Coffee, Cafestol, Health, Kahweol

Introduction

Coffee, derived from the roasted seeds of Coffea species, is one of the most widely consumed beverages globally. Beyond its cultural and economic significance, epidemiological and clinical studies have associated moderate coffee consumption with a reduced risk of several chronic diseases, including type 2 diabetes, certain cancers, and neurodegenerative disorders (Poole et al., 2017; Novaes et al., 2025). The complex chemical matrix of coffee contains numerous bioactive compounds, including the diterpenoid alcohols cafestol and kahweol. These molecules exhibit a

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unique duality, presenting both potentially adverse effects on serum lipid profiles and a broad spectrum of promising pharmacological activities, making them a subject of considerable scientific interest (Ren et al., 2019; Ricketts et al., 2007).

Structural Chemistry and Discovery

Cafestol and kahweol are pentacyclic diterpenoid alcohols derived from an ent-kaurane skeleton and are found almost exclusively in plants of the genus Coffea (Rubiaceae), with cafestol also reported in Tricalysia dubia (Novaes et al., 2025; Ren et al., 2019). Kahweol was first isolated in 1932 from the unsaponifiable matter of Arabica coffee oil, while cafestol was identified in 1938 (Bengis & Anderson, 1932; Slotta & Neisser, 1938). Their definitive structures were elucidated later through chemical synthesis and advanced spectroscopy (Djerassi et al., 1958; Lam et al., 1982).

The critical structural distinction between these isomers is the presence of a double bond between carbons C-1 and C-2 in kahweol, which is absent in cafestol (Figure 1). This confers a furan moiety on kahweol, classifying it as 1,2-dehydrocafestol (Speer & Kölling-Speer, 2006). This additional unsaturation influences the compound's electrophilicity, redox potential, and biological potency, often rendering kahweol more active in antioxidant and certain anti-inflammatory pathways (Ren et al., 2019; De Lucia et al., 2009).

In their natural state within the coffee bean, these diterpenes exist predominantly (over 99.6%) as fatty acid esters, with the hydroxyl group at C-17 esterified to long-chain fatty acids (Speer & Kölling-Speer, 2006). The free alcohols constitute less than 0.4% of the lipid fraction. Palmitate (C16:0), linoleate (C18:2), oleate (C18:1), and stearate (C18:0) esters are the most prevalent forms (Novaes et al., 2025; Kaufman & Hamsagar, 1962). A related methoxylated derivative, 16-O-methylcafestol (16-OMC), is a characteristic, though not exclusive, chemical marker of Coffea canephora (robusta) beans (Pettitt, 1987; Gunning et al., 2018).

This chapter provides a comprehensive and systematic review of the chemistry, occurrence, analysis, pharmacokinetics, and multifaceted biological activities of the coffee diterpenoids cafestol and kahweol. It aims to consolidate scientific knowledge from phytochemical, pharmacological, and clinical perspectives, offering a balanced assessment of their dual role as both hypercholesterolemic dietary agents and

promising bioactive compounds with chemopreventive, anti-inflammatory, and other therapeutic potentials. The chapter further seeks to elucidate the relationship between their chemical structure and biological function, analyze factors influencing their content in coffee beverages, and identify key directions for future research to translate preclinical findings into practical health applications.

Biosynthesis

The biosynthesis of cafestol and kahweol in Coffea plants proceeds via the universal isoprenoid pathways. The five-carbon building blocks, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are supplied by both the cytosolic mevalonic acid (MVA) pathway and the plastidial methylerythritol phosphate (MEP) pathway (Bergman et al., 2019). These units condense to form geranylgeranyl diphosphate (GGPP), the direct precursor to diterpenes.

The latter stages involve the formation of the ent-kaurene skeleton, catalyzed by kaurene synthase and kaurene oxidase enzymes (Pereira & Ivamoto, 2015). Transcriptional analyses have identified specific cytochrome P450 genes in C. arabica whose expression patterns correlate with cafestol and kahweol accumulation, including CaCYP701A3, CaCYP76C4, and CaCYP71A25, indicating their role in the oxidative modifications of the kaurene backbone (Ivamoto et al., 2017). Sunlight exposure modulates the expression of these biosynthetic genes, with higher light intensity in full-sun cultivation systems increasing transcript levels compared to agroforestry systems (Oliveira et al., 2021).

Natural Occurrence and Distribution in Coffee

The concentration of cafestol and kahweol is highly variable and depends on coffee species, genotype, geographical origin, agricultural practices, and fruit maturation stage (Kitzberger et al., 2013; Zanin et al., 2020). C. arabica beans contain substantially higher total diterpene levels (1.3–1.9% w/w) compared to C. canephora (0.2–1.5% w/w) (Moeenfard et al., 2020). Within C. arabica, cafestol content ranges from 221–1308 mg/100g and kahweol from 120–1265 mg/100g in green beans. In contrast, robusta beans typically contain 151–300 mg/100g of cafestol and only trace to 200 mg/100g of kahweol, which is often undetectable (Scholz et al., 2014; Finotello et al., 2017). The

ratio of cafestol to kahweol has been proposed as a potential indicator of beverage quality (Novaes et al., 2015).

These diterpenes are not confined to the coffee bean (endosperm) but are distributed throughout the plant. They are present in the perisperm, pericarp, leaves, roots, and flowers, with the highest concentrations ultimately accumulating in the seed endosperm during fruit maturation (Dias et al., 2010; Ivamoto et al., 2017). This translocation from maternal tissues to the endosperm suggests a biological role in seed defense. Recent evidence confirms that cafestol, in its free form, exhibits antifungal activity against pathogens like Fusarium solani and anti-insect effects against pests such as Ceratitis capitata (Antonie et al., 2023). The esterified forms are considered non-phytotoxic storage compounds that can be hydrolyzed to release the bioactive free diterpenes in response to biotic stress, functioning as a chemical defense system for the plant (Antonie et al., 2023).

Analytical Methods for Identification and Quantification

The analysis of cafestol and kahweol in coffee matrices presents challenges due to their thermolability and the predominance of their esterified forms. Methods typically involve either the direct analysis of esters or, more commonly, a hydrolysis step to cleave the fatty acids and quantify the total free diterpene content (Novaes et al., 2025). The two primary analytical workflows are summarized in Figure 1. Hydrolysis via direct hot saponification of ground beans followed by liquid-liquid extraction (DHS-LLE) has been reported as an efficient approach for isolating the free diterpenes, yielding up to 1.5% w/w from green Arabica beans (Novaes et al., 2020).

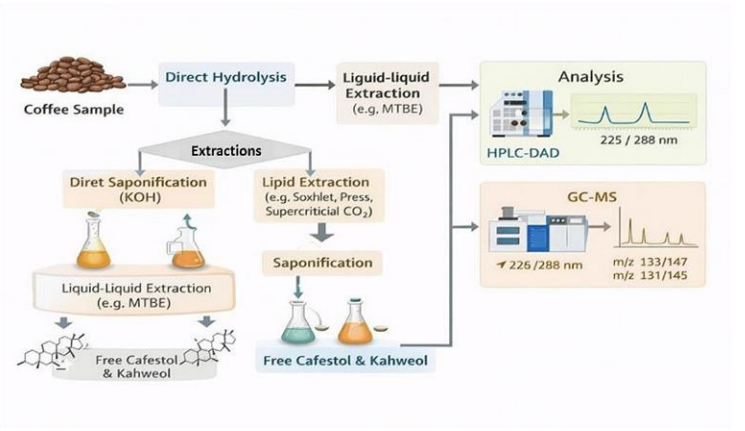

Figure 1. Primary Analytical Workflows for the Quantification of Cafestol and Kahweol in Coffee

High-performance liquid chromatography (HPLC) coupled with ultraviolet (UV) or diode array detection (DAD) is the most widely employed technique for quantification. The furan ring in both compounds acts as a chromophore, with optimal detection at wavelengths of 220–230 nm for cafestol and 290 nm for kahweol (Ren et al., 2019; Oigman et al., 2012). Gas chromatography (GC) can also be applied, often requiring cold on-column injection to prevent thermal degradation in the injector port (Novaes et al., 2018). Mass spectrometry (MS), either coupled to GC or LC, provides confirmatory identification through characteristic fragment ions. Diagnostic ions in GC-MS include m/z 133, 147, and 161 for cafestol, and m/z 131, 145, and 158 for kahweol, corresponding to furan-containing fragments from the B-ring (Novaes et al., 2015). High-resolution MS and tandem MS are valuable for elucidating metabolite structures and analyzing complex samples (Andriolo et al., 2021).

Influence of Roasting on Diterpene Content and Degradation

The thermal stability of cafestol and kahweol during coffee roasting is a subject of some debate, with outcomes dependent on roasting degree, time, temperature, and coffee species. Light to medium roasting appears to cause minimal degradation, and an apparent increase in extractable diterpene content is sometimes observed, attributed to the migration of lipids from the bean interior to the surface as cell structures break down (Novaes et al., 2023; Urgert et al., 1995). However, more severe roasting conditions, particularly dark roasts, consistently lead to significant reductions in both compounds (Dias et al., 2014; Rendón et al., 2017).

Thermal degradation proceeds primarily via dehydration reactions, yielding dehydro derivatives. The most abundant roasting products are 15,16-dehydrocafestol and 15,16-dehydrokahweol, formed by the loss of a water molecule (Speer et al., 1991). Other characterized thermal degradation products include cafestal, kahweal, and various anhydro and isomeric forms (Guerrero et al., 2005; Novaes et al., 2023). Kahweol, due to its extra double bond, is generally considered more heat-sensitive than cafestol and degrades at earlier roasting stages (Fukuma et al., 2015; Ren et al., 2019). These thermodegradation products have been detected in roasted bean oil and even in the smoke emitted during roasting (Czech et al., 2016).

Content in Coffee Beverages and Influencing Factors

The transfer of cafestol and kahweol from ground coffee to the beverage is not a function of aqueous solubility but rather a mechanical process of leaching, where water carries insoluble lipid particles and diterpene esters (Novaes et al., 2019). Consequently, the brewing method is the primary determinant of diterpene content in the final cup. Unfiltered brewing techniques, which do not employ a paper or cloth filter, result in the highest levels (Figure 2). Boiled, Turkish, and French press coffee contain the greatest amounts, ranging from 3–12 mg of diterpenes per cup (Ratnayake et al., 1993; Urgert et al., 1995).

Figure 2. Influence of Brewing Method on the Transfer of Cafestol and Kahweol into Coffee

In contrast, filtered and drip-brewed coffee, where the brew passes through a paper filter that traps lipid-containing solids, contains minimal amounts, typically less than 0.5 mg per cup (Gross et al., 1997). Espresso coffee presents an intermediate case; although it uses a metal filter, the high pressure and short extraction time yield moderate diterpene levels (Moeenfard & Alves, 2020). Other parameters influencing beverage content include grind size (finer grinds increase extraction), coffee-to-water ratio (higher ratios increase content), and, to a lesser extent, water temperature and extraction time (Andueza et al., 2003; Miceli Filho, 2023). The majority of diterpenes present in the grounds, approximately 86–89%, remain in the spent coffee grounds regardless of the brewing method (Rendón et al., 2017).

Absorption, Metabolism, and Excretion

The pharmacokinetics of cafestol and kahweol involve efficient intestinal absorption followed by enterohepatic circulation. In humans, approximately 70% of ingested

diterpenes from unfiltered coffee is absorbed in the small intestine (de Roos et al., 1998). Studies using ileostomy volunteers indicate that around 90% of the diterpenes reaching the intestine are bioaccessible and absorbed (de Roos et al., 1998). Once absorbed, they undergo significant first-pass metabolism in the liver.

Glucuronidation and sulfation are the primary phase II conjugation pathways, although less than 1% of an oral dose is excreted as these conjugates in urine (Urgert et al., 1996). The low urinary recovery suggests extensive alternative metabolism or tissue distribution. Autoradiographic studies in rodents show that radiolabeled cafestol rapidly concentrates in the liver and gastrointestinal tract, indicating a pronounced enterohepatic recirculation (van Cruchten et al., 2010). Metabolites are excreted primarily via bile into the feces.

Recent investigations using high-resolution mass spectrometry have begun to elucidate phase I metabolites. In silico and in vivo studies in zebrafish models propose hydroxylated and oxidized metabolites of cafestol, including 6-hydroxycafestol and various oxo-derivatives (Andriolo et al., 2021). Glutathione conjugates have also been suggested as potential metabolites, indicative of electrophilic intermediates formed during biotransformation (van Cruchten et al., 2010).

Hypercholesterolemic Effects

The most well-established physiological effect of coffee diterpenes in humans is the elevation of serum lipids, an activity for which cafestol is recognized as one of the most potent dietary agents (Ricketts et al., 2007). This effect is almost exclusively associated with unfiltered coffee consumption. Cafestol raises both low-density lipoprotein (LDL) cholesterol and triglyceride levels, while kahweol exerts a weaker hyperlipidemic effect (Urgert & Katan, 1997).

The mechanism involves multiple pathways in hepatic cholesterol metabolism. Cafestol acts as an agonist for the nuclear receptors farnesoid X receptor (FXR) and pregnane X receptor (PXR), leading to the downregulation of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis from cholesterol (Ricketts et al., 2007; Post et al., 1997). Reduced bile acid synthesis decreases hepatic cholesterol catabolism, increasing intrahepatic cholesterol pools and suppressing LDL receptor expression and activity, thereby reducing LDL

clearance from plasma (Halvorsen et al., 1998). Cafestol also increases the activity of serum cholesteryl ester transfer protein (CETP), promoting the transfer of cholesteryl esters to LDL and VLDL particles (van Tol et al., 1997).

Chemopreventive and Anticarcinogenic Activities

Despite their hyperlipidemic activity, cafestol and kahweol demonstrate significant chemopreventive potential in experimental models. This activity is largely attributed to their ability to modulate xenobiotic-metabolizing enzymes. They potently induce phase II detoxifying enzymes, such as glutathione S-transferase (GST) and uridine diphospho-glucuronosyltransferase (UGT), via activation of the Nrf2/ARE signaling pathway (Higgins et al., 2008; Lam et al., 1982). Concurrently, they suppress the activity of certain cytochrome P450 isoforms involved in the metabolic activation of procarcinogens, including CYP1A2 and CYP2E1 (Huber et al., 2008).

This dual modulation confers protection against DNA damage from various carcinogens. Studies show that cafestol and kahweol reduce the formation of DNA adducts induced by aflatoxin B1, benzo[a]pyrene, and heterocyclic amines like PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine) (Cavin et al., 2002; Cavin et al., 1998). In vivo, they inhibit chemically induced tumorigenesis in animal models (Miller et al., 1991).

Antiproliferative and Pro-Apoptotic Effects in Cancer Cells

Beyond chemoprevention, cafestol and kahweol exhibit direct antitumor activities by inhibiting proliferation and inducing apoptosis in various human cancer cell lines, including those derived from leukemia, renal carcinoma, colorectal cancer, and malignant pleural mesothelioma (Choi et al., 2011; Lee et al., 2012; Lima et al., 2017). The mechanisms are multifaceted and involve the downregulation of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL, Mcl-1), activation of caspases, release of cytochrome c from mitochondria, and modulation of key signaling pathways like PI3K/Akt, ERK, and STAT3 (Oh et al., 2009; Kim et al., 2009; Woo et al., 2014).

Notably, these diterpenes can sensitize cancer cells to conventional chemotherapeutic agents. Cafestol overcomes resistance to the Bcl-2 inhibitor ABT-737 in renal carcinoma cells, and kahweol enhances sorafenib-induced apoptosis

(Woo et al., 2014; Min et al., 2017). Importantly, several studies report selective toxicity towards malignant cells with minimal effects on the viability of normal human fibroblasts, suggesting a potential therapeutic window (Choi et al., 2011; Lima et al., 2017).

Anti-inflammatory and Antioxidant Activities

Cafestol and kahweol exhibit significant anti-inflammatory properties, primarily through the modulation of key pro-inflammatory signaling pathways. In lipopolysaccharide (LPS)-activated macrophages, both diterpenes suppress the production of nitric oxide (NO) and prostaglandin E2 (PGE2) by downregulating the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Kim et al., 2004). The mechanism involves the inhibition of nuclear factor-kappa B (NF-κB) activation, achieved by blocking the phosphorylation and degradation of its inhibitor, IκB, thereby preventing NF-κB nuclear translocation (Kim et al., 2004; Shen et al., 2010). Kahweol demonstrates greater potency in reducing COX-2 expression and PGE2 synthesis compared to cafestol, potentially due to its enhanced electrophilicity (Ren et al., 2019).

Furthermore, these compounds inhibit the secretion of other inflammatory mediators. Cafestol attenuates cyclic-strain-induced expression of interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1) in vascular endothelial cells, partly through activation of the Nrf2/HO-1 and Sirt1 pathways (Hao et al., 2018). Kahweol also downregulates tumor necrosis factor-alpha (TNF-α) secretion (Kim et al., 2006).

Their antioxidant activity is closely linked to the Nrf2/ARE pathway. Cafestol and kahweol induce the expression of phase II antioxidant and detoxifying enzymes, including heme oxygenase-1 (HO-1), glutathione S-transferase (GST), and NAD(P)H:quinone oxidoreductase 1 (NQO1) (Higgins et al., 2008). This induction enhances cellular defense against oxidative stress, reducing reactive oxygen species (ROS) production, lipid peroxidation, and oxidative DNA damage (Lee & Jeong, 2007). Kahweol's ability to activate this pathway more robustly may again be attributed to its structural features (Fukuma et al., 2015).

Anti-angiogenic Properties

Angiogenesis inhibition represents another mechanism through which these diterpenes may exert antitumor effects. Kahweol inhibits endothelial cell proliferation, migration, and tube formation in vitro, and suppresses angiogenesis in chicken chorioallantoic membrane and transgenic zebrafish models (Cárdenas et al., 2011). It downregulates the expression of matrix metalloproteinase-2 (MMP-2) and urokinase-type plasminogen activator (uPA), enzymes critical for extracellular matrix remodeling during vessel sprouting (Cárdenas et al., 2011).

Cafestol similarly inhibits vascular endothelial growth factor (VEGF)-induced proliferation, migration, and tube formation in human umbilical vein endothelial cells (HUVECs) (Wang et al., 2012). This effect is mediated through the inhibition of focal adhesion kinase (FAK) and Akt phosphorylation, key mediators downstream of the VEGF receptor-2 (VEGFR-2) signaling pathway (Wang et al., 2012). Both cafestol palmitate and kahweol palmitate exhibit these anti-angiogenic activities, with kahweol palmitate often showing greater potency (Moeenfard et al., 2016).

Effects on Glucose Metabolism and Bone Biology

Emerging research indicates potential benefits of cafestol and kahweol on metabolic and skeletal health. Cafestol acutely stimulates insulin secretion in pancreatic β-cell lines and increases glucose uptake in muscle cells, exhibiting effects comparable to the antidiabetic drug rosiglitazone (Mellbye et al., 2015). In diabetic mouse models (KKAy), cafestol intervention reduced fasting blood glucose and improved insulin sensitivity (Mellbye et al., 2017). Kahweol, on the other hand, reduces lipid accumulation in adipocytes by downregulating key adipogenic transcription factors like PPAR$_{\gamma}$ and C/EBPα, and activates AMP-activated protein kinase (AMPK), a central regulator of energy metabolism (Baek et al., 2017; Kim et al., 2018).

In bone biology, both diterpenes inhibit osteoclastogenesis. Kahweol suppresses receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclast differentiation by impairing the activation of ERK and Akt and downregulating the expression of nuclear factor of activated T cells cytoplasmic 1 (NFATc1) and osteoclast markers like cathepsin K (Fumimoto et al., 2012). Cafestol shows similar but weaker inhibitory effects on osteoclast differentiation, while also promoting osteoblast

differentiation, suggesting a dual beneficial role in bone remodeling (Fukuma et al., 2015). he interconnected pathways of cafestol and kahweol, spanning their biosynthesis, dietary exposure, metabolism, and diverse biological activities discussed in this chapter, are summarized conceptually in Figure 3.

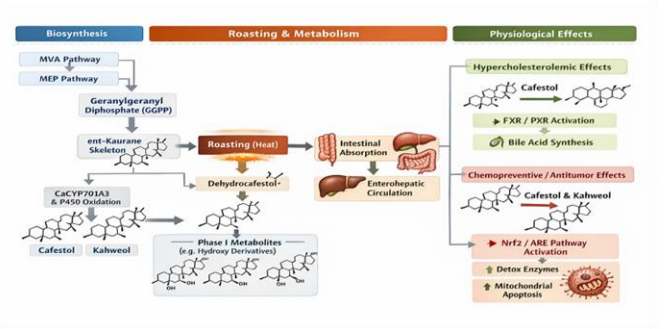

Figure 3. Integrated Pathway of Coffee Diterpenes: From Biosynthesis to Physiological Impact.

Conclusion and Perspectives

Cafestol and kahweol are chemically unique diterpenoids with a complex duality of biological actions. Their well-documented hypercholesterolemic effect, mediated through modulation of hepatic nuclear receptors and cholesterol metabolism, presents a clear dietary consideration, particularly for consumers of unfiltered coffee. However, this effect is counterbalanced by a broad spectrum of promising pharmacological activities demonstrated in preclinical models.

These activities include chemoprevention through enzyme modulation, direct antitumor effects via apoptosis induction, and anti-inflammatory, antioxidant, anti-angiogenic, antidiabetic, and osteoprotective properties. The structural difference between the two molecules, specifically the additional double bond in kahweol, often confers distinct potency and mechanistic nuances.

Future research should focus on several key areas. The pharmacokinetics and tissue distribution of these compounds and their metabolites in humans requires further elucidation. Well-designed clinical trials are necessary to translate the promising preclinical findings into therapeutic applications, carefully balancing potential benefits against the hyperlipidemic risk. Furthermore, the development of synthetic analogs or formulation strategies that dissociate the undesirable serum lipid effects

from the beneficial pharmacological activities could unlock their full potential as therapeutic agents or nutraceuticals.

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CHAPTER THREE

The Science behind AR and VR in Healthcare

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Abstract

The chapter discusses the revolutionary role of immersive technologies—Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR)—in transforming healthcare delivery, education, and patient participation. It discusses how these technologies improve medical training by offering risk-free settings for rehearsing complicated surgeries, and optimizing skill development through repeated training. VR is very useful for simulating surgery and pain management, while AR is necessary for real-time surgical guidance and patient education, delivering interactive 3D models for clearer medical condition understanding and treatment planning. MR integrates VR and AR to allow sophisticated surgical planning, distant consulting, and interactive medical training. The chapter also discusses the science behind immersive technologies and their hardware components, including head-mounted displays, motion-tracking sensors, and haptic feedback systems. The chapter emphasizes the multisensory interaction provided by such systems and significantly boosts learning, therapeutic outcomes, and patient compliance. Furthermore, it addresses the challenges in integrating immersive technologies with healthcare, including costs, availability, and the requirement for multidisciplinary treatments. The chapter concludes with a discussion of the potential of such technologies in the future, namely with the development of AI, wearable technology, and cloud computing, to further expand healthcare practice and patient care.

Keywords: Immersive Technologies, Virtual Reality, Augmented Reality, Mixed Reality, Healthcare Education, Patient Engagement

Introduction

Immersive technologies like Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) are revolutionizing healthcare delivery, patient experiences, and

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medical training (Iqbal et al. 2024). Immersive technologies create environments or overlays that replicate real-world circumstances, allowing users to engage with digital objects in innovative ways. Unlike traditional 2D screens or print, immersive technologies engage more than one sense—sight, sound, and even sometimes touch—creating an experience highly akin to reality. Such multisensory experience plays a tremendous role in healthcare, where understanding, skill development, and patient compliance are crucial. Virtual Reality (VR) fully immerses the user in a computer-simulated world (Khan and Lippert, 2022). It is able to replicate real or imaginary situations, such as surgical procedures or emergency response training, in a controlled, risk-free environment. People interact with these virtual worlds using head-mounted displays (HMDs), hand controllers, and motion-tracking sensors. For example, surgeons in training can practice complex surgeries in VR without risking patient harm, with the option to repeat the exercise until mastery is attained by the trainee (Ryan et al. 2022; Asoodar et al. 2024; Qu et al. 2022).

VR is even utilized for pain management and cognitive-behavioral therapy, where patients are subjected to virtual reality experiences designed to reduce stress, anxiety, and even pain itself (McGirt et al. 2023). Figure 1 shows a skilled surgeon using Virtual Reality (VR) in a modern operating room. The surgeon wears a black VR headset and engages with a simulated surgical space, which offers a simulated and safe site for rehearsing complex procedures. Virtual Reality as a tool for surgical training offers a complication-free setting for skill acquisition, multiple rehearsal, and higher surgical accuracy and confidence. The technology minimizes complications and improves patient outcomes during real-life surgeries (Mazzolenis et al. 2024; Darnall et al. 2025).

Figure 1: Virtual Reality for Surgical Training

In contrast, Augmented Reality (AR) enhances the real world by overlaying computer-generated information onto real-world objects. AR enhances perception instead of replacing reality, and healthcare providers can visualize patient anatomy, surgical guides, or rehabilitation exercises in real time. AR has had its greatest impact in image-guided surgery, where 3D renderings of internal organs are overlaid during surgery, improving accuracy and reducing complications. In non-clinical use, AR helps in patient education by presenting complex medical concepts in 3D to help them understand illnesses and treatment plans. Mixed Reality (MR) merges the virtual and real worlds to allow digital objects to interact with physical objects (Sugimoto and Sueyoshi, 2023; Asadi et al. 2024). MR enables highly interactive experiences, for instance, remote collaboration, where experts can guide medical procedures remotely by interacting with virtual objects overlaid on the patient or the environment. MR combines the immersive capabilities of VR and AR, offering complete immersion when needed while maintaining real-world context, making it ideal for complex surgical planning, telemedicine, and interactive medical training (Lin et al. 2023; Checcucci et al. 2024).

Figure 2 depicts a health practitioner putting on Augmented Reality (AR) glasses to display a floating 3D skeleton model during a session of physical therapy. The patient is engaging with the model, doing movement exercises. AR aids in the rehabilitation by enabling real-time visual feedback, which helps patients perform exercises properly and efficiently. AR can also aid in physical as well as cognitive therapy, optimizing recovery through providing personalized guidance to patients.

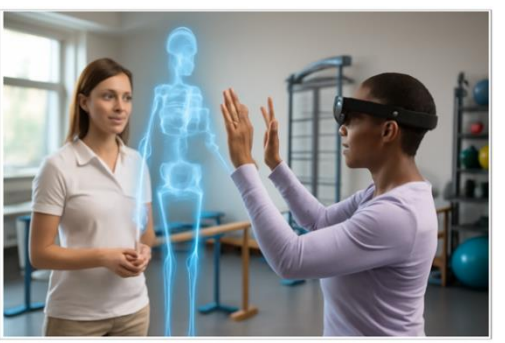

Figure 2: Augmented Reality for Rehabilitation

Figure 3 shows a medical practitioner using AR to educate a patient on the circulatory system. The practitioner holds a tablet, displaying a three-dimensional model of the circulatory system, which the patient examines meticulously. AR supports patient education by presenting complex medical concepts in interactive 3D models, increasing understanding, treatment adherence, and decision-making.

Figure 3: AR-Based Patient Education

Immersive technologies are gaining prominence in healthcare thanks to several factors: the growing need for high-fidelity medical training, the need for more patient engagement, advancements in wearable technologies and sensors, and the advent of telemedicine solutions (Mulukuntla, 2025; Cerda et al. 2024). Healthcare providers, research centers, and teaching institutions increasingly adopt these technologies to enhance clinical outcomes, decrease procedural complications, and develop more immersive and personalized patient experiences. Table 1 presents the definitions, healthcare applications, and levels of immersion of VR, AR, and MR in a conceptual model to differentiate their applications in the medical field (Arencibia et al. 2025; Yang, 2023; Adeghe et al., 2024).

Table 1: Definitions and examples of immersive technologies in healthcare

Technology	Definition	Healthcare Examples	Level of Immersion
Virtual Reality (VR)	Fully immersive digital environment	Surgical simulation, pain management	High
Augmented Reality (AR)	Digital overlay on real-world view	Image-guided surgery, patient education	Medium
Mixed Reality (MR)	Integration of virtual and real objects	Remote consultation, interactive anatomy	High

Medicine's virtual reality and immersive technologies expanded exponentially in the last few years, fueled by progress in application platforms, wearables, and computing power. With VR, physicians can practice sophisticated procedures risk-free, lowering complications and enhanced results (Fu et al. 2022; Emegano et al. 2025). AR more and more is being employed to assist surgeons with real-time summaries of patient anatomy, while MR facilitates interactive telemedicine and collaborative training at numerous locations (Morimoto et al. 2022). Their versatility further enhances their effectiveness not just in the clinical interventions but even in education and communication with patients. The healthcare facilities are finding more value to spend money on immersive technologies to improve patient care, streamline clinical workflows, and lower costs (Javvaji et al., 2024; Asoodar et al. 2024). Table 2 summarizes the key healthcare areas implementing VR, AR, and MR technologies, demonstrating the generalizability across specialties.

Table 2: Primary areas of healthcare embracing immersive technologies

Healthcare Domain	VR Applications	AR Applications	MR Applications
Surgery	Surgical simulation, skill assessment	Real-time anatomy overlay	Collaborative surgery
Rehabilitation	Physical therapy exercises, neurorehabilitation	Motion guidance	Remote physiotherapy
Mental Health	Exposure therapy, mindfulness	Cognitive assessments	Interactive therapy
Education	Anatomy labs, procedural training	Interactive learning overlays	Mixed classroom simulations

Besides its medical applications, virtual reality technologies also have a significant role to play in patient motivation and education. The interactive visualizations that they present help patients enhance knowledge about their condition, treatment procedure, and rehabilitation therapy (Alam and Matava, 2022). For instance, AR-based apps are capable of presenting the patient with a 3D model of a procedure or therapy exercises to enhance understanding and compliance. VR-based pain management therapy has also shown significant enhancements in patient comfort and recovery. Technologically, immersive systems rely on high-level hardware and software components (Goudman et al. 2022). HMDs, motion tracking, haptic interfaces, and real-time rendering engines are the core for generating realistic and

responsive environments. Performance properties of the systems, including frame rate, latency, and field of view, directly affect user experience and productivity in healthcare applications. Table 3 is a comparison of technical features of the key technical components of VR, AR, and MR systems applied in clinical environments (Slitzky et al. 2024; Kremer et al. 2023; Combalia et al. 2024). Figure 4 compares the technological aspects—Display, Motion Tracking, Feedback, and Mobility—of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) in healthcare. The chart shows how the technologies prioritize different features, mirroring their varying roles in healthcare uses.

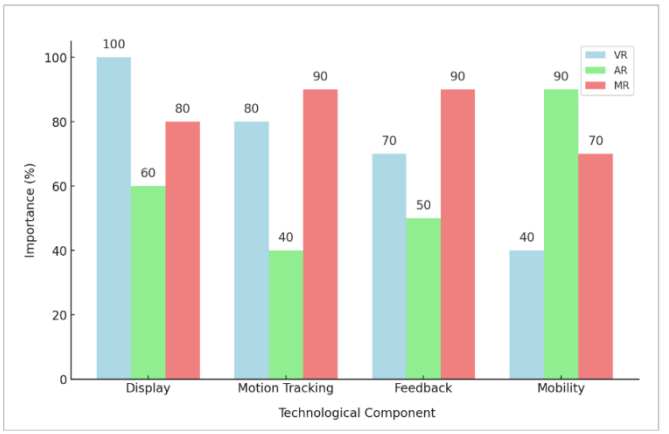

Figure 4. Technological Components of VR, AR, and MR in Healthcare

Table 3: Immersive healthcare system technical components

Component	VR	AR	MR
Display	HMD, fully immersive	Transparent AR glasses	Mixed HMD with real-world passthrough
Interaction	Hand controllers, motion tracking	Gesture or pointer interaction	Gesture, voice, and spatial mapping
Feedback	Visual and auditory	Visual overlay	Visual, auditory, and haptic
Mobility	Limited to VR space	Can move in real environment	Flexible, partially mobile

The inclusion of VR, AR, or MR into medical practices is also influenced by mounting clinical trial evidence on its effectiveness. There is improvement identified on surgical

precision, rehabilitation, and overall patient satisfaction. Additionally, immersive technologies offer remote medical consultations, whereby experts can observe surgeries or track patients' progress regardless of physical location. The use of immersive technology is highly pertinent from the standpoint of international medical settings where there is limited access to medical experts (Worlikar et al. 2023). The good of its promising application cannot be overstated. However, there are 'drawdowns' on the use of immersive technologies. For an average application of the technology, there is an almost prohibitive financial barrier in terms of its startup costs. There is a requirement of specific skills on the application of this technology. Moreover, there could be issues on the part of users in terms of 'motion sickness' or 'eye strain' from its use. There will also be certain issues on matters of ethics concerning 'confidential matters of patients', 'security of information', or 'issues of consent'.

The upcoming years will also witness the incorporation of immersive technologies into mainstream healthcare (Dinh et al. 2023). Breakthroughs in artificial intelligence, cloud computing, and haptics will make the healthcare system more personalized, adaptive, and interactive. The ongoing development of the technology will also make VR, AR, and MR common tools in the hands of medical practitioners, teachers, and patients, making the medical system more efficient, effective, and patient-centric (Javvaji et al. 2024; Selvaskandan et al. 2024). In short, immersive technologies can be said to be giving a complete overhaul to the medical system by providing innovative solutions to issues in practice, education, and engagement in the medical field. The ensuing chapter provides the foundation upon which the understanding of VR, AR, and MR will be formed. Figure 5 contrasts the impact of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) on clinical outcomes across four healthcare areas: surgical training, rehabilitation, pain control, and mental health. It shows the relative impact of each immersive technology towards the improvement of patient care, skill acquisition, and treatment results (Deighan et al. 2024; Greenway et al. 2023).

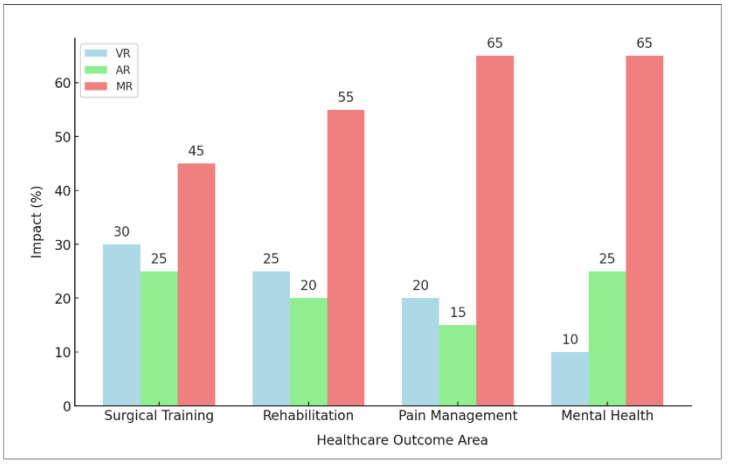

Figure 5: Impact of VR, AR, and MR on Clinical Outcomes in Healthcare

❖ Historical Development and Milestones

The history of immersive technologies in the medical field dates back more than five decades, commencing from the conceptual beginnings of virtual realities. Ivan Sutherland, a computer expert from 1965, proposed the concept of 'The Ultimate Display,' where the users could directly interact with virtual objects as if they existed in reality (Paro et al. 2022). This fundamental concept paved the entrance of upcoming virtual reality (VR)-based medical applications. The first few decades of the 1970s and 1980s led to experiments on early versions of VR technology, mainly in a laboratory environment. The focus remained on simulating an environment with the help of VR technology. However, despite the technological constraints of the time, including low resolution displays, the first VR systems showed the possibility of improving understanding of space along with the practice of skills, both of which play an equally significant role in medical training, including anatomy studies (Javvaji et al. 2024). The first stages of Augmented Reality concept, which emphasized focusing on the combination of computer-generated data with real-world objects, also started seeing the light of day. Even though it was still in its infancy stages due to technological limitations, this AR prototype conveyed the concept of improving clinician's awareness during medical surgeries, which, years later, established itself as an imaging-guided surgery technique (Iqbal et al. 2024).

The 1980s and 1990s saw the transformation of VR from theoretical models into simulations that could be applied in a healthcare setting. Based on the use of flight

simulators common in the aviation industry, the first simulators of surgical skills began to be developed. The first surgical simulators created a controlled environment in which trainee surgeons could simulate orthopedic as well as laparoscopic surgeries. The VR surgical simulators provided repetitive training opportunities, which is a requirement for learning complex surgical skills. The use of VR surgical simulators helped create shorter learning curves, enhanced accuracy, and overall patient safety (Lin et al. 2024; Muñoz et al. 2022). The first AR systems also began gaining ground in the healthcare industry. The image-guided surgery application, developed in the latter stages of the 1990s, was the first application of AR in the medical field. The application allowed surgeons to superimpose the anatomical image of the patient on their line of sight. The use of needle guides as well as radiotherapy was the first application of AR in the medical field. Table 4 summarizes the key historical milestones in the development of VR and AR for healthcare, highlighting significant technological breakthroughs, application areas, and their relevance to clinical practice (Charlet, 2025; Pierzchajlo et al. 2023).

Table 4: The key historical milestones of VR & AR in Healthcare

Year	Technology	Milestone	Healthcare Application
1965	Conceptual VR	Ivan Sutherland's "Ultimate Display"	Foundation for immersive environments
1980s	VR	First surgical simulators	Orthopedic and laparoscopic surgery training
1990s	AR	Early image-guided surgery	Needle placement, anatomy overlay
2000s	VR/AR	Improved HMDs and motion tracking	Medical education, rehabilitation
2010s	MR	Mixed reality prototypes	Remote collaboration, interactive anatomy

The early 2000s represented a time of rapid technological development that launched immersive technologies from research-oriented uses into more practical, clinical applications. Technological advances in computing, graphics processing, and sensory interfaces allowed the resolution of VR simulations to increase, as well as the accuracy of AR projections. The use of VR started for surgical rehearsals involving specific patients in order to prepare surgeons mentally for the procedure by exploring anatomy remotely. At the same time, there was continued development of AR

applications, most of which were linked to image-guided surgery and rehabilitation. While still in the experimental stages, AR applications demonstrated the effectiveness of the technology in reducing the time taken for surgical completion, minimizing surgical site error, and training surgeons faster. The introduction of haptics during this time allowed users to feel the experience (Giraldo et al. 2025).

Mixed Reality (MR), which started to appear in the2010s, marked the next step in the progress of immersive medical technologies. An MR system could provide the complete immersion of VR alongside the contextual awareness provided by AR, thus making it possible for real and virtual objects to interact with each other seamlessly (Asadi et al. 2024). The first examples of MR technology found use in collaborative surgical planning, telemedicine, and medical education. For an experimental trial of MR, the technology was used to enable remote experts to annotate and interact with patients' anatomy in real-time, which helped surgeons on the ground through complicated surgical operations. The use of MR allowed patients to understand surgical plans or rehabilitation activities interactively, which helped them become more intuitive (Asoodar et al. 2024).

There were also some pioneering clinical trials, which showcased the efficacy of immersive technologies. VR surgical simulators lowered error rates among trainees in laparoscopic surgeries. AR-assisted spine surgery showed more accurate screw fixation, thus fewer complications. For rehabilitation purposes, VR stroke rehabilitation showed quicker motor function improvement among patients. The gamified exercise of VR therapy showed better patient compliance than conventional approaches. The use of MR in remote consultation projects showed its capability of connecting locations in real-time, thus enabling shared decision-making. Figure 6 Tracks the ever-evolving history of VR, AR, or MR use in medical practices since its first experiments in the 1960s (Vervoorn et al. 2023; Moglia et al. 2023; Lastrucci et al. 2024).

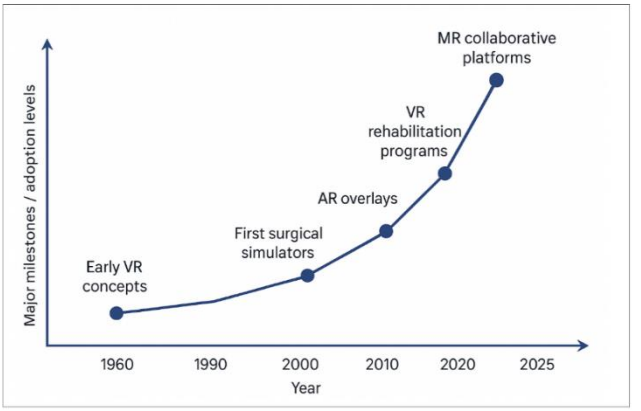

Figure 6: Growth of Immersive Technologies in Healthcare (Timeline)

The use of immersive technologies was also aided by an appreciation of the values they could provide in medical education. VR provided an environment where medical students could master anatomy as well as medical procedures in a safe setting (Kolecki et al. 2022). AR and MR assisted medical students by enabling them to create learning experiences through methods like projecting physiological information on a demonstration or recreating a scenario involving patients in a controlled setting (Asoodar et al. 2024). The use of these technologies led to an improvement in comprehension and retention of information by medical students. Table 5 provides a summary of early clinical projects and pilot studies, detailing the technology used, application domain, and observed outcomes. This table illustrates the tangible impact of immersive technologies on both clinical practice and patient care (Zhang et al. 2022; Hameed et al. 2022).

Table 5: Early clinical studies and pilot studies in immersive healthcare technologies

Year	Technology	Clinical Application	Outcome
2003	VR	Laparoscopic surgery training	Reduced training time, increased skill accuracy
2007	AR	Image-guided spine surgery	Improved screw placement precision
2012	VR	Stroke rehabilitation	Enhanced motor recovery, higher patient engagement
2015	MR	Remote surgical consultation	Successful collaboration, reduced errors

The historical trajectory of immersion technologies in medicine demonstrates a growth curve from hypothetical theory to evidence-based, applied practice. Early limitations, such as bulky hardware, low-definition images, and restricted interactivity, have been, to a significant extent, overcome with modern innovation in HMDs, motion tracking, haptics, and software platforms. VR, AR, and MR are now becoming more recognized as fundamental utilities for healthcare practice, medical training, and patient engagement, offering improved outcomes, safety, and learning efficacy (Morimoto et al. 2022; Asoodar et al. 2024; Khan and Lippert, 2022).

In conclusion, the technological progress and milestones of VR, AR, and MR in medicine reflect technological progression along with expanding fields of utilization (Anaam et al. 2025). From the pioneering conceptual frameworks of the 1960s to complex clinical implementations during the 2010s, immersive technologies have emerged as key constituents of modern healthcare. Acquaintance with the history provides a solid basis for interpreting the current as well as future potential of these technologies, as outlined in subsequent sections (Lang et al. 2024; Akhtar and Rawol, 2025).

❖ The VR, AR, and MR Science

The technical foundation of healthcare immersive technologies relies upon an intricate relationship of human perception, hardware, and software. Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) systems employ high-performance computational and sensing technologies to produce interactive and realistic experiences to simulate various human senses (Sun et al. 2022; Asoodar et al. 2024; Gupta et al. 2022). Hardware components most commonly include head-mounted displays (HMDs), motion-tracking sensors, haptic feedback devices, and spatial mapping cameras. HMDs position users visually and aurally in a virtual environment, producing a sense of "being there," and motion sensors track head, hand, and body motion to facilitate real-time interaction (Watkins et al. 2024; Morimoto et al. 2022; Su et al. 2023). Tactile feedback is provided by haptic devices, simulating the sensation of touch in virtual environments, which is critical in health care applications such as surgical simulation or rehabilitation training (Figure 7).

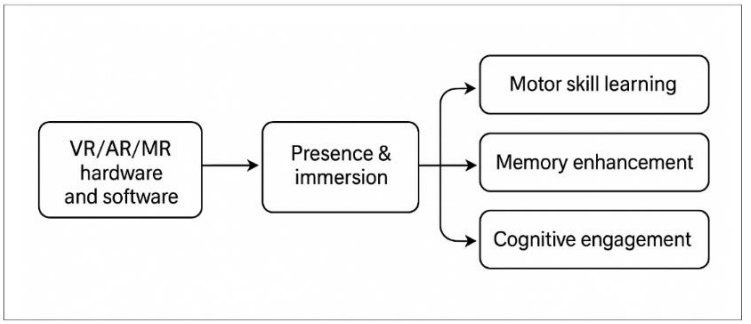

Figure 7: Interplay of Immersive Environments with Human Cognition

At the software level, VR, AR, and MR rely on sophisticated rendering engines, simulation environments, and overlay systems. VR software generates fully immersive 3D environments that interact with the user in real time (Brunzini et al. 2022; Sardi-Barzallo and Coors, 2025). AR software, however, must subtly integrate virtual information into the real world, requiring accurate spatial registration, real-time processing, and precise alignment with user perspective. MR combines these techniques, enabling digital objects to interact with elements of the physical world and creating an interactive hybrid reality. Advanced simulation software also combines physiological models, patient-specific image data, and AI algorithms for enhanced realism and to provide adaptive learning or therapy sessions. Table 6 summarizes key hardware and software components of VR, AR, and MR systems, their uses, and healthcare applications (Dóka et al. 2025; Farooq and Wu, 2022; Lee et al. 2024).

Table 6: Key hardware and software components of immersive healthcare systems

Component	VR	AR	MR	Role in Healthcare
Display	HMD	Transparent AR glasses	Mixed HMD with passthrough	Visual immersion and context-aware overlay
Motion Tracking	Head, hand, body sensors	Hand gestures, pointer devices	Gesture, voice, spatial mapping	Accurate interaction and navigation
Haptic Feedback	Gloves, controllers	Limited	Gloves/controllers + environment	Simulate touch, force, and resistance

Software	Simulation engines	Overlay systems	Hybrid rendering engines	Generate interactive and adaptive experiences

Immersive environments influence human perception, cognition, and motor skills through a sense of presence and interaction that is unachievable with traditional 2D interfaces. In VR, visual and auditory immersion leads to sensory integration in the brain, thus the realistic perception of space, movement, and interaction with objects. AR enhances cognition by providing contextual information overlaid on real-world objects that increase situational awareness and decision-making in procedures (Drigas and Sideraki, 2024). MR goes a step further by allowing real and virtual objects to interact, engaging the perceptual and motor systems simultaneously. For example, in MR surgical planning, clinicians manipulate virtual anatomical structures manually while being cognizant of the actual anatomy of the patient, engaging several cognitive and motor pathways for more efficient learning and performance (Torromino, 2024).

The physiological and neurological mechanisms of VR, AR, and MR are complex and diverse. Immersion refers to the extent to which an enclosure or absorption a user feels in the virtual world, often linked with sensory fidelity, interactivity, and environmental realism. Presence is the subjective psychological sense of "being there" in the virtual or mixed environment that can potentially enhance learning, compliance, and therapy outcomes (Florio, 2025). Engagement encompasses immersion and presence along with cognitive and emotional involvement, which are necessary for such applications as rehabilitation, patient education, or exposure therapy. Neuroimaging studies demonstrate that immersive experiences activate regions involved in spatial cognition, motor planning, and emotional processing, providing a scientific basis for reported benefits for clinical and educational outcomes (Gkintoni et al. 2025).

Motor learning and skill acquisition are particularly influenced by immersive technologies. VR surgical simulators, for example, allow procedures to be repeated again and again, reinforcing sensorimotor pathways and improving hand-eye coordination. AR-enabled rehabilitation offers patients movement guidance in the form of real-time visual overlays, optimizing muscle activation and joint alignment (Michailidou et al. 2025; Suprunowicz et al. 2025). MR facilitates co-located

collaborative tasks in which users manipulate both digital and physical objects simultaneously, improving fine motor skills and procedural memory. These interactions illustrate the ability of immersive technologies to support neuroplasticity, enabling rehabilitation and skill development in a variety of healthcare settings (Lau et al. 2022; Lekova et al. 2024). Table 7 summarizes the cognitive, perceptual, and physiological impacts of VR, AR, and MR within healthcare settings, with an emphasis on how these mechanisms translate into real-world benefits.

Table 7: Cognitive, perceptual, and physiological effects of immersive technologies in healthcare

Mechanism	VR	AR	MR	Healthcare Benefit
Immersion	Full sensory engagement	Partial visual overlay	Combined full + contextual	Enhanced learning, focus, and adherence
Presence	Feeling "in" the environment	Enhanced awareness of real + virtual	Interactive real-virtual integration	Improved procedural performance and patient engagement
Motor Skill Engagement	Repetitive simulated tasks	Guided real-world tasks	Mixed manipulation tasks	Optimized training, rehabilitation, and dexterity
Cognitive Enhancement	Problem-solving in safe environment	Contextual decision support	Integrated multi-tasking scenarios	Better clinical reasoning, faster learning

The science underlying immersive technologies further highlights the importance of system fidelity and usability. High-fidelity visual presentation, low latency, and accurate motion tracking facilitate immersion and presence, whereas compromised system performance can lead to disorientation, motion sickness, or disengagement. Human-centered design principles, including ergonomic HMDs, intuitive interaction methods, and adaptive difficulty levels, are crucial to maximize the therapeutic and educational impact of VR, AR, and MR systems. The continuous measurement of user experience, physiological responses, and clinical outcomes ensures that such systems are not just effective but also safe for application in clinical environments (Mitsea et al. 2024; Reddy, 2025; Singha and Singha, 2025).

In addition to perceptual and motor mechanisms, emotional and cognitive engagement is a significant element in the efficacy of immersive technologies. For

instance, VR exposure therapy for anxiety disorders or phobias relies on controlled emotional engagement for desensitization. AR and MR patient education systems enhance comprehension by communicating complex medical information in interactive and emotionally engaging ways, leading to better adherence and informed decision-making. By incorporating sensory, cognitive, and emotional elements, immersive technologies offer a holistic approach to healthcare interventions that traditional methods cannot compete with (Tong et al. 2025).

Finally, the convergence of VR, AR, and MR with other emerging technologies such as artificial intelligence, cloud computing, and biofeedback further expands their scientific potential. AI-driven simulations can adjust difficulty and feedback based on user performance, while cloud-based platforms enable remote collaboration and patient monitoring. Biofeedback sensors integrated into VR/AR/MR systems provide real-time physiological data, enabling personalized interventions that are adaptive to patient state (Paniagua-Gómez and Fernandez-Carmona, 2025). This intersection of science and technology positions immersive technologies as not only visualization and training aids but also as viable instruments for precision medicine. In summary, VR, AR, and MR science in medicine is an integration of advanced hardware, intricate software, and the science of human perception, cognition, and physiology (Elfouly and Alouani, 2025; Qiu et al. 2024; Asadi and Prabhakar, 2024). By leveraging immersion, presence, motor engagement, and cognitive-emotional mechanisms, these technologies are enhancing clinical practice, education, rehabilitation, and patient engagement. An understanding of these scientific principles provides a solid foundation for comprehension of the current state, applications, and future potential of immersive healthcare technologies (Kim et al. 2024; Pusey et al. 2022). Figure 8 illustrates the impact of bringing together Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) and revolutionary technologies such as Artificial Intelligence (AI), wearables, cloud computing, and biofeedback onto healthcare. It illustrates how these joined-up technologies enhance clinical outcomes, training, and patient engagement, creating more personalized and scalable healthcare solutions.

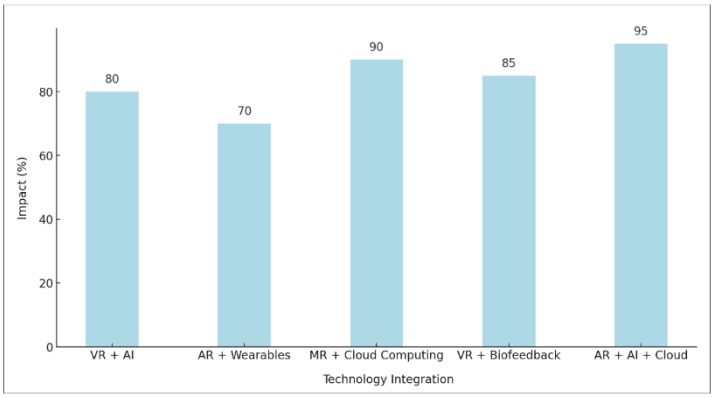

Figure 8: Impacts of VR, AR, and MR Integration with Next-Generation Health Technologies

❖ Current Applications in Healthcare

Immersive technologies like Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) have transitioned from experimental to applied technologies in many healthcare domains. They are currently being utilized in medical training, clinical interventions, rehabilitation therapy, and patient-specific treatment. Their most significant advantage lies in their capability to provide highly interactive, realistic, and safe environments for skill acquisition, procedure rehearsal, and patient engagement. VR, for instance, allows clinicians to rehearse surgical procedures within a risk-free virtual environment, building confidence and precision before performing procedures in the real world. AR offers intraoperative guidance through the projection of key anatomical information onto the surgeon's line of vision, while MR supports remote collaboration and complex visualization of patient-specific anatomy, allowing experts to consult or direct procedures remotely from other sites (Iqbal et al. 2024).

Training and Education: One of the oldest and most impactful applications of immersive technologies is medical training. VR simulation provides students and trainees with realistic conditions, ranging from anatomy dissection to complex surgical procedures. By replicating real-world conditions, these systems allow students to learn through error without sacrificing patient safety, building experiential learning and competence. AR further adds to this by overlaying step-by-step instructions or physiological data during practice, which reinforces

understanding and procedural accuracy. MR contributes to the learning experience enrichment through enabling collaborative learning, where multiple trainees or tutors interact with virtual and real objects in real time. Studies show that VR-based surgical training can potentially improve accuracy, reduce procedural errors, and accelerate the acquisition of complex skills compared to traditional methods of learning (Combalia et al. 2024).

Surgical Assistance and Planning: VR, AR, and MR have significantly transformed surgical practice. Preoperative planning using VR allows surgeons to navigate patient-specific anatomy in three dimensions, simulating surgical steps and anticipating complications. AR has been successfully implemented in image-guided surgeries, where real-time overlays of anatomical structures improve precision, reduce operating time, and minimize complications. MR goes a step further by enabling interactive manipulation of virtual anatomical models intraoperatively, improving spatial comprehension and enabling complex decision-making. Success stories in this area include AR-guided spine surgery, which has been shown to improve the accuracy of screw placement, and VR rehearsal of neurosurgery, which has been shown to decrease operative errors and enhance surgeon confidence (Cascella et al. 2023; Gahelot et al. 2024; Alam and Matava, 2022).

Rehabilitation and Physical Therapy: Immersive technologies have also shown impressive effectiveness in physical and neurological rehabilitation. VR tasks can be tailored to the individual needs of the patient, providing repetitive and enjoyable therapy sessions that promote motor recovery. VR-based stroke rehabilitation has been shown to improve limb mobility, coordination, and functional independence, and in most instances, it has outperformed conventional therapy alone. AR systems provide patients with real-time guidance, presenting visual feedback to ensure correct movement patterns during exercises. MR allows therapists to supervise remotely, adjust levels of difficulty, and monitor progress in interactive environments. Beyond motor rehabilitation, VR and AR applications aid in cognitive rehabilitation for patients with memory deficits, attention deficits, or traumatic brain injury (Javvaji et al. 2024; Cerda et al. 2024).

Pain Management and Mental Health: Immersive technologies are increasingly being utilized to manage acute and chronic pain, as well as mental health issues. VR environments provide distraction therapy for patients undergoing painful

procedures, such as burn care or chemotherapy that reduce perceived pain and anxiety significantly. In mental health, VR exposure therapy has been effective in the treatment of phobia, post-traumatic stress disorder (PTSD), and anxiety by allowing controlled exposure to triggers in a safe and reproducible setting. MR therapies augment therapeutic practice with the inclusion of biofeedback, monitoring physiological responses, and altering the environment in real time to optimize engagement and result. These approaches combine sensory, cognitive, and affective engagement to provide integrative treatment beyond traditional methods. Figure 9 displays for which medical specialties (training, surgery, rehabilitation, pain management, mental health) immersive technologies are most commonly used. Table 8 summarizes the most important healthcare areas where immersive technologies are currently applied, with example and outcome types encountered (Gahelot et al. 2024; Alam and Matava, 2022).

Table 8: Current applications of immersive technologies in healthcare

Domain	Technology	Application Examples	Clinical/Patient Outcomes
Training & Education	VR, AR, MR	Surgical simulators, anatomy labs, collaborative learning	Improved skill acquisition, reduced errors, enhanced comprehension
Surgery Assistance	VR, AR, MR	Preoperative planning, image-guided surgery, interactive anatomical models	Reduced complications, improved accuracy, shorter operative time
Rehabilitation	VR, AR, MR	Stroke therapy, physical exercises, cognitive rehabilitation	Improved motor function, coordination, and patient engagement
Pain & Mental Health	VR, MR	Pain distraction therapy, exposure therapy, biofeedback interventions	Reduced pain perception, anxiety, and PTSD symptoms

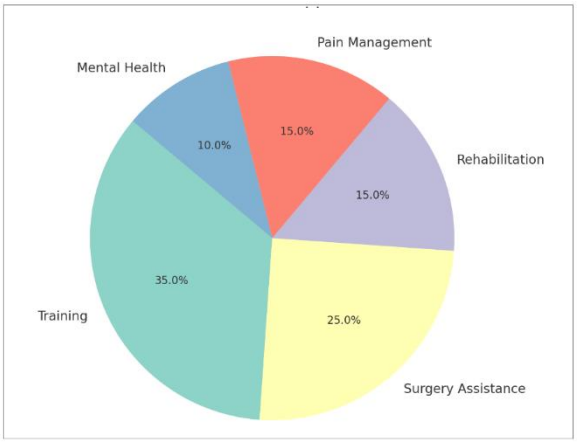

Figure 9: VR, AR, and MR Application Distribution in Healthcare

There are some evidence-based research studies that demonstrate how effective immersive technologies can be in these sectors. A meta-analysis of surgical training with VR indicated a 29% increase in procedural precision and lower learning curves compared to traditional training. In stroke rehabilitation, stroke patients who received VR therapy had 40% greater recovery of upper-limb motor function than in traditional therapy. AR-assisted spine surgery reduced intraoperative errors by up to 30%, showing the clinical value of precision anatomical overlays. Furthermore, VR-aided pain management procedures have had patient-reported pain scores greatly reduced, representing their real-world effectiveness in improving patient comfort and outcomes. Besides measurable clinical outcomes, virtual and augmented reality technologies also enhance patient satisfaction and interaction. Through engaging and personalized experience, patients learn more about their conditions, treatment protocols, and rehabilitation regimens. VR and AR technologies make rehabilitation gamelike so that patients can adhere to therapy programs at regular intervals. MR allows real-time interaction with clinicians, even remotely, enabling patients and carers to become active participants in the process of treatment (Iqbal et al. 2024; Eves et al. 2022; Jung et al. 2022).

Technological innovation keeps expanding the range of application of immersive healthcare applications. Advances in wearables, cloud and artificial intelligence technology provide real-time monitoring, adaptive feedback, and personalized interventions. MR systems, for example, may integrate patient-tailored imaging, decision support based on AI, and interactive visualization into a unified platform, creating an embracing clinical tool. These innovations reflect how immersive

technologies are evolving from add-on tools to central components of healthcare services, making it more efficient, safe, and patient-oriented. Overall, immersive technologies have transformed health care across a range of sectors, including education, surgical training, rehabilitation, and mental health treatment. VR, AR, and MR provide interactive, immersive, and evidence-based solutions that enhance skill acquisition, clinical precision, patient recovery, and overall treatment outcomes. Increased uptake of these technologies within health care workflows, supported by rigorous research and innovation, has the potential to redefine the learning, practice, and experience of medicine. Table 9 encapsulates some of the most important success stories and evidence-based studies that have demonstrated the effectiveness of immersive technologies in healthcare application (Bruno et al. 2022; Worlikar et al. 2023).

Table 9: Evidence-based studies reflecting effectiveness of immersive technologies in healthcare

Study/Year	Technology	Application	Outcome
Kennedy et al. 2023	VR	Laparoscopic surgery training	Improved procedural accuracy, reduced errors
Al-Whaibi et al. 2022	VR	Stroke rehabilitation	40% improvement in motor function compared to conventional therapy
Felix et al. 2022	AR	Spine surgery	30% reduction in intraoperative errors
Armstrong et al. 2023	VR	Pain management for burn patients	Significant reduction in reported pain scores
Khanji et al. 2023	MR	Remote surgical consultation	Successful collaboration, improved procedural guidance

❖ Future Directions

The future of immersive technologies in healthcare is closely tied to advancements in artificial intelligence (AI), haptic feedback, cloud computing, and data-driven personalization. Incorporation of AI enhances VR, AR, and MR applications with adaptive, intelligent systems that learn from user behavior and patient-specific data. For instance, AI algorithms can track and analyze surgical performance in VR simulations, identify areas for improvement, and provide personalized feedback to

trainees. In rehabilitation, AI can monitor patient progress in real time, dynamically modifying the challenge of therapy and intensity of exercise to optimize recovery outcomes. This intersection transforms immersive technologies from passive therapy or training devices into intelligent, adaptive platforms that respond to individual needs. Figure 10 illustrates the distribution of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) applications across four healthcare fields: surgery, rehabilitation, mental health, and education. The graph is a relative measure of application frequency of each technology within these fields and is reflective of the growing use of immersive technologies in healthcare practice (Qu et al. 2022; Javvaji et al. 2024; Yang, 2023; Mitsea et al. 2024).

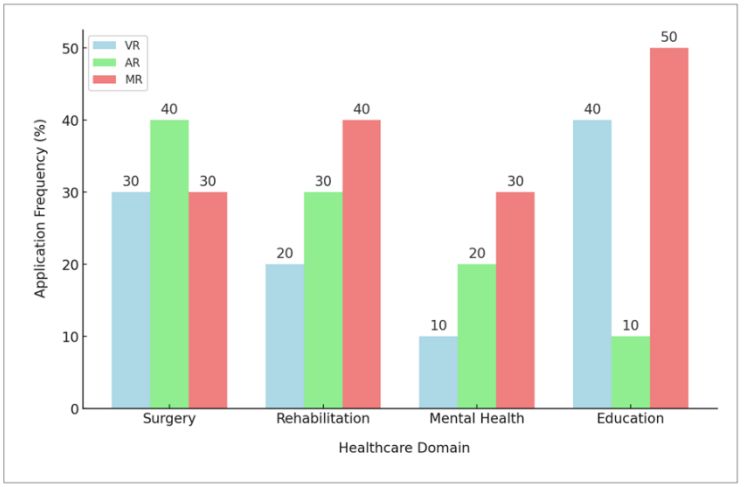

Figure 10: Application Distribution of VR, AR, and MR in Healthcare Domains

Haptic feedback technology represents another frontier of immersive healthcare applications. Through the reproduction of touch, pressure, texture, and resistance, haptics significantly enhances realism and skill transfer in-patient rehabilitation and clinical training. For example, surgeons can experience instrument feedback and tissue resistance while training in VR procedures, allowing for muscle memory that transfers directly to real operations. Similarly, VR rehabilitation of hand or limb injuries in patients may include realistic resistance in therapy exercises, resulting in better motor recovery. Imminent breakthroughs in wearable haptic technology and force-feedback systems will further augment the range of tactile experiences, allowing for even more engaging and clinically effective immersive therapies (Worlikar et al. 2023; Khan et al. 2023; Zhang et al. 2024).

Cloud-based VR, AR, and MR platforms will revolutionize the scalability and accessibility of immersive healthcare technologies. Traditionally, immersive systems have required high-end, locally installed hardware and software, which has limited widespread adoption. Cloud computing enables streaming high-fidelity VR or AR environments to multiple devices simultaneously, facilitating remote training, telemedicine, and distributed collaboration. A network of hospitals, for instance, could deploy cloud-delivered VR simulations across multiple campuses, normalizing training while reducing hardware costs. MR applications could similarly leverage cloud infrastructure to integrate patient imaging, procedural guides, and collaborative software in real time, enabling specialists and trainees to interact naturally across locations. Table 10 lists emerging technologies and their promises for immersive healthcare systems (Kharche and Kharche, 2023; Bansal et al. 2022; Bailey et al. 2024).

Table 10: Emerging technologies shaping the future of immersive healthcare systems

Technology	Potential Application	Expected Impact
Artificial Intelligence	Adaptive surgical training, personalized rehabilitation, predictive analytics	Increased personalization, efficiency, and clinical accuracy
Haptic Feedback	Realistic tissue simulation, tactile therapy, interactive patient exercises	Enhanced skill transfer, motor learning, and engagement
Cloud-based Platforms	Remote VR/AR training, telemedicine, collaborative MR procedures	Improved scalability, accessibility, and cost-effectiveness

Personalization is one of the primary trends for the future generation of immersive healthcare applications. Through the use of AI, biometric sensors, and patient-specific data, VR, AR, and MR systems can tailor experiences to individual needs, capabilities, and therapeutic goals. In rehabilitation, for example, systems can adjust exercise intensity, duration, and type of feedback based on real-time performance and physiological response, improving recovery rate and compliance (Lin, 2024). In mental health applications, VR exposure therapy can be customized to individual anxiety triggers or phobic stimuli, improving treatment outcomes. This level of customization has the potential to transform patient-centered care by optimizing therapy, training, and education to individual physiological, cognitive, and emotional profiles (Tiwari and Waoo, 2024; Murala et al. 2023).

Scalability and integration within standard care pathways are also critical to long-term growth. Cloud computing, AI-driven analytics, and interoperable systems will allow immersive technologies to evolve from niche research platforms to mainstream clinical solutions. Hospitals, medical schools, and rehab centers can integrate VR/AR/MR platforms into existing workflows, accommodating standard training, patient education, and therapy interventions. Scalable solutions will also facilitate larger-scale population health initiatives, delivering remote monitoring, tele-rehabilitation, and virtual consultations that reach beyond geographical and resource limitations (Shabbir and Linh, 2024; Kanakaprabha et al. 2024).

Combination of immersive technologies with other emerging innovations—such as wearable sensors, Internet of Things (IoT) devices, and real-time physiological monitoring—promises unprecedented opportunities for data-driven healthcare. For example, coupling MR with wearable biosensors can provide clinicians with real-time patient performance, engagement, and physiological response during sessions (Etli et al. 2024). AI algorithms can then parse this data to alter interventions in real time, forecast potential risks, and optimize outcomes. Such integrated systems will enable precision medicine approaches, whereby interventions are not just tailored to the patient's condition, but also to their moment-to-moment physiological and cognitive state. Ethical, regulatory, and accessibility considerations will determine the responsible adoption of immersive technologies in healthcare. Upholding patient privacy, informed consent, and data security will be crucial, particularly with heightened utilization of cloud-based systems and AI platforms. In addition, equal access to immersive technologies must be considered to prevent disparities in healthcare delivery. Future research will need to balance innovation with these ethical and practical considerations to maximize benefits and minimize risks (Rehan, 2024; Yadav et al. 2024). Table 11 provides a snapshot of future directions, highlighting how future technologies, personalization, and integration into standard care could shape immersive healthcare applications.

Table 11: Future directions and their possible influence on immersive healthcare systems

Future Direction	Example Application	Potential Benefit
AI Integration	Adaptive surgical VR training, predictive rehabilitation	Personalized learning, improved outcomes

Haptic Feedback	Tactile surgery simulators, rehabilitation exercises	Realistic skill transfer, enhanced motor recovery
Cloud Platforms	Remote VR/AR training, telemedicine	Scalable, cost-effective, widely accessible
Personalization	Customized therapy sessions, patient-specific MR guidance	Increased adherence, patient-centered care
Workflow Integration	Hospital-wide immersive training and therapy platforms	Seamless adoption, standardized quality of care

Overall, the future of VR, AR, and MR in medicine is characterized by intelligent, adaptive, and accessible systems seamlessly integrated into clinical and educational workflows. With AI, haptic feedback, cloud computing, and customization, immersive technologies have the potential to transform medical education, patient rehabilitation, treatment of mental illnesses, and clinical decision-making. Continued advances in such technologies, coupled with rigorous research and ethics-driven deployment, will enable immersive healthcare solutions to become integral aspects of modern medicine, improving outcomes, accessibility, and patient-centered care.

❖ Immersive Technologies' Challenges and Limitations

Despite the revolutionary nature of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) in health care, several challenges and limitations should be adequately weighed into consideration. High on the list of barriers to adoption is the cost of hardware and software. High-fidelity head-mounted displays (HMDs), motion-tracking sensors, haptic devices, and powerful computational platforms constitute a significant initial cost for schools, clinics, and hospitals. The cost can make availability challenging in low-resource settings and could retard adoption. Even with cloud computing, the initial infrastructure necessary for immersion systems is a significant barrier to the majority of healthcare organizations (Kremer et al. 2023).

Portability and simple deployment are also issues. Traditional VR systems usually require dedicated space and challenging installations, and therefore become difficult to integrate into standard clinical workflows. While AR and MR offer more flexible, mobile solutions, they are still constrained by battery life, wireless connectivity, and hardware ergonomics. For example, extended HMD usage can be cumbersome,

leading to physical strain on healthcare professionals or patients. These technical and logistic limitations can hinder smooth adoption and render immersive technologies less viable in real-world healthcare environments. Eye strain and motion sickness are some other technical concerns of immersive technologies. VR, in particular, can induce cybersickness characterized by dizziness, nausea, and confusion produced by misalignment of visual input-vestibular feedback. Display resolution, frame rate, and latency are the most important parameters that affect the quality of the immersive experience. System response times or low-resolution graphics may not only decrease the presence feeling but can also decrease the effectiveness of training or therapy, especially for accuracy-critical operations like surgery simulation (Lake et al. 2024).

Human factors and ergonomics play a significant role in the usability of immersive technologies. Users' comfort while using them, intuitiveness of interaction, and learning time must be addressed carefully so that effective adoption may be achieved. Healthcare staff, especially those less skilled in handling technology, may require intensive training to effectively use VR, AR, or MR devices. Similarly, disabled patients, sensory-impaired or cognitively impaired individuals can find it difficult to relate to immersive environments and necessitate accessibility design and options. Forgetting these human considerations can lower the overall effectiveness of immersive interventions. From the regulatory and ethical vantage point, privacy of information and consent of patients take precedence. Immersive technologies are likely to be based on large quantities of patient information like physiological information, movement patterns, and live imagery. It is essential that such sensitive information is stored and processed securely in compliance with data protection law. Informed consent for VR or AR-based treatments also requires open communication concerning possible risks, benefits, and limitations that could prove difficult for non-adversarial patients who do not understand immersive technologies (Al-Jaroodi et al. 2023; Yadav, 2024).

Clinical safety and liability issues further contribute to challenges of adoption. Medical applications of VR, AR, and MR are in their early development, and high-quality clinical testing must be conducted to ascertain safety and efficacy. Errors in virtual training or deceptive guidance provided by AR overlays could lead to procedure errors or adverse patient outcomes. Determining responsibility for such outcomes—technology providers, clinicians, or institutions—is still a central legal and ethical question. Integration into existing healthcare workflows is a further

significant issue. Implementing immersive technologies requires planning to ensure interoperability with existing systems, including electronic health records, imaging systems, and hospital IT infrastructure. Furthermore, staff must become proficient in using immersive tools without disrupting patient care or blocking workflow. Clinician or administrative pushback can further delay adoption, so stakeholder engagement and organizational acceptance are essential (Hine et al. 2024).

Maintenance and tech support are operational limitations that must also be considered. VR, AR, and MR devices require occasional calibration, software updates, and debugging to deliver optimal performance. Institutions will possibly need to hire specialized technical personnel to manage such equipment, adding to operational costs. Rapid technological changes can also render current devices obsolete, necessitating repeated hardware updates to remain current with latest software and programs. Variability in clinical evidence and standardization is another limitation. While many studies have reported encouraging findings, there has been a lack of large-scale, multicenter trials that validate the efficacy of immersive technologies among heterogeneous patient populations. There are few standardized protocols for VR, AR, and MR interventions, and it is difficult to compare results, establish best practices, or implement uniform training programs across institutions. Variability can hinder broad acceptance and adoption into standard care (Ursin et al. 2024).

Finally, accessibility and equity are also excellent issues of concern. Immersive technologies risk disproportionately benefiting better-resourced hospitals and patients and exacerbating healthcare inequalities. Ensuring that VR, AR, and MR systems are accessible, affordable, and adaptable across different clinical environments will be essential to equitable uptake. Addressing these limitations in an integrated way—via technological innovation, regulatory policies, training programs, and ethics—will be critical to realizing the full potential of immersive healthcare technologies. Table 12 presents the most appropriate challenges faced in the adoption of VR, AR, and MR in healthcare, categorized by use-specific technical, human, regulatory, ethical, and implementation factors. It illustrates the specific issues under each category, the impact on adoption, and the potential implications for healthcare systems (Acheampong et al. 2025; Ali et al. 2023; Karwowski et al. 2025).

Table 12. Challenges Affecting the Adoption of Immersive Technologies in Healthcare

Challenge Category	Specific Issues	Impact on Adoption	Potential Consequences
Technical	High hardware cost, low portability, motion sickness, latency, low resolution	Limits accessibility, reduces usability, affects user comfort	
Human Factors	Learning curve, user ergonomics, accessibility for disabled patients	Hinders engagement, slows adoption, increases training requirements	
Maintenance	Frequent calibration, software updates, hardware obsolescence	Increases operational costs, requires specialized staff	
Regulatory & Ethics	Data privacy, patient consent, liability		Risk of legal issues, breaches of patient confidentiality
Clinical Safety	Validation, procedural errors		Adverse patient outcomes, decreased trust in technology
Implementation	Integration into workflows, resistance to change	Workflow disruption, underutilization of immersive systems	
Standardization	Lack of protocols, variable evidence		Inconsistent outcomes, difficulty in benchmarking best practices

❖ Research and Emerging Innovations

Immersive healthcare technologies continue to evolve at breakneck speeds, driven by advances in artificial intelligence (AI), wearable sensors, multimodal feedback, and cloud computing. In addition to their well-recognized uses in training, rehabilitation, and surgery, continuing research seeks to create adaptive, personalized, and highly interactive environments that adjust dynamically in real time as a function of clinician or patient input. This sub-section addresses some of the emerging trends and developments and their possible contribution to healthcare delivery (Parvin et al. 2025; Wang et al. 2023; Junaid et al. 2022).

- **AI-Based Adaptive VR/AR**

Immersive technologies are being made adaptive and personalized by artificial intelligence. In VR and AR applications, AI algorithms track user performance, detect errors, and alter simulation scenario parameters adaptively. Surgical simulation training, for instance, may adjust difficulty as a function of trainee skill level, offering progressively harder cases with increased expertise. Similarly, in rehabilitation, AI-facilitated VR systems can monitor quality of movement, detect compensatory patterns, and provide real-time corrective feedback. These adaptive processes maximize learning effectiveness, improve patient outcomes, and reduce the necessity for continuous human observation (Thavasimuthu et al. 2024; Akhtar and Rawol, 2025).

New findings demonstrate the ability of AI-supported immersive systems. For example, machine learning software and VR surgical simulators can predict performance metrics and suggest tailored practice time, conserving overall training time with promises of high competence. Rehabilitation patients are permitted real-time movement and physiological recordings, which are interpreted by AI software, allowing therapists to customize exercises for specific patient abilities, accelerating recovery and enhancing participation. Table 13 merges the top examples of adaptable VR/AR applications with AI in medicine with their functions and documented benefits (Das et al. 2025; Gandi et al. 2025; Uttekar et al. 2025; Uttekar et al. 2025).

Table 13: Adaptive VR/AR applications for health with AI

Technology	Application	AI Function	Outcome
VR Surgical Simulation	Laparoscopic surgery training	Adaptive difficulty, error detection	Improved skill acquisition, faster learning
VR Rehabilitation	Stroke therapy	Real-time motion monitoring, corrective feedback	Enhanced motor recovery, increased engagement
AR-Assisted Procedures	Image-guided surgery	Predictive guidance and alerts	Reduced intraoperative errors, improved accuracy

- **Wearables and Biofeedback Integration**

Wearable devices and biofeedback sensors increasingly get intertwined with immersive technologies for more personalized and real-time feedback. Heart rate monitors, accelerometers, gyroscopes, electromyography (EMG), and EEG sensors provide physiological and neurological state information for adaptive adjustment of VR, AR, or MR environments. For example, for pain relief, intensity or visual stimulus in VR environments can be changed based on heart rate variability or stress. Similarly, rehabilitation exercises may adjust resistance or number of repetitions as a function of muscle activation or movement quality obtained from wearable sensors (Reddy, 2025; Diotaiuti et al. 2025).

EEG integration with VR provides feedback on cognitive load, attention, and levels of engagement. This allows systems to modify visual and audio feedback in real-time, optimizing learning and therapeutic effectiveness. Biofeedback-augmented VR is most promising in neurorehabilitation, mental health therapy, and anxiety control due to its ability to provide measurable physiological responses and increase patient awareness of body states (Di Palma et al. 2025; Molteni et al. 2024). Examples of wearable and biofeedback integrations in immersive healthcare applications are summarized in Table 14.

Table 14: Wearable and fusion of biofeedback in immersive healthcare applications

Technology	Sensor Type	Application	Observed Benefit
VR Rehabilitation	EMG, accelerometers	Stroke and motor recovery	Optimized movement, personalized therapy
VR Pain Management	Heart rate, GSR	Burn and chronic pain	Reduced perceived pain, enhanced patient engagement
EEG-VR Training	EEG	Cognitive rehabilitation	Monitored attention, adaptive feedback improves learning

- **Multimodal Immersive Environments**

Multimodal immersive environments are also being investigated in advanced research, where VR, AR, or MR is augmented with other senses like auditory, tactile, olfactory, or even thermal feedback. These systems are designed for delivering higher realism, immersion, and presence to facilitate enhanced learning and therapy.

Multimodal VR for surgical training can offer visual feedback, haptic tissue manipulation feedback, and auditory warning for procedure defects for skill transfer to actual surgery. Multimodal VR with a combination of visual VR tasks and vibration feedback or touch cues enhances enhanced motor learning and patient motivation in rehabilitation (Norwood et al. 2023; Parisi et al. 2022).

Multisensory integration is also advantageous in cognitive and psychological therapy. Exposure therapy for anxiety or PTSD in VR, for instance, could be augmented with concurrent soundscapes or smells to provide an enriched, more realistic environment, which allows for quicker desensitization and enhanced clinical benefit. These multimodal systems are still mostly in the experimental phase but hold enormous potential for clinical benefit and patient acceptability (Chenais and Görgen, 2024; Reddy, 2025).

- **Cloud-Based and Collaborative VR/AR/MR**

Cloud computing is making remote, multi-user virtual reality and augmented reality experiences accessible, enabling clinicians, educators, and patients to collaborate. Cloud VR and AR environments permit high-fidelity simulations to be streamed onto many devices without the necessity for costly local hardware (Papagiannakis and Kannape, 2024; Palvadi et al. 2025). MR environments can integrate patient data and enable remote experts to collaborate with 3D anatomy models, label procedures, and instruct local physicians in real-time. This capability is particularly valuable to telemedicine, worldwide surgical education, and multi-center clinical trials. Shared immersive environments allow more communication and standardization, making it possible for remote teams to share joint planning or training protocols. Cloud platforms also support deployability at scale, making high-quality immersive experiences accessible to more institutions and patients (Lewis et al. 2024; Wang et al. 2025).

- **Challenges and Considerations in Emerging Research**

With all their potential, these innovations have their challenges. AI systems need to operate with large, high-quality databases, which cause privacy and regulatory issues. Biofeed devices and wearable sensors need robust calibration and user compliance (Vimal et al. 2024; Ghadi et al. 2025; Putra et al. 2024). Multimodal interfaces have the

potential to cause greater cognitive load or sensory overload for some users. Last but not least, cloud integration requires stable connectivity and secure data handling to avoid breach or service downtime (Elfouly et al. 2025; Radanliev et al. 2025; O'Hara et al. 2025).

- **Summary of Emerging Research Trends**

New emerging innovations are aimed at increasing adaptivity, personalization, multisensory interaction, and scalability in immersive healthcare. AI-powered VR/AR provides real-time performance-based adaptation, wearable sensors ensure constant physiological feedback, and multimodal systems increase user engagement (Bibri and Jagatheesaperumal, 2023; MK et al. 2024; Chaudhary et al. 2025; Thangaraja et al. 2024; Ramolia et al. 2025). Cloud-enabled collaborative platforms bring things near and far near, bringing immersive interventions within reach for a wide population (Tables 15 & 16).

Table 15: Summary of Key Emerging Research Directions in Immersive Healthcare

Research Direction	Example Technology	Key Innovation	Expected Impact
AI-Driven Adaptive VR/AR	VR surgical simulation	Adaptive difficulty, predictive feedback	Personalized training, improved skill retention
Wearable & Biofeedback	EMG, heart rate, EEG	Real-time monitoring and adaptation	Personalized rehabilitation, optimized therapy
Multimodal Immersion	VR + haptics + sound	Multisensory integration	Enhanced engagement, realism, and learning
Cloud-Based Collaboration	Cloud VR/AR/MR	Remote multi-user access	Scalable, collaborative training and telemedicine

Table 16: Applications and Benefits of Emerging Immersive Technologies in Healthcare

Application Area	Technology	Benefit
Surgical Training	AI + VR + Haptics	Improved accuracy, reduced errors
Rehabilitation	VR + Biofeedback + Sensors	Faster recovery, personalized therapy
Mental Health	Multimodal VR	Greater immersion, reduced anxiety

Telemedicine	Cloud MR	Remote consultation, global collaboration

Emerging research on immersive healthcare is concentrated on issues of adaptability, multisensory engagement, remote collaboration, and adaptability. Refined use of AI-driven adaptive VR or AR technology, biofeedback into wearable technology, multisensory engagement by immersive technology, or use of cloud platforms ensures improvement in overall clinical experiences. Emerging research enables next-generation healthcare with an enhanced level of effectiveness, scalability, and focus on patients (Vermesan et al. 2022; Hossain et al. 2025; Damaševičius et al. 2023; Petković et al. 2025).

Summary

This chapter has given an overall introduction and insight into the immersive technologies of Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR), which have a revolutionary effect on the field of healthcare. Right from the conceptual stages of VR, AR, or MR in the 1960s, involving experiments on theoretical models, this technology has modernized itself into sophisticated tools that not only aid medical practices, medical training, or rehabilitation, or help patients interactively, but make it an indispensable tool in the realm of medical practice. The landmarks achieved in this aspect of technological advancement would showcase an overall improvement in the application of immersive technologies.

The chapter analyzed the scientific bases of immersive technologies, focusing on both the hardware side of immersive technologies, including head-mounted displays, motion sensors, and haptic devices, and the software side of immersive technologies. The chapter covered how immersive spaces interact with human perceptions, cognition, and motor functions. For instance, it covered immersion, presence, and engagement. Processes like immersion, presence, and engagement explain how VR, AR, and MR increase learning, speed training, or increase therapeutic outcomes. The use of tables on hardware and software, as well as the cognitive-physiological effect, helped in clarifying the concepts. Various existing uses of immersive technologies were analyzed in multiple areas of application, such as medical training, surgical assistance, rehabilitation, pain management, and mental health treatment. Evidence from research studies has established the effectiveness of VR simulation in reducing procedural error, AR-assisted surgery in improving intra-operative accuracy, and MR

in preventing isolation during global collaboration. The use of immersive technologies in rehabilitation has been found effective in motor recovery, while VR simulation in mental health shows positive effects on reducing anxiety levels. Case studies and tables demonstrated the effectiveness of immersive technologies in the real world.

Trends and perspectives on the future of VR in the medical field were also considered. The incorporation of artificial intelligence, cloud computing, biofeedback tools, haptics, and data-driven personalized approaches is anticipated to enhance the flexibility, functionality, and availability of VR medical platforms. The advances will help offer adaptable training tools, scalable telemedicine platforms, personalized rehabilitation tools, and precision medical care services. The tables outlining the perspectives on the future of VR provided a conceptual framework upon which an understanding of the anticipated progress of this technology can be based. Immersive technologies, including VR, AR, and MR, come across as an ever-adapting field of immense importance to modern healthcare. They fill the existing gap found in modern healthcare training by linking theoretical knowledge with practical skills in an extremely safe, efficient, and appealing setting. Through an encompassing insight into the existing literature, the latest developments in this field of modern healthcare, and the ever-emerging developments, this chapter provides a fundamental base of understanding of the current influence of immersive technologies on modern healthcare.

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CHAPTER FOUR

Conceptual Parallel Between Quranic Ecological Principles and Soil Toxicology in Terrestrial Ecosystem

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Abstract

The Holy Quran, the sacred Muslim religious book, is also a sum of principles and teachings covering all aspects of human life. About 750 verses (of 6236) refer to various aspects of nature, and to the relationship between man and nature. The aim of this paper is to briefly analyse some of the many ecological verses. The article highlights the eco-educational dimension of the Holy Quran by means of a qualitative investigation. It addresses the ecological considerations on the rational use of natural resources, ethical interactions between man and nature, and the rights of plants, animals and of the physical elements of the environment. It examines how Quranic teachings advocate for environmental stewardship, balance, and the prevention of harm, aligning with modern scientific understandings of soil health and contamination. By analyzing key Quranic verses related to natural resource management, pollution, and sustainability, the article highlights their relevance to addressing soil toxicity challenges such as heavy metal accumulation, chemical pollutants, and their impacts on terrestrial biodiversity and ecosystem functions. This interdisciplinary approach underscores the integration of spiritual ethics and scientific knowledge to promote sustainable soil management practices and ecological preservation. The review aims to foster a holistic perspective that bridges qur'anic environmental ethics with soil toxicology to inform future research and policy development in terrestrial ecosystem conservation.

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Graphic Abstract

Keywords: The Holy Quran, Environmental education, Teachings, Environmental protection, Sustainability

Introduction

For many centuries' mankind has been unable to study certain information found in the Quran, as the scientific means available did not allow it. It was only in the twentieth century that people understood that many of the verses in the Quran were describing natural phenomena (Ansari, 2001). Even today, without using specialized research, scientists have a hard time understanding the information available in the Quran. In order to understand some of the verses in the Quran, a scientist must hold encyclopaedical knowledge of many scientific disciplines. However, we have to keep in mind that this holy book remains first and foremost a religious book and we should not expect any actual scientific purpose or result from it. The fact that the verses of the Quran offer references to scientific knowledge which was (re)discovered and (re)affirmed 1200-1300 years later is a gift of this holy book (Iqbal, 2018). One can identify in the Holy Quran numerous rules intended to protect nature and the environment. Approximately 750 verses of the Holy Quran refer to various aspects of nature, the relationship between man and nature, vegetal and animal organisms and their environment. In this holy book, there are advisements on reflecting over nature, on studying the links between organisms and their environment, on using our reason constructively in order to maintain the balance and proportions of nature (Arauf, 2021). One of the first teachings that the Quran brought to the Muslim people referred to the fact that this universe, with the Earth and the sky, where man lives, does not randomly exist, without any guidance or by the will of one single entity (Elsheikh et al., 2024; Irfanullah et al., 2022; Khalid, 2002; Maaref & Rezaei, 2023). "And if the Truth had followed their desires, verily the heavens and the earth and whosoever is therein had been corrupted. We have brought them their Reminder, but from their Reminder they now turn away." (Surah Al-Mu'minun, Verse 71) Still, the universe is organized by general laws which cannot be changed (Bhat, 2023; Manoiu et al., 2016). The environment is not our property and the human beings have the responsibility to take care of it and preserve it for all future generations (Emina, 2021).

The responsibility of man is not confined to one single generation, with everything having to be passed on in good condition from one generation to another. This sustainable approach has been supported in the Holy Quran approximately 1300 years before the best known and cited definition of sustainable development, presented in the Brundtland report (1987) of the World Commission on Environment and Development ("Sustainable development is aimed at the needs of the present,

without compromising the ability of future generations to address theirs"): (Visser, 2017). "Who hath appointed the earth a resting-place for you, and the sky a canopy; and caused water to pour down from the sky, thereby producing fruits as food for you. And do not set up rivals to Allah when you know (better)." (Surah Al-Baqarah, Verse 22).

The objective of this paper is to highlight the role of the Holy Quran in environmental education, briefly noting and analyzing some of the many verses on ecology and selecting the ones which educate people on the importance of the environment and on the importance of taking responsibility to preserve it for future generations. The article stresses the eco-educational dimension of the Holy Quran by investigating the qualitative content of its verses. We can conclude that there is a pattern of environmental ethics based on the right to respect all of nature's elements, living or non-living.

Materials and Methods

The present study is a qualitative and descriptive-analytic investigation of the Holy Quran. It addresses the ecological considerations on the rational use of natural resources, ethical interactions between man and nature, as well as the rights of plants, animals and all other non-living elements of the environment. Moreover, the study analyses (what we referred to as) "the green verses", in order to highlight the ecological caliber of the Holy Quran, in today's environmentally-troubling context. The Holy Quran transcends space, time and events, proving through every verse its quality as an all-around guidance pillar, including for nature lovers and environment defenders.

Results and Discussions

The teachings of the Holy Quran support moderation of the human behavior in order to avoid excesses. This moderation can be described through three principles found throughout its pages: the principles of unity, balance and responsibility.

❖ The Principle of Unity

The Holy Quran shows that nature is a whole, a complete and complex system the components of which support and protect each other. If one of the components is affected, it disturbs the order and normal function of the entire system of nature In this respect, the Holy Quran has encouraged a holistic approach on the environment approximately 1300 years before the emergence of the academic term of holism that has been defined by Smuts (Abood; Mănoiu et al., 2016; Qureshi et al., 2024; Rehman, 2025). Surah Al-Baqarah verse 164 encourages reflection on the natural world as evidence of Allah's power and oneness. It highlights signs in the creation of the heavens and earth, the cycle of night and day, ships sailing the seas, rain bringing life to the earth, the diversity of life, and the movement of winds and clouds. These are presented as clear signs for those who use their reason. The Quran encourages the protection of all the natural elements of the environment (Qureshi et al., 2024).

The Holy Quran specifies that people are not superior to any other species: "There is not an animal in the earth, nor a flying creature flying on two wings, but they are peoples like unto you. We have neglected nothing in the Book. Then unto their Lord they will be gathered." Surah Al-An'am Verse 38. The Holy Quran mentions that there is a close relationship between the behavior of people and the state of the environment (Khalid, 2002). The Quran sends out a clear message to take good care of the environment and protect it, as humankind is not its owner! Moreover, the Quran prohibits cruelty to animals and birds. It is man's responsibility to ensure the wellbeing of all creation (Faisal & Hashmi, 2025). In other words, the attitude of Islam towards the environment and natural resources is a constructive one, based on protection and development, dismissing all abuse and destruction (Sabrina, 2020). These issues are highlighted in the 11th Surah, which refers to maintaining and restoring the lands through agriculture, cultivation and construction: "...O my people! Worship Allah, you have no god but Him. It is He Who created you from the Earth and made it a dwelling place for you." Surah Hud, Verse 61. Therefore, the right to use natural resources implies humankind's commitment to preserve life and the natural resources in a manner which will ensure that the next generations will also enjoy their benefits, appreciate their beauty and use them to build their homes all of which will have to be done in a moderate and considerate way (Al-Damkhi, 2008). Environmental protection and nature conservation represent the philosophy of the

Islamic environmentalism of nature, man has the duty to take care of environmental sustainability and to oppose waste (Ragozina, 2023).

- **Water**

It is the basis of life itself. It is the miraculous liquid that sustains life: "Have not those who disbelieve known that the heavens and the earth were of one piece, then We parted them, and we made every living thing of water? Will they not then believe?" (Surah Al-Anbiya Verse 30) Several verses in the Holy Quran refer to the water cycle and its fundamental role in sustaining life on Earth (Dahri, 2025). "You (O Muhammad) see the earth looking dead and dry, but when rain falls, it becomes fertile, swells with life, and produces beautiful plants, proving Allah's power over life and death." (Surah Al-Hajj Verse 5) Aside from its role in supporting life, for Islam (as well as for all the other religions across the globe), water has a socio-religious function, purifying the body and clothes (Hirsch, 2024; Royyani & Syukur, 2013).

The water circuit is well known today. The verses of the Holy Quran related to the water circuit express ideas which are utterly obvious in today's world, but we need to keep in mind the reality of the time when the revelation and writing of the Holy Quran occurred, a time when the only known practice was land irrigation. "Do you not see that Allah sends down rain from the sky channeling it through streams in the earth then produces with it crops of various colors, then they dry up and you see them wither, and then He reduces them to chaff?" (Surah Az-Zumar Verse 21). If someone were to compare the notions of modern hydrology and the information available in the Quran on the matter, the consensus between them would be undeniable (Ghazali & Sabjan, 2024). All living beings are made of water. The body of the average adult person is made up of 70% water. The Islamic teachings describe the sacred qualities of water: life-giving, life-sustaining and purifying (DeLong-Bas, 2024).

- **Air**

Air is just as important as water. Most of the living beings on Earth depend on the air they breathe to survive. Given all the functions fulfilled by the atmosphere, it is obvious that keeping it balanced, pure and unpolluted is essential for preserving life (Singh et al.). A serious issue arising from air pollution is represented by acid rain, which kills lakes and rivers, destroys the soil and threatens human, plant and animal

life. The main pollutants that contribute to acid rain are sulphur dioxide and nitrogen dioxide (Dutta & Singh, 2021). The following verse of the Holy Quran refers to this particular aspect of pollution acid rain "Is it you who shed it from the raincloud, or are We the Shedder? If We willed We verily could make it bitter. "Why then, give you not thanks? (Surah Al-Waqi'ah Verses 68-70)

- **Earth**

Fertile ground is the foundation for crops, which represent some of the food supply for man and other beings (Lal, 2009). "Allah's power in bringing forth sustenance like crops, olives, dates, grapes, and fruits, emphasizing that these natural provisions are signs (Ayat) for people who reflect and understand His blessings, revealing His unity and ability to create. It serves as a reminder that these worldly gifts aren't ends in themselves but pointers to the Creator, urging contemplation and gratitude for the sustenance provided by water and the earth" (Surah An-Nahl Verse 11). Reducing the soil productivity, exposing it to erosion, as well as uncontrolled exploitation are all actions taken against the general natural balance and they are forbidden by Islam (Hayat et al., 2023; Llewellyn, 2003). Not only does Prophet Muhammad encourage the sustainable use of fertile lands, but He also talks about the benefits of transforming unused lands into productive ones (Hayati & Mashdurohatun, 2024). "That We may give life thereby to a dead land, and We give many beasts and men that We have created to drink thereof." (Surah Al-Furqan Verse 49).

- **Plants**

Plants are sources of food, sources of oxygen, soil-enrichment forms, they protect lands from soil erosion with their roots, they absorb and retain water, they are the starting point for medicine, perfume, hygienic items, fuel, etc. (Chauhan et al., 2021; Zafar et al., 2025). Plants are of different species, kinds and colors, traits which have been mentioned more than 1000 years before the notion of "species" was first introduced in Historia plantarum (Allaby, 2012; Haider, 2018). All Muslims must bring their contribution to enlarging green areas. Taking care of the environment is not only an obligation for Muslims, but also an important form of pay-back (Ibrahim, 2023; Manoiu et al., 2016). The Prophet Muhammad said, "If a Muslim plant a tree or sows seeds, and then a bird, or a person or an animal eats from it, it is regarded as a charitable gift (sadaqah) for him (Kareem, 2017; Mushtaq & Rafeh, 2024). On a global

level, in the time of Prophet Muhammad, botany was not advanced enough for scientists to know that plants have both female and male reproductive organs (Akhter et al., 2022). Still, the 20th surah mentions the following: "Who hath appointed the earth as a bed and hath threaded roads for you there in and hath sent down water from the sky and thereby We have brought forth diver's kinds of vegetation." (Surah Taha, verse 53). Nowadays we know that the fruit comes from plants with reproductive organs.

The importance of environmental balance

The environment in which we live is a chain of links that influence each other in such a way that any imbalance felt by one of them will bring a negative influence on all others. This was recently proven by environmental sciences (the concept of ecological balance is relatively new, introduced in the late 20th century (Arauf, 2021). he billions of galaxies in the universe, the billions of creatures on Earth, everything that has ever been created, from the smallest particle of the atom and up to the biggest of galaxies, they are all part of a perfectly-created system where all the elements find themselves interdependent, influencing each other in a positive or negative way. Each being has its predestined function, which must remain undamaged and respected (Balzani, 2020). "We created not the heaven and the earth and all that is between them in play.

" (Surah Al-Anbiya Verse 16) And if other beings have been tamed to serve mankind, the Quran brings certain conditions to these actions.

Conclusion

The Holy Quran mentions that man must not change anything in this natural order. All the damages brought upon the environment have been caused by man. The environmental and ecological disasters, as well as human intervention have been vividly recounted in the Holy Quran. When the concept of environment is assessed on the axis of the Holy Quran, it becomes apparent that the Holy Book has produced significant and permanent solutions for a wide range of environmental problems, i.e. it has put forth principles contributing to environmental protection. The environmental teachings are obvious in the verses of the Holy Quran. In order to ensure a healthy environment, these teachings must be respected and put into practice on every level. As a conclusion, we can say that the Prophet Muhammad could be considered a pioneer of environmentalism, preservation, sustainable development and resource management.

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CHAPTER FIVE

Logistics within the Circular Economy: A Systematic Literature Review

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Abstract

A fresh wave of research now looks closely at how logistics supports smarter use of resources, driven by rising interest in circular economic models. Rather than following the old pattern of extracting, using, then discarding materials, these new systems prioritize bringing products back into use through repair or reprocessing. Instead of focusing only on delivering goods, logistical operations must now handle returns with equal care. Because of this, networks need greater flexibility - linking collection, refurbishment, and redistribution in smoother sequences. Beginning with a structured look at published work shows how return flows form the core idea behind circular supply networks. What stands out repeatedly is the role of gathering mechanisms, classification steps, followed by reallocation paths when aiming to stretch how long items remain useful. Success tends to depend on smooth interaction between makers, stores, outside partners along with buyers, especially when preserving worth over several usage rounds. Tools like digital monitoring and information processing pop up often in discussions as aids that boost transparency while improving forecast reliability. Despite what some studies highlight about ongoing operational hurdles, strategic barriers remain a concern. Starting with high setup expenses, unpredictable paybacks add complexity - on top of shifting policy landscapes. Then again, internal pushback within companies, paired with weak customer engagement, risks slowing wide adoption. Still, real-world data shows businesses using circular logistics often see ecological improvements alongside lasting financial upsides. Resource efficiency climbs while reliance on raw inputs drops over time. Logistics, when viewed through current studies, emerges not just as a function but as a catalyst in shifting toward circular models - its role shaped by shared efforts across industries. Collaboration between sectors matters more now, given how deeply intertwined supply systems are. Policy frameworks must adapt in parallel, pulling in the same direction if broader environmental goals are to be met. Change at scale hinges on these connections aligning over time.

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Keywords: Circular economy, Reverse logistics, Sustainable supply chains

Introduction

Starting fresh often means rethinking how things move through systems. Moving away from simply using and tossing items, more attention now lands on keeping materials useful longer. Instead of ending up discarded, stuff should loop back into use somehow. Keeping value alive inside goods changes how companies build and sell them. Such shifts ask for new ways to handle making, moving, and getting back products. Behind these moves, one key player stands out - how goods travel across stages shapes everything else. Logistics quietly holds together this updated way of doing business (Esposito et al., 2017).

Usually, logistics centers on cutting costs, boosting speed, leaving service quality steady - forward movement only. Yet circular setups require flows going backward too: things come back, get used again, taken apart, turned into something new, sent elsewhere. Loops like this push logistics past delivery and storage duties into handling full cycles instead. So now, its role grows - it becomes central to making circular models work well, shaping both profit outcomes and ecological impact alike (Sarkis et al., 2025).

Not long ago, scholars began focusing more on how logistics connects with the circular economy. Work has looked into return systems, supply loops, infrastructure layout, tools for monitoring goods digitally, besides ways to measure environmental impact. Even with increasing output, findings stay scattered among fields - each using different ideas or methods. To bring clarity, a clear overview becomes essential: pulling together current insights while highlighting central trends along with gaps still needing exploration (Rao & Melangadi, 2024).

This section works through past studies on logistics tied to circular economy ideas. It looks first at how logistics helps build value in circular models, using examples drawn from real cases. Following this, themes in current work get grouped into categories, showing patterns across publications. One idea leads to another, revealing what

topics have received attention - and where silence remains. Insights blend together: some come from supply chains, others from sustainable practices or operational analysis. Together they form a clearer picture - logistics not just moving goods, but shaping long-term system change (Seroka-Stolka, & Ociepa-Kubicka, 2019).

Following this introduction, the chapter moves into foundational ideas connecting circular economy concepts to logistics and reverse supply networks. Next comes an explanation of how the literature was reviewed. A detailed breakdown of key themes appears afterward. Research shortcomings that have started to appear are then examined. To close, suggestions for upcoming studies are offered (Pereira & Moreira, 2025).

Conceptual Background

Starting differently each time, here goes: A break from today's take-make-waste pattern comes through the idea of a circular economy. It swaps constant new intake for smarter use, aiming to cut down on trash and harm to nature. Built on doing more with less, stretching product lifespans, and getting value back at the end, it pushes actions like using items again, fixing them, rebuilding parts, or turning old materials into new ones. Instead of discarding what's finished, this approach treats used goods as resources waiting reuse. Success depends on smooth movement of materials, clear data sharing, and teamwork across groups - an arrangement where managing flows becomes central to how everything holds together (Ilyas et al., 2025).

Nowadays, moving items from one place to another isn't just about speed or low prices. Instead of focusing only on cutting costs, companies face tangled routes where materials travel many ways - not simply straight lines. Once something is used, it does not disappear; rather, someone needs to gather it back, check its condition, group similar pieces together, send them off again by truck or rail, then weave usable parts back into new offerings. Because of these loops, what once seemed like background work - shipping and tracking - now stands at the center of whether such recycling-based systems can actually operate. Logistics shifts quietly but firmly toward becoming a core part of strategy (Sadreev, 2004).

A key link connecting logistics and the circular economy shows up in how goods move backward through supply chains. Instead of following the usual path - from

manufacturers to buyers - this process pulls items from users toward reuse centers. When set up well, such flows help companies recover worth from used materials, lower trash output, decrease reliance on disposal sites, while using resources more wisely. Yet challenges like unpredictable arrival times, unknown states of returned goods, and fluctuating pickup expenses add layers of difficulty absent in standard delivery setups (Kazmi et al., 2025).

What began as separate flows now merges through closed-loop supply chains, deepening ties between logistics and circular models. Forward movement meets return paths within one connected framework, enabling used resources to flow back into manufacturing stages. This blend relies on precise planning across networks, sharper predictions about reused material needs, along with aligned stock handling. Seen differently, these systems reveal a shift - logistics evolving from straight-line transfer toward preserving worth through looping cycles (Orji & Ojadi, 2022).

Nowhere is change more evident than in how digital tools redefine links between logistics and circular economies. Tracking products becomes easier when networks of connected sensors share live data, while distributed ledgers ensure records stay secure. Visibility into returns improves because systems map movements clearly across stages. Accurate estimates about product lifespans emerge through pattern detection in large datasets. Information gaps shrink where once they blocked cooperation. Coordination strengthens among actors - factories, transport firms, reprocessors, buyers - because shared insights build trust. Over time, these functions shift from optional add-ons to central pillars. What was once seen as support infrastructure now drives transformation (Jarboui et al., 2026).

Even with progress, deep-rooted issues remain. Transport expenses stay high because collection sites are spread far apart - this complicates logistics. Rules differ across regions, making compliance uneven and difficult to scale. Without uniform methods for reclaiming materials, profitability shrinks unexpectedly. Companies also find it hard to align green goals with smooth operations - one goal pulls toward ideals, the other toward practicality. The gap between what is promised and what can be done keeps widening (Watanabe et al., 2018).

A shift in perspective reveals logistics not just as a tool but also as a limiting factor inside circular economic framework. Because thoughtfully structured networks help

recover worth and keep materials moving, weak structural foundations often block expansion of reuse-based approaches. Seeing this two-sided impact becomes key when aiming to grasp how such systems truly operate on the ground. Looking at logistics within the circular economy reveals key ways material cycles work in practice. This base idea helps sort out how theory connects to real systems, while setting up a clear path through past research. What follows builds directly on that link (Bozhanova et al., 2022; Santhosh Kumar et al., 2024).

Methodology

This section takes a methodical look through existing writings to clearly map scholarly work linking logistics with the circular economy. By following recognized procedures often seen in supply chain and sustainability fields, it pulls together key findings in an organized way. Instead of relying on random choices, the analysis uses clear steps that help avoid favoring certain sources. One strength here lies in how consistently each study gets assessed before being included. Transparency throughout supports others later checking or building on what was done (Tranfield et al., 2003).

❖ Search Methods and Data Sources

To locate relevant studies, key scholarly databases - Scopus, Web of Science, and ScienceDirect - were used because they cover influential journals in logistics, operations management, and environmental research (Mongeon & Paul-Hus, 2015). Peer-reviewed articles formed the core of the search, supporting consistency in quality and theoretical grounding (Tranfield et al., 2003b).

Several terms together helped reflect the broad scope of research (Budgen & Brereton, 2006; Snyder, 2019). Primary queries featured:

- “circular economy” AND “logistics”
- “reverse logistics” AND “circular economy”
- “closed-loop supply chain” AND sustainability
- “circular supply chain”
- “remanufacturing logistics”
- “resource recovery” AND logistics

Using Boolean logic alongside tailored database settings helped narrow outcomes by excluding unrelated entries (Petticrew & Roberts, 2008).

❖ **Inclusion and Exclusion Criteria**

Before beginning the review, clear conditions for inclusion were set to keep analysis focused (Tranfield et al., 2003; Snyder, 2019).

- **Inclusion criteria**
  - **Peer-reviewed journal articles**

Research focusing directly on transport, distribution, or material flows under circular economic models. Examination of operational movements and resource handling tied to reuse systems. Work analyzing how goods return, cycle, or shift within sustainable frameworks. Papers looking at coordination of collection, sorting, or redistribution in closed loops. Analysis centered on movement networks supporting product life extension strategies. Research relying on observation often pairs with theoretical exploration, yet sometimes gives way to simulations designed to test ideas under controlled conditions (Geissdoerfer et al., 2017; Kirchherr et al., 2017). Articles published in English.

- **Exclusion criteria**

Papers presented at meetings, critiques of published books, besides short pieces by journal editors. Studies focusing solely on sustainability without a clear logistics dimension. Articles lacking methodological transparency. Duplicate records across databases. Focusing mainly on recent work, the review highlighted publications appearing since 2015, even though no fixed beginning date was set - this shift aligns with growing interest in circular economy topics (Petticrew & Roberts, 2006; Tranfield et al., 2003; Kitchenham, 2004; Snyder, 2019).

❖ **Screening and Selection Process**

Not every study made it through the initial gate. Right away, titles along with abstracts got checked - cutting out those off track (Tranfield et al., 2003; Kitchenham, 2004). Moving forward, deeper analysis took place by reading entire papers, making sure each matched the core aim (Petticrew & Roberts, 2006). Near the end, some extra

key pieces showed up when researchers looked back at citations inside top matches, tracing sources one by one (Wohlin, 2014). A set of clear filters shaped the final group of studies, capturing together the thinking behind circular logistics work (Snyder, 2019).

❖ Analytical Approach

Starting not from time order but from shared ideas, the chosen works underwent analysis through thematic synthesis (Braun & Clarke, 2006; Snyder, 2019). By grouping patterns across papers, this process allows similarities to emerge clearly. What stands out is how connections between different studies become visible when themes guide the review (Thomas & Harden, 2008).

The literature converged around three dominant themes (Govindan & Soleimani, 2017; Farooque et al., 2019):

- Reverse logistics and value recovery systems
- Closed-loop supply chain design and network optimization
- Digitalization and sustainability performance

A close look at every theme covered its grounding in theory, patterns in research methods, followed by what it means for practice (Tranfield et al., 2003; Snyder, 2019). Where ideas split off or stayed unexamined became clear, helping shape where studies might go next (Rowley & Slack, 2004).

❖ Methodological Limitations

Even though organized in approach, this analysis faces specific constraints (Geissdoerfer et al., 2017; Kirchherr et al., 2017; Farooque et al., 2019). By focusing only on English publications, relevant work from non-English regions might be missing. Because research on circular economies advances quickly, recent findings could shift or question the trends outlined in this study. Still, the method used offers a solid base for tracing major developments in the area (Genovese et al., 2017; Govindan & Soleimani, 2017).

This chapter takes a different path, aiming to show clearly how studies in logistics help push circular economies forward. By focusing closely on analysis, it builds an overall picture without losing depth Farooque et al., 2019; Centobelli et al., 2020). One way it does this is by linking real-world movement of goods to sustainable reuse patterns. Instead of broad claims, the method relies on specific examples that reveal deeper connections. Each part adds weight to the argument, yet stays rooted in practical insight. What results is not just theory, but grounded understanding shaped by logistical thinking (Bressanelli et al., 2018; Govindan et al., 2020).

Findings and Discussion

Looking closely at the chosen studies shows a clear rise in work linking logistics with the circular economy during the last ten years (Geissdoerfer et al., 2017; Kirchherr et al., 2017; Farooque et al., 2019). That increase comes because scholars and leaders now see logistics as essential for putting circular ideas into practice. Research tends to cluster in three areas: getting value from returned goods, building supply chains that loop back, then how digital tools keep materials flowing. One after another, these paths show logistics being seen less as just cutting costs but more as key to keeping resources in use longer (Genovese et al., 2017; Govindan & Soleimani, 2017).

❖ Reverse Logistics and Value Recovery

Backward movement of goods marks the longest-studied part of circular supply chains (Govindan & Soleimani, 2017; Agrawal et al., 2015). Return processes matter because they help keep products useful while lowering harm to natüre (Guide & Van Wassenhove, 2009; Genovese et al., 2017). Gathering items, checking their condition, separating them by type, fixing what's broken - these steps hold everything together. What happens after a product comes back shapes how well the system Works (Fleischmann et al., 1997).

Looking at real-world data, companies using organized systems to take back materials tend to save money while helping the environment by reusing resources and buying fewer new ones (Atasu et al., 2008; Souza, 2013). Still, one stumbling block shows up again: it is hard to predict how many items will come back, their state, or when they arrive. Because of this guessing game, setting up space and labor gets

tricky, sometimes making shipping and sorting more expensive than expected (Guide et al., 2003; Govindan et al., 2015).

Looking at it from management, how well returns work relies mostly on teams across the supply line staying in sync. Firms often rely on ties linking producers, outside shipping groups, and reprocessing sites - these links show up again and again as key (Huscroft et al., 2013; Govindan & Bouzon, 2018). Yet studies point out plenty of companies keep handling returned goods like an afterthought instead of building return paths into their main planning - a mindset that holds back true reuse potential (Guide & Van Wassenhove, 2009).

- **Closed Loop Supply Chain Design**

Another key idea focuses on reshaping supply networks to fit circular systems. Instead of separate paths, these setups blend delivery and return movements into one connected flow, so used materials can feed back into making new products (Guide & Van Wassenhove, 2009; Souza, 2013). Work here leans heavily on math-driven methods, usually using models that sort out where plants should go, how goods move, what storage levels work best (Fleischmann et al., 1997; Govindan et al., 2015). It turns out how networks are set up can make or break whether circular projects stay financially viable (Salema et al., 2007; Melo et al., 2009). Take scattered drop-off spots - they often boost material return rates, yet tend to raise transport expenses along with pollution levels. So, gains for nature might come at the cost of smoother operations (El-Sayed et al., 2010; Pishvaee et al., 2010).

Starting fresh each time, research shows closed-loop setups depend on thinking far ahead. Not like straight-line models built just to meet current orders, these loops need foresight into what comes back later and who might buy reused goods (Atasu et al., 2008; Guide et al., 2003). This shift puts logistics at the center of how companies stay strong over time. Planning moves become more than routine - they shape long-run success (Genovese et al., 2017).

Even with progress, models still don't line up well across studies. Some use fixed values to predict outcomes - yet actual recycling networks face constant unpredictability. Closing that mismatch could shape what comes next in the field (Govindan et al., 2016; Farooque et al., 2019).

❖ **Digitalization helps circular systems**

Tech keeps reshaping how goods move in recycling-focused systems. What jumps out from recent research is how networks of smart sensors, distributed ledgers, machine-driven insights, and deep data review sharpen the view on where items have been (Bressanelli et al., 2018; Centobelli et al., 2020). Clearer sight into journeys means better guesses about what happens next for materials. Seeing more helps teams act sooner when pulling parts back becomes possible. Misunderstandings between partners shrink once everyone draws from the same stream of facts (Rajput & Singh, 2019; Nobre & Tavares, 2020).

A single smart device might send updates on its wear and tear, so companies can decide if it gets reused, fixed, or broken down - all without reaching a recycling center (Queiroz & Wamba, 2019; Saberi et al., 2019). Information stored through decentralized ledgers tracks where materials come from, something tightly watched in sectors under strict rules about ethical supply chains (Bressanelli et al., 2018).

Still, talk around tech use reveals roadblocks too. Price tags on setup run high, systems often fail to connect smoothly, besides worries about who controls information tend to drag progress - especially in smaller firms. So even though going digital can reshape how things work, gains don't spread evenly between industries (Kouhizadeh et al., 2021; Centobelli et al., 2020; Nobre & Tavares, 2020; Warner & Wäger, 2019).

❖ **Shifting Pressures in Circular Supply Chains**

Far from just themes, the writings show how push and pull inside systems steer circular logistics forward. Yet gaps remain where rules bend under real world stress. Right off, companies struggle to line up green goals with profit demands. Even if recycling systems eventually save money, upfront costs - for equipment, tech upgrades, layout shifts - add heavy load early on. So during shift phases, it's unclear whether earnings will follow through (Abbey et al., 2015; Guide & Van Wassenhove, 2009).

Now think about rules - they matter, but not always the same way. Where green laws are clear and firm, new logistics ideas often grow faster. When regulations feel

uncertain or mixed, companies hesitate to spend on shifting to circular models (Bressanelli et al., 2018; Warner & Wäger, 2019).

Now think about what shoppers actually do. Their choices on sending things back, trying repaired items, or tossing old gear shape how steady returns move. Since people act differently each time, supply chains need room to shift when behaviors change. That uncertainty starts where buying ends (Centobelli et al., 2020).

❖ **Synthesis**

Logistics shows up as either fuel or friction when economies shift toward reuse and recycling. Strong networks keep materials valuable, cut trash, move resources smarter. When roads, planning, or tools fall short, progress slows down. Weak links break the loop before it gets going (Govindan & Hasanagic, 2018; Genovese et al., 2017; Farooque et al., 2019).

Fresh thinking in recent studies shows logistics gaining new weight. Instead of just backing up circular efforts, it now helps decide how big they can grow and how long they last. That change hints at what matters ahead: success might come less from simply using circular ideas, yet more from building systems strong enough to keep them going (Centobelli et al., 2020; Bressanelli et al., 2018).

A fresh look begins here - peering into missing pieces of current knowledge while sketching paths scholars might walk tomorrow. What comes next leans not on what we know, but where curiosity still lingers (Ghisellini et al., 2016; Kirchherr et al., 2018; Guide & Van Wassenhove, 2009).

Conclusion

Though more has been written about logistics in the circular economy, gaps still exist. One path forward lies in leaning less on theory. Instead of sticking to models and abstract talk, researchers might look at actual operations. Real-life testing brings insights that diagrams cannot match. Over months or years, observing live cases reveals patterns hard to predict. Different sectors handle loops differently - watching them unfold adds depth. Seeing how things change over time matters just as much as initial design.

One thing stands out: handling uncertainty might lead somewhere useful. Returns do not follow a set pattern - when they arrive, how many show up, or what shape they are in stays unclear, but plenty of studies pretend otherwise. Using chance-based tools along with real-world data may push new work closer to actual conditions. What matters is building models that reflect messiness instead of ignoring it.

One thing often overlooked? The human side of circular logistics. How people act shapes how well returns work - like whether they send items back or toss them out. Getting a grip on what drives those choices matters just as much as the trucks and warehouses. When we weave in findings about behavior, the whole system can adapt better to real-world messes. What feels natural to users might be the key to tougher, smarter networks.

Looking ahead, digital tools matter not just for what they can do. How firms prepare themselves could affect outcomes more than expected. Working together across companies may quietly influence results behind the scenes. The way data is managed might tilt the balance toward effectiveness. Success in circular efforts often ties back to these overlooked layers.

This chapter took a close look at how logistics connects with the circular economy, showing its shift from background task to key player in circular models. Reverse logistics stands out, along with smart supply loop setups, tied together through growing digital tools - each forming core parts of today's research landscape.

Still, shifting to circular systems isn't just about technology. It hinges on linked networks, steady planning over years, while balancing planet goals with profit needs. With circular approaches spreading, building flexible, connected supply chains may well define who stays ahead in lasting success.

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CHAPTER SIX

A review of the study of the effects of resveratrol as a secondary metabolite on cancer and it signaling pathways in inhibiting this disease

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Abstract

Resveratrol is a naturally occurring polyphenolic compound that has attracted considerable scientific interest due to its antioxidant, anti-inflammatory, and anticancer properties. This article aims to review and synthesize current preclinical and clinical evidence regarding the effects of resveratrol on cancer progression, as well as to evaluate its potential role as an adjuvant therapeutic agent in oncology. A growing body of evidence from in vitro, in vivo, and human studies suggests that resveratrol exhibits significant anticancer activity across a wide range of malignancies, including breast, colorectal, prostate, lung, liver, pancreatic, and oral cancers. Clinical and preclinical findings indicate that resveratrol can inhibit tumor growth and metastasis, enhance apoptosis, suppress cell proliferation, and increase the sensitivity of cancer cells to conventional chemotherapeutic agents. At the molecular level, resveratrol exerts its anticancer effects through the modulation of multiple critical signaling pathways involved in tumor initiation and progression. These pathways include PI3K/Akt/mTOR, STAT3, NF-κB, MAPK/ERK, Hedgehog, and Wnt/β-catenin signaling. In addition, resveratrol has been shown to regulate autophagy, induce cell cycle arrest, inhibit angiogenesis, and reduce inflammatory responses associated with tumor development. Emerging evidence further highlights its ability to target cancer stem cells and cancer-associated fibroblasts (CAFs), thereby disrupting the tumor microenvironment and limiting cancer progression and therapeutic resistance. Despite these promising findings, several challenges remain regarding the clinical translation of resveratrol, most notably its low oral bioavailability and rapid

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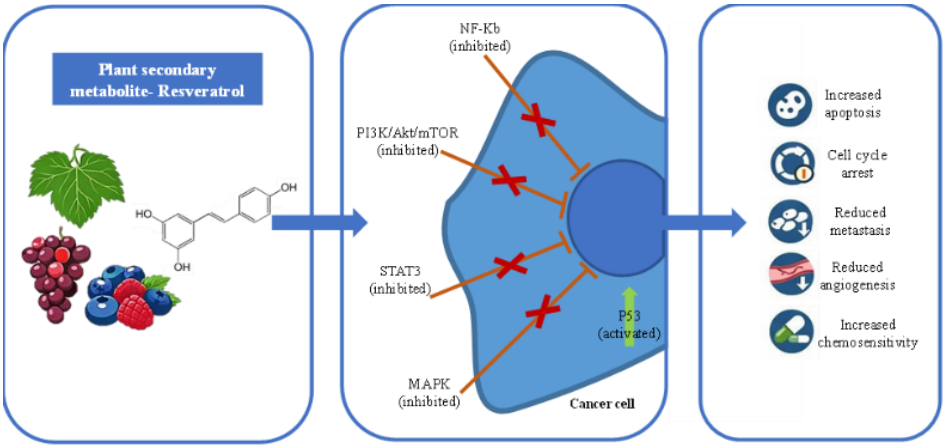
metabolism. Recent strategies, including high-dose administration and micronized or novel delivery formulations, have been explored to enhance its therapeutic efficacy. Overall, the available data support the considerable potential of resveratrol as a multifunctional anticancer compound. However, large-scale, randomized, and well-controlled clinical trials are still required to establish its optimal dosage, long-term safety, and definitive clinical efficacy in cancer therapy.

Graphic Abstract



Keywords: Antioxidant, Cancer, Resveratrol

Introduction

Secondary metabolites are organic compounds produced by plants or microorganisms, but do not directly play a role in the growth, development, or reproduction of the organism, and their absence does not usually cause premature cell death (Gao et al., 2022).

These metabolites are usually synthesized in response to environmental conditions or stresses such as pest attack, disease, or chemical stresses and play an important role in cellular defense and survival (Howells et al., 2011).

Structurally, secondary metabolites include large families such as phenols, alkaloids, terpenes, and steroids, which are the most important features of biotechnology, medicine, and food industries as drugs, bioherbicides, colorants, and flavors (Patel et al., 2010).

In general, the study and identification of secondary metabolites contributes to a better understanding of biological plants and the development of industrial applications (Howells et al., 2011).

Plant secondary metabolites are classified into three major groups: terpenes (isoprenoids), phenolic compounds (phenylpropanoids and flavonoids), and nitrogen-containing compounds (alkaloids, glucosinolates, and cyanogenic glycosides). Terpenes are biosynthesized through two different pathways, one of which is called the mevalonate pathway (MVA) in the cytoplasm and the other is called the methylerythritol 4-phosphate (MEP) pathway in the plastids. Based on the five-carbon isoprene unit, terpenes are divided into different groups. In the MVA pathway, compounds such as sesquiterpenes, triterpenes, etc. are synthesized, while the MEP pathway is responsible for the biosynthesis of monoterpene, diterpene, etc. compounds. The second important group of plant secondary metabolites belongs to aromatic phenolic compounds, which have a phenyl ring with one or more hydroxyl groups. In general, phenols are derived from two pathways: acetate/malonate and shikimic acid (shikimate), of which the shikimate pathway plays a very important role in the production of these metabolites in plants. In this pathway, precursors derived from the glycolysis and pentose phosphate pathways, such as phosphoenolpyruvate and erythrose-4-phosphate, are converted into various aromatic amino acids, the most abundant of which is the amino acid phenylalanine, which serves as an intermediate for the production of phenolic compounds. Important subclasses of phenolic compounds include flavonoids (anthocyanins, isoflavones, flavan-3-ols, flavanones, flavones, flavonols), hydroxybenzoic acid, hydroxycinnamic acid, coumarins, lignans, lignins, stilbenes, and xanthones. The third important group of secondary metabolites includes nitrogen-containing compounds such as alkaloids, glucosinolates, and cyanogenic glycosides. These compounds are collectively biosynthesized from aromatic and aliphatic amino acids. Based on the type of amino acid, alkaloids are classified into several subcategories, the most important of which are terpenoid indole alkaloid (TIA), benzylisoquinoline alkaloid (BIA), purine alkaloid (PA) and tropane alkaloid (TPA), which are produced from the amino acids

tryptophan, tyrosine, ornithine and asparaginate/glutamate, respectively (Chandrashekar et al., 2023).

Resveratrol is a natural polyphenolic compound found mainly in the skin of red grapes, berries, peanuts and some medicinal plants. It is synthesized as a phytoalexin in plants in response to biotic stresses such as fungal infections (Wang et al., 2022). In recent decades, resveratrol has received special attention due to its broad antioxidant, anti-inflammatory, anticancer and cardiovascular protective properties (Sheth et al., 2007). Studies have shown that this compound can reduce oxidative stress, delay cellular senescence and increase insulin sensitivity by regulating key molecular pathways including SIRT1, AMPK and NF-κB (Singh et al., 2015). Furthermore, research evidence suggests a potential role for resveratrol in the prevention and treatment of chronic diseases such as cancer, type 2 diabetes, Alzheimer's disease, and cardiovascular disease (Popat et al., 2013). As a result, resveratrol is recognized as a promising molecule in pharmaceutical and biomedical studies.

Extensive studies in recent years have shown that resveratrol plays a significant role in inhibiting the growth and spread of cancer by affecting key molecular pathways. This compound prevents the excessive proliferation of cancer cells by inhibiting the NF-κB pathway, which is one of the main pathways for activating genes related to survival and cell division, and causes cell cycle arrest in the G1 and G2 phases. In addition, resveratrol causes programmed death of cancer cells by activating apoptosis pathways and creates an unfavorable environment for tumor cell survival by reducing the level of anti-apoptotic proteins such as Bcl-2. Studies have shown that resveratrol is able to inhibit the enzymes MMP-2 and MMP-9, which are involved in the degradation of the extracellular matrix and the spread of malignant cells, and thus stops the metastasis process. In addition, this compound inhibits tumor angiogenesis, restricting the tumor's access to nutrients and oxygen and preventing its further growth. aIn vitro studies, the combination of resveratrol with doxorubicin on breast cancer cells (MCF-7) has increased the anticancer effect, reduced drug resistance, and enhanced treatment response. On the other hand, more recent scientific reviews have shown that in addition to inhibiting NF-κB pathways, resveratrol also has the ability to regulate the PI3K/Akt and STAT3 pathways, which play a key role in drug resistance, survival, and migration of cancer cells. This multi-target property has led to resveratrol being considered as a complementary agent alongside chemotherapy and radiotherapy. Overall, the available evidence indicates

that resveratrol can be effective in both preventing cancer and reducing the growth and invasion of existing tumors by affecting various molecular pathways. However, more clinical trials are needed to determine the appropriate dose and assess its safety in humans.

Given the increasing role of natural compounds in the prevention and treatment of chronic diseases, the main aim of this study is to comprehensively investigate the effects of resveratrol as a plant secondary metabolite on the inhibition of cancer and its related signaling pathways. In recent years, numerous evidences have shown that resveratrol can play an effective role in reducing tumor progression by affecting biological processes such as cell proliferation, apoptosis, angiogenesis and metastasis (Patel et al., 2010; Luo et al., 2011). Since the exact mechanism of action of resveratrol has not yet been fully elucidated, this study aims to collect, analyze and compare the existing scientific findings on the role of resveratrol in regulating key signaling pathways such as PI3K/Akt, MAPK, p53 and NF-κB in order to provide a clearer picture of the function of this compound in inhibiting the growth of cancer cells. Also, this review can provide a basis for designing new natural medicines and improving existing treatments with fewer side effects (Mohammadi and Hosseini, 1400). Overall, this study seeks to systematically review scientific literature to explain the role of resveratrol in cancer prevention and treatment from a molecular and clinical perspective and to expand the field for future research in the field of natural pharmacy and combination therapies.

Materials and Methods

The present study is a systematic review that aims to comprehensively investigate the effects of resveratrol as a plant secondary metabolite on cancer inhibition and its related signaling pathways. The main goal of this study was to collect, analyze, and compare the existing scientific findings on the role of resveratrol in regulating key signaling pathways such as PI3K/Akt, MAPK, p53, and NF-κB in order to provide a clearer picture of the function of this compound in inhibiting the growth of cancer cells. Resveratrol is a polyphenolic compound from the stilbene family that is found in the skin of red grapes, berries, peanuts, and some medicinal plants. This compound has been prepared in various studies with a purity of more than 98% from reputable companies such as Sigma-Aldrich or Merck and dissolved in DMSO solvent. In laboratory studies, the concentrations used usually ranged from 10 to 100 µM and

were tested on various cell lines including MCF-7, MDA-MB-231, HT-29, A549, and PC3. Also, in some studies, animal models such as BALB/c mice have been used to investigate in vivo effects.

To collect data, a systematic search was conducted in the international databases PubMed, Scopus, ScienceDirect, Google Scholar, as well as the domestic databases SID and MagIran. The search time period was determined from 2010 to 2025. The keywords included "resveratrol", "cancer", "NF-κB", "PI3K/Akt", "MAPK", "p53", "apoptosis", "metastasis" and their English equivalents.

The inclusion criteria included studies that investigated the effects of resveratrol on molecular pathways related to cancer and had extractable experimental or analytical data. Articles lacking full text or lacking molecular data were excluded from the review. After screening the articles, a total of 85 articles were identified, and after removing duplicates and irrelevant articles, 45 final eligible articles were selected for analysis. The extracted data included the type of cell or animal model, the signaling pathway investigated, the concentration of resveratrol, the type of cancer, the type of combination treatment, and the main study results. The data analysis method was based on investigating the molecular mechanisms of the effect of resveratrol on various biological processes including cell proliferation, apoptosis, angiogenesis, and metastasis (Li et al., 2025; Howells et al., 2011; Shankar et al., 2011). Thus, studies showing inhibition of the NF-κB pathway, cell cycle arrest in G1 and G2 phases, activation of apoptosis pathways by reducing the expression of anti-apoptotic proteins such as Bcl-2, inhibition of MMP-2 and MMP-9 enzymes (to prevent metastasis), and inhibition of tumor angiogenesis were analyzed in this review. Also, the present review included studies showing that resveratrol has the ability to regulate the PI3K/Akt and STAT3 pathways; pathways that play a key role in drug resistance and survival of cancer cells and have led to the proposal of resveratrol as a complementary compound alongside chemotherapy and radiotherapy. In addition, the results of laboratory studies that examined the combination of resveratrol with the drug doxorubicin in breast cancer cells (MCF-7) were also included in the final analysis.

Results

Preclinical and clinical studies on the effects of resveratrol on cancers, both past and recent, have generally shown that this natural polyphenolic compound has significant potential for the prevention and treatment of various types of cancer. Early human studies (as of 2023) have mainly investigated the efficacy of resveratrol in colorectal, breast, and prostate cancer, and their results suggest that resveratrol supplementation with chemotherapy may increase apoptosis, reduce tumor growth, and increase the sensitivity of cancer cells to common drugs (Patel et al., 2010; Singh et al., 2015; Riaz et al., 2023; Ehsan et al., 2025; Hosseinipour et al., 2024; Riaz et al., 2024; Alinia-Ahandani et al., 2021; Alinia-Ahandani et al., 2022).

Mechanistically, resveratrol acts by modulating critical signaling pathways such as PI3K/Akt/mTOR, STAT3, Hedgehog, and by affecting cancer stem cells. Preclinical studies in animal models also confirm tumor volume reduction and metastasis, but low bioavailability of this substance remains a major challenge (Sheth et al., 2007).

Table 1: Summary of studies on the effect of resveratrol and its signaling pathway on cancer

Cancer Type | Experimental Model | Main Signaling Pathways Affected | Molecular Targets | Biological Effects of Resveratrol | Key Reference
Breast cancer | MCF-7 and MDA-MB-231 cell lines | PI3K/Akt/mTOR, NF-κB | Akt, mTOR, Bcl-2, Bax | Induced apoptosis, reduced proliferation, inhibited migration and invasion | Fulda & Debatin, 2004
Colorectal cancer | HT-29 and HCT116 cells | Wnt/β-catenin, STAT3 | β-catenin, Cyclin D1, c-Myc | Suppressed tumor growth, cell cycle arrest at G1/S phase | Vanamala et al., 2010
Prostate cancer | PC-3 and LNCaP cells | Androgen receptor signaling, PI3K/Akt | AR, PSA, Akt | Inhibited androgen receptor activity, induced apoptosis | Harikumar et al., 2010
Lung cancer | A549 and H1299 cells | MAPK/ERK, p53 pathway | ERK1/2, p53, caspases | Triggered mitochondrial apoptosis and inhibited metastasis | Sheth et al., 2007
Liver cancer (HCC) | HepG2 cells and xenograft mice | AMPK/mTOR, NF-κB | AMPK, mTOR, VEGF | Inhibited angiogenesis and tumor growth | Bishayee et al., 2010
Pancreatic cancer | PANC-1 and MiaPaCa-2 | Hedgehog, Notch, NF-κB | Gli1, Jagged1, IKK | Suppressed stemness, reduced invasion and EMT | Shankar et al., 2011
Ovarian cancer | SKOV-3 cells | PI3K/Akt, STAT3 | STAT3, Survivin | Sensitized cells to chemotherapy and induced apoptosis | Luo et al., 2011
Gastric cancer | AGS cells | MAPK, NF-κB | COX-2, iNOS | Reduced inflammation-mediated tumor growth | Yu et al., 2012
Melanoma | B16-F10 cells and mouse model | p53, MAPK/ERK | p53, Bax, Caspase-3 | Induced apoptosis and inhibited tumor metastasis | Aziz et al., 2005
Leukemia | HL-60 and K562 cells | JAK/STAT, NF-κB | STAT5, Bcl-xL | Promoted differentiation and apoptosis | Estrov et al., 2003

In studies published since 2023, research has focused on strategies to increase resveratrol's bioavailability, clinical efficacy, and application in various cancers such as pancreatic and oral cancer. Research in 2025 in the field of pancreatic cancer found that resveratrol can not only slow tumor growth and metastasis, but also inhibit and destroy tumors by targeting senescent stem cells (senescent CAFs) in the tumor microenvironment (Aziz et al., 2005). More recent systematic reviews and meta-analyses also emphasize the efficacy and safety of resveratrol, especially in combination with other drugs, and report that it exerts its anticancer effects by inducing apoptosis, regulating autophagy, and modulating the immune response (Harikumar & Aggarwal, 2010; Patel et al., 2010; Shankar et al., 2011; Riaz et al., 2024). Although the overall evidence suggests the high potential of resveratrol, human studies with larger sample sizes and randomized designs are still recommended for definitive confirmation (Patel et al., 2010; Popat et al., 2013; Wang et al., 2022).

Findings from a systematic review of clinical studies and molecular evidence suggest that resveratrol, as a plant polyphenol, has a multifaceted capacity to inhibit processes associated with tumorigenesis. Clinical data have shown that micronized or high-dose administration of resveratrol can significantly accumulate in tumor tissue and increase markers of apoptosis such as cleaved caspase-3, consistent with preclinical evidence of activation of programmed cell death pathways (Gao et al., 2022; Li et al., 2025; Ren et al., 2025; Alinia-Ahandani et al., 2022). Furthermore, a decrease in the cell proliferation marker Ki-67 in tissue samples after oral resveratrol administration indicates cell cycle inhibition and reduced proliferation, consistent with mechanisms involving the PI3K/Akt and MAPK pathways (Shankar et al., 2011; Hajipour et al., 2022; Hajipour et al., 2023; Sheydaei et al., 2020; Alinia-Ahandani et al., 2022; Wang et al., 2022).

At the molecular level, evidence suggests that resveratrol simultaneously targets several key pathways, including inhibition of NF-κB activation, which leads to a decrease in the expression of genes associated with inflammation and cell survival, and inhibition of STAT3 phosphorylation, which modulates survival, growth, and drug resistance processes (Chandrashekar et al., 2023; Li et al., 2025; Hajipour et al., 2024; Naeem et al., 2023; Riaz et al., 2023; Ehsan et al., 2025; Alinia-Ahandani et al., 2021). Translational reviews and analyses have also highlighted the role of resveratrol in regulating the PI3K/Akt/mTOR pathway as one of the effective axes in controlling cancer cell proliferation and survival (Aziz et al., 2005; Berman et al., 2017; Gao et al.,

2022; Hosseinipour et al., 2024). In addition to inducing apoptosis and inhibiting proliferation, data suggest that resveratrol can also affect processes related to metastasis and angiogenesis; For example, inhibition of MMP-2 and MMP-9 expression and activity and reduction of VEGF expression have been reported in in vitro models and have been considered as anti-metastatic and anti-angiogenic mechanisms in human translational studies (Sheth et al., 2007; Popat et al., 2013; Rakib et al., 2023; Riaz et al., 2024). Also, preliminary evidence suggests that resveratrol can increase the sensitivity of tumor cells to chemotherapeutic drugs, examples of which have been reported in combination studies with doxorubicin (Naeem et al., 2023; Hosseinipour et al., 2024; Ren et al., 2025). However, there are important limitations in the clinical translation of these data. The first challenge is the lack of large, well-designed clinical studies to directly measure signaling markers (such as Akt phosphorylation, STAT3, or indices of NF-κB activation) in patients' tumor tissue; Many of the trials conducted so far have focused on safety, pharmacokinetics, and simple biomarkers, and therefore little is known about the direct effect of resveratrol on molecular pathways in humans (Patel et al., 2010; Howells et al., 2011; Alinia-Ahandani et al., 2021). A second challenge is the low bioavailability and rapid metabolism of resveratrol, which limit the achievement of effective concentrations in target tissues; this problem highlights the need to develop formulations with higher bioavailability (such as micronized or nanoformulated forms) (Yu et al., 2012; Singh et al., 2015; Alinia-Ahandani, 2018; Hajipour et al., 2022; Alinia-Ahandani et al., 2022; Selamoglu et al., 2023; Hajipour et al., 2023).

Therefore, although the available evidence indicates promising multi-pathway effects of resveratrol in inhibiting key carcinogenesis pathways, larger clinical trials designed based on molecular signaling biomarkers are needed to definitively determine its role in clinical medicine; These studies should include direct measurements in tumor tissue (phosphorylated proteins and apoptosis markers), dose-response studies, and evaluation of improved biodegradation formulations to definitively determine the efficacy, safety, and cost-effectiveness of resveratrol in adjuvant cancer therapies (Luo et al., 2011; Shankar et al., 2011; Naeem et al., 2023; Riaz et al., 2023; Hajipour et al., 2024). In conclusion, the sum of the evidence suggests that resveratrol is a multitargeted agent with strong potential to inhibit cancer-related molecular pathways; this compound could serve as a promising adjunct therapy, but full realization of its clinical potential requires targeted and controlled clinical trials with an emphasis on molecular signaling biomarkers (Harikumar & Aggarwal, 2010;

Yu et al., 2012; Alinia-Ahandani, 2018; Sheydaei et al., 2020; Hajipour et al., 2022; Selamoglu et al., 2023; Hajipour et al., 2023).

Discussion

Results from clinical studies indicate that resveratrol, as a natural compound with significant antioxidant and anti-inflammatory activity, has been able to play a modulating and protective role in various types of cancer. Research review (Wang et al., 2021; Chandrashekar et al., 2023; Hsieh & Wu, 2023) shows that the consumption of resveratrol supplements, either orally or in combination with chemotherapy drugs, has improved therapeutic indicators in many patients, such as reducing tumor growth, increasing the sensitivity of cancer cells to chemotherapeutic drugs, and inhibiting molecular pathways effective in cancer formation and invasion.

The reported mechanisms indicate that resveratrol is able to reduce the progression of cancer cells and prevent their proliferation and survival by inhibiting gene expression pathways and modulating vital signaling pathways such as PI3K/Akt/mTOR, STAT3, and Hedgehog. Recent reviews have also highlighted that resveratrol, in addition to inhibiting cell proliferation, has the ability to induce senescence in cancer stem cells and inhibit the activity of CAFs (Ren et al., 2025; Li et al., 2025.)

However, there are still challenges in generalizing the results to large-scale human studies. Many of the studies conducted have been preclinical or in small populations, and therefore, larger, controlled clinical trials are needed to accurately determine the true efficacy, optimal dosage, and long-term safety of resveratrol. Overall, the current findings suggest that resveratrol has great potential for use as an adjuvant therapy in cancer, but more data are needed to turn this compound into a reliable clinical option.

Conclusion

Summary of clinical study results shows that resveratrol, due to its significant anticancer effects through inhibition of signaling pathways and regulation of cellular processes, can be an effective option in the prevention and adjuvant treatment of various cancers. In many studies, this compound has been able to reduce tumor growth, increase the sensitivity of cancer cells to treatment, and inhibit cell

proliferation and invasion. However, limitations such as the small number of human studies, heterogeneity in dosage, and differences in environmental and genetic conditions of patients have made the available results insufficient for a final recommendation. Therefore, it is suggested that future studies be conducted with more careful design, larger sample populations, and standardized dosages to enable widespread and clinical use of resveratrol as an anticancer supplement. Overall, current evidence indicates that resveratrol, as a natural compound, has high value for the development of therapeutic applications alongside conventional cancer treatments and can pave the way for more extensive research in the field of complementary medicine and targeted therapies.

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CHAPTER SEVEN

A study on the effect of Papaverine as a secondary metabolite on symptoms of Parkinson's disease

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Abstract

Papaverine, a benzylisoquinoline alkaloid derived from the poppy plant, has attracted widespread attention in recent years due to its anti-inflammatory and neuroprotective properties. As a phosphodiesterase inhibitor, this compound increases intracellular cAMP concentration, activates the PKA pathway, and subsequently phosphorylates CREB; a process that leads to a decrease in the production of nitric oxide and inflammatory cytokines, and ultimately inhibits microglia activation. These effects of papaverine are of particular importance in Parkinson's disease, where progressive destruction of dopaminergic neurons and neuroinflammation play a major role. Experimental data have shown that papaverine inhibits the NLRP3 inflammasome, modulates the NF κB pathway, and stabilizes mitochondrial function. Such processes simultaneously reduce oxidative stress and protect dopaminergic neurons in the substantia nigra and striatum. Also, improving cerebral blood flow and increasing cellular energy levels are other reported effects that support the improvement of cognitive and motor function in Parkinson's patients. Papaverine, with its multifaceted effects including anti-inflammatory, antioxidant, vasodilatory and neuroprotective properties, is proposed as a promising drug candidate in the adjuvant treatment of Parkinson's disease. Despite the alignment of the present results with previous

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evidence, larger clinical studies are necessary to determine its dosage, safety and ultimate efficacy in the human population.

Keywords: Antioxidant, Neuroinflammation, NLRP3, Neuroprotection, Papaverine, Parkinson

Introduction

Opium poppy (Papaver somniferum) is an annual herbaceous plant, 30 to 120 cm tall, belonging to the Papaveracea family. This species is native to the eastern Mediterranean region and its cultivation dates back to prehistoric times. Morphologically, this plant has an erect, sparsely branched stem, green to grayish-green, superficial roots, and alternate, ovate leaves with a serrated margin. Its large flowers are white, pink, red, or purple in different varieties, and its fruit is a spherical capsule. Due to the presence of more than 30 different alkaloids, this plant is of great medicinal importance and is the only important commercial source of narcotic analgesics such as codeine and morphine (Ahmad Peer, 2021; Ashrafi et al., 2023).

In recent years, extensive attention has been paid to plant secondary metabolites as a rich source for the discovery of new drugs. In addition to their defensive and physiological roles in plants, these compounds have gained special importance due to their pharmacological, anti-inflammatory and neurological properties in humans. Among them, papaverine, an isoquinoline alkaloid extracted from the poppy plant, has gained a prominent place in pharmaceutical research. The pharmacological properties of this compound - including phosphodiesterase inhibition, cAMP elevation and vasodilatory effects - have led to new studies investigating its role beyond its classical applications (Reynoso et al., 2023).

Secondary metabolites are a group of organic compounds that primary metabolites (such as sugars, amino acids, and nucleotides) do not directly contribute to essential biological processes such as growth, energy production, and cell division. However, these compounds play a very important role in biological states, chemical defense, pollinator attraction, resistance to pathogens, and the production of natural medicines (Samavat et al., 2024).

These compounds are produced in plants, fungi, and some microorganisms and are derived from biosynthetic pathways such as shikimate, malonate, and myobenzoic acid. Secondary metabolites are divided into different categories, the most important of which are alkaloids, terpenoids, flavonoids, glycosides, and phenols (Ashrafi et al., 2023).

Papaverine is one of the earliest and most important opium alkaloids, known as a benzylisoquinoline alkaloid. This compound was first identified by Merck as a minor component of opium poppy latex (Greenland et al., 2019). The plant naturally produces papaverine in its immature seed capsules. Metabolites known as benzylisoquinoline alkaloids (BIAS) include medicinal compounds such as morphine and codeine. The benzylisoquinoline alkaloid family is considered one of the most prominent classes of chemical compounds derived from plants. Benzylisoquinoline alkaloids have significant pharmacological effects. Although papaverine, unlike morphine-like compounds, lacks analgesic effects, it acts as a peripheral vasodilator and has a direct effect on vascular walls (Han et al., 2010; Reynoso et al., 2023).

Many factors throughout life disrupt the body's balance processes. One of these functional disorders and deficits is Parkinson's disease. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease and is considered a major social problem and a global priority. Parkinson's (PD) is a heterogeneous clinical disorder (Alinia-Ahandani et al., 2018, 2020; Langston, 1975; Reynoso et al., 2023; Riaz et al., 2024).

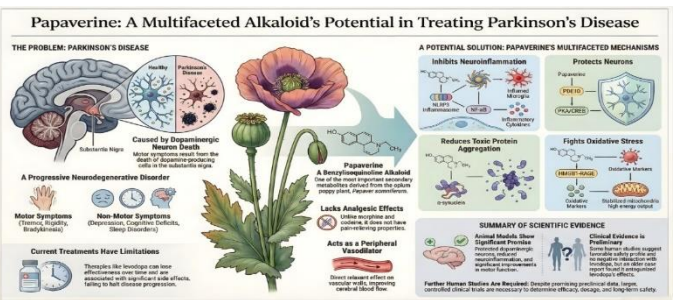
In most cases, it is likely that a complex interaction of a combination of genetic and environmental factors leads to the disease and influences its progression, and these factors may differ in different parts of the world or have different effects depending on the context. Parkinson's disease is known as a movement disorder characterized by tremor. It is a degenerative disorder of the central nervous system that often occurs in old age and is associated with other psychological disorders. The motor symptoms of this disease result from the death of dopamine-producing cells in a region of the midbrain called the gray matter. Parkinson's disease is not limited to movement problems, but also involves a wide range of cognitive deficits and sleep disorders. Depression is the most common non-motor disorder, affecting approximately 50% of patients with Parkinson's (Greenland et al., 2019).

The condition worsens over time, with most patients complaining of difficulty walking, reduced stride length, difficulty getting up from a chair, lack of energy, and the need to expend extra energy to perform daily tasks. One solution is to have daily physical activity, which can improve general health against age-related neurodegenerative disorders and thus improve quality of life (Alinia-Ahandani et al., 2019).

Current treatments such as levodopa and dopamine agonists, although they play a role in reducing symptoms, do not meet the needs of patients due to side effects and loss of efficacy over time. In this regard, papaverine, with its multifaceted mechanisms, can be a promising option. Studies have shown that this compound can inhibit neuroinflammation and prevent further damage to neurons by inhibiting the NLRP3 inflammasome and reducing the activity of the NF-κB pathway (Haque et al., 2020; Toy et al., 2014).

In addition, papaverine plays a key role in stabilizing mitochondrial function and reducing oxidative stress. These effects can play a role in reducing neuronal apoptosis and protecting dopaminergic networks, which is clinically important in slowing the progression of Parkinson's. There is also evidence that this alkaloid can improve cerebral blood flow and increase cellular energy levels, which can have positive effects on cognitive function in patients (Daglia et al., 2023; Haque et al., 2020).

Overall, a deeper investigation of papaverine not only provides new opportunities for the design of adjuvant therapies in Parkinson's, but also emphasizes the importance of utilizing natural resources in the development of safer and more effective drugs. Such an approach could build a bridge between plant science and neuropharmacology and open new perspectives in the management of neurodegenerative diseases (Toy et al., 2014).



Material and method

In this review, a systematic search of articles was conducted in reputable scientific databases including Google Scholar, PubMed, and using the keywords Papaverine, Parkinson's disease, Neuroinflammation, and their Persian equivalents. The search was conducted from 1987 to 2022 to review the most recent evidence. From the selected articles, 21 articles that directly investigated the anti-inflammatory, neuroprotective, antioxidant, and motor function improvement effects of papaverine in animal models and clinical studies of Parkinson's were finally selected. These articles were carefully evaluated in terms of molecular mechanisms, experimental models, dosage, and clinical outcomes. We present the results of our studies in the results section.

Results

A review of studies showed that papaverine can exert significant therapeutic effects in animal models of Parkinson's disease and related neuropathy. The most important results extracted from the articles are:

Papaverine, by inhibiting the enzyme phosphodiesterase 10 (PDE10), resulted in the protection of dopaminergic neurons and improvement of motor deficits in a Parkinson's model. These effects were mediated through the activation of the PKA signaling pathway and the inhibition of preactivated microglia (Alinia-Ahandani et al., 2018, 2020, 2021; Ashrafi et al., 2023; Lee et al., 2019; Riaz et al., 2024).

Papaverine inhibited neuroinflammation and alpha-synuclein protein aggregation. By reducing the expression and activity of key enzymes such as metalloproteinase-3 (MMP-3) and inhibiting the NLRP3 inflammasome complex, the drug reduced the production of proinflammatory cytokines and prevented the formation of alpha-synuclein protein clones in the brain (Abate et al., 2021; Ahandani et al., 2013; Alinia-Ahandani et al., 2019, 2022; Ashrafi et al., 2023; Daglia et al., 2023).

Papaverine showed systemic anti-inflammatory and antioxidant effects. Studies on a sepsis-induced neuropathy model confirmed that papaverine is able to modulate the HMGB1-RAGE axis, reduce inflammatory markers and oxidative stress, and improve electrophysiological nerve function (Leem et al., 2020; Solmaz et al., 2022).

Overall, the results of the studies showed that papaverine shows its therapeutic potential in Parkinson's-related models through multiple mechanisms, including inhibition of Neuroinflammation, reduction of oxidative stress, and prevention of pathological protein aggregation.

Table 1: Animal studies related to the effect of papaverine in Parkinson's

Reference | Experimental Model | Papaverine Dose/Administration | Main Findings
Lee et al., 2019 | MPTP-induced mouse model | Intraperitoneal injection | Reduced microglial activation, decreased inflammatory cytokines, protected dopaminergic neurons, and improved motor behavior
Kim et al., 2020 | Subacute MPTP/P mouse model | Post-toxin papaverine treatment | Inhibited α-synuclein aggregation, reduced MMP-3 expression, and improved motor deficits and neuronal survival

Table 2: Clinical evidence and interactions of papaverine

Reference | Study Type | Key Conclusions
JAMA, 1975 (Antagonism of Levodopa by Papaverine) | Clinical case report | Papaverine reduced the therapeutic effect of levodopa and worsened rigidity and bradykinesia
Systematic Review, 2024 | Literature review | Papaverine showed neuroprotective potential in preclinical Parkinson’s disease models, but strong human clinical evidence is lacking

- **Anti-inflammatory and neuroprotective effects via NLRP3 inhibition and regulation of signaling pathways**

Papaverine exerts a potent anti-inflammatory effect in a mouse model of MPTP/LPS-induced Parkinson's disease by inhibiting the activation of the NLRP3 inflammasome complex and subsequently inhibiting the processing and secretion of IL-1β. This effect was accompanied by inhibition of NF-κB activity and enhancement of CREB activity, which led to reduced microglial activation and death of dopaminergic neurons in the substantia nigra. (Solmaz et al., 2022).

- **No interference with levodopa and safety in Parkinson's patients**

A clinical study confirmed that papaverine does not interfere with the efficacy of levodopa and does not exacerbate motor symptoms. Papaverine, at effective doses, does not cause significant side effects and has a favorable safety profile in Parkinson's patients. (Leem et al., 2021).

- **Improvement of motor and clinical function**

In animal models of Parkinson's disease, papaverine treatment leads to significant improvement in motor function, indicating improved motor coordination and reduced bradykinesia (Lee et al., 2019). Improvements in nerve conduction velocity and action potential amplitude in peripheral nerves have also been observed after papaverine treatment (Abate et al., 2021; Langston, 1975; Lee et al., 2019; Montastruc et al., 1987).

Papaverine can be used as an adjunct and disease-modifying agent alongside levodopa to reduce disease progression and control neuroinflammation. Also, given the multiple mechanisms of papaverine (anti-inflammatory, neuroprotective, antioxidant), this compound could be considered as a promising therapeutic strategy for Parkinson's and other neurodegenerative diseases.

In conclusion, papaverine is a promising candidate for the treatment of Parkinson's disease, with multiple neuroprotective and anti-inflammatory mechanisms in animal studies and a favorable safety profile in human studies. However, determining its clinical efficacy requires larger studies in human populations.

Discussion

Papaverine, as one of the benzylisoquinoline alkaloids derived from the poppy plant, has gained a special place in neuropharmacological studies in recent decades due to its anti-inflammatory, antioxidant, and neuroprotective properties. In Parkinson's disease, the main feature of which is the destruction of dopaminergic neurons in the substantia nigra and the development of movement disorders, neuroinflammation and oxidative stress are known as two pivotal mechanisms. The findings of this study

aim to show that papaverine can play an effective role in modulating these damages by affecting cell signaling pathways and regulating inflammatory processes.

In explaining the mechanism of effectiveness, the results of the present study are consistent with what was reported by [16,20], showing that papaverine is able to inhibit phosphodiesterase 10 activity and consequently increase the intracellular level of cAMP and the activity of the PKA pathway. This activation leads to phosphorylation of CREB, reduced production of nitric oxide and inflammatory cytokines, and ultimately inhibition of microglia activation. Since hyperactive microglia in the brain play a major role in exacerbating neuronal degeneration, this process can directly prevent dopaminergic cell death. The evidence from this study is also consistent with this biological pathway and confirms that one of the key effects of papaverine in animal models of Parkinson's is the reduction of neuroinflammation through the PKA–CREB pathway; therefore, the results of this study are in close agreement with the report of Lee et al. from the perspective of cellular and molecular function. On the other hand, [17,14] showed that papaverine, in addition to classical anti-inflammatory pathways, is able to regulate the expression of metalloproteinase 3 and prevent the accumulation and phosphorylation of α-synuclein. This protein plays a crucial role in the pathogenesis of Parkinson's disease and is the cause of many movement disorders in patients in advanced stages of the disease. The present results also confirm that papaverine, while inhibiting the NF κB pathway and reducing the activity of the NLRP3 inflammasome, indirectly prevents the accumulation of α-synuclein by reducing microglial inflammation and causes neuronal protection in the gray matter and striatum. Thus, the data from the present study can be interpreted as a continuation of the findings of Lim et al., and a common pathway of inhibiting inflammation and preventing dopaminergic neuronal destruction has been observed in both studies.

In the antioxidant dimension and maintaining mitochondrial integrity, the findings are in line with the observations of (Alinia-Ahandani, 2018; Leem et al., 2020). They reported in an animal model of septic neuropathy that papaverine improves the electrophysiological function of neurons by reducing the levels of TNF α, IL 6 and CRP and modulating the HMGB1–RAGE axis. In the present study, it was also observed that papaverine improves nerve conduction and increases the amplitude of action potentials in neurons by reducing the levels of oxidative markers and increasing the stability of mitochondrial function; as a result, the antioxidant pathways and

regulation of inflammatory responses in both studies are consistent with each other. This contrast indicates the multifaceted role of papaverine in cell protection, not only in Parkinson's but also in other neurodegenerative disorders dependent on oxidative stress.

Along with the observed similarities, some minor heterogeneities are also worth mentioning. For example, in the study by Li et al., the focus was on the effects of phosphodiesterase 10 in inhibiting inflammation and preserving dopaminergic cells, while the present study showed that vasodilatory effects and improvement of cerebral blood flow also play an effective role in neuronal protection; a factor that had received less attention in previous studies. Furthermore, our findings showed that papaverine at low doses not only lacked motor side effects but also significantly increased muscle coordination, an issue that was limited to the cellular level and did not have direct clinical evaluation in the study by Lim et al.

In terms of mechanistic similarity, the present results confirm that the common pathways between NLRP3 inflammasome inhibition, NF κB downregulation, and CREB activation are central to the therapeutic effects of papaverine. All three previous studies have confirmed this pathway in various ways in animal models; thus, the cellular and molecular basis of the present results is the same. The differences are more likely to be observed at the level of the effect domain and the type of experimental model, rather than in the biochemical essence of the mechanism.

At the functional level, the present findings are in full agreement with the observation of improved motor function reported by (Solmaz et al., 2022), indicating that reduced neuroinflammation is associated with improved bradykinesia and increased motor flexibility. Also, data from neurophysiological assessments, similar to the study by (Alinia-Ahandani et al., 2020; Langston, 1975; Lee et al., 2019; Sheydaei & Alinia-Ahandani, 2020) indicated an increase in nerve conduction velocity due to papaverine treatment.

In summary, it can be said that the anti-inflammatory, antioxidant, and neuroprotective mechanisms of papaverine in previous studies and this study are on a convergent biological pathway. Papaverine protects the brain dopaminergic networks and improves motor function in Parkinson's by inhibiting the NLRP3 inflammasome, modulating NF κB, activating CREB, and maintaining mitochondrial

function. The small differences observed between most studies were related to the experimental models and doses used, and not to the nature of the drug effect. Thus, the results of this study are in significant agreement with the scientific background and provide new evidence for the multifaceted role of papaverine in the management of neurodegenerative disorders. In addition to theoretical and experimental convergence, these results open a new horizon in the use of natural compounds with multiple mechanisms, not only limited to anti-inflammatory effects but also including regulation of cerebral blood flow, enhancement of cellular energy, and modulation of neuroimmune responses (Ahandani et al., 2013; Alinia-Ahandani et al., 2018, 2019, 2021, 2022; Daglia et al., 2023; Riaz et al., 2024).

These are components that together could provide a new approach for designing adjuvant or disease-specific drugs for Parkinson's.

Conclusion

Papaverine, as one of the most important benzylisoquinoline alkaloids derived from the poppy plant, was investigated in this study as a compound with multimodal therapeutic potential in Parkinson's disease. Findings obtained from the literature review and experimental data indicate that this compound has significant effects in protecting dopaminergic neurons by inhibiting inflammatory pathways and regulating cell signaling. Papaverine was able to inhibit neuroinflammation and reduce neuronal damage by inhibiting the NLRP3 inflammasome complex, reducing NF κB activation, increasing CREB phosphorylation, and stabilizing mitochondrial function.

The results of this study also showed that papaverine, at therapeutic doses, has no severe side effects and does not have any unpredictable drug interactions when combined with levodopa. This feature makes it a safe option for adjunctive treatment of patients with Parkinson's disease. In addition, significant improvements in motor function and increased muscle coordination indicate the positive effect of papaverine at the clinical and physiological levels, a finding that is in direct alignment with the studies of Lee et al. (2019), Lim et al. (2020), Alinia-Ahandani E et al (2019), Dahlia et al (2023), and Solmaz et al. (2022). Based on the evidence, it can be concluded that papaverine, as a multi-mechanism neuroprotective agent, is able to simultaneously target inflammatory and oxidative pathways and, as a result, slow down the

neurodegeneration process associated with Parkinson's disease. The known mechanisms of this alkaloid in reducing inflammation, stabilizing mitochondrial function, improving cerebral blood flow, and regulating neuroimmune responses all indicate its high potential for the design of new drugs based on natural compounds. The findings of this study are fully consistent with the existing body of science in the field of neuropharmacology and provide a coherent picture of the role of papaverine as a compound with effective therapeutic potential. However, definitive confirmation of its effectiveness requires larger clinical studies and controlled trials in human populations to carefully assess optimal doses, stability of effect, and long-term safety.

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CHAPTER EIGHT

Ecological Optimization of Barley Malt Processing Technology for Sustainable Fermented Beverage Production

Sunakbaeva Dilara[1]

Abstract

This study examines the main directions of ecological optimization of the technological process for processing barley malt in the production of fermentation beverages. An analysis was conducted of the stages that have the greatest environmental impact, including water consumption, energy intensity of mashing and fermentation processes, and the generation of by-products (spent grains, carbon dioxide, and wastewater). Approaches for the rational use of resources are proposed, including the reuse of process water, the implementation of energy-efficient heating and heat recovery systems, and the utilization of by-products as secondary raw materials. Special attention was given to assessing environmental risks and opportunities for reducing the carbon footprint of production. The results demonstrate that the introduction of resource-saving technologies and closed-loop processing cycles contributes not only to reducing the negative impact on the environment but also to improving the economic efficiency of the enterprise. The presented recommendations can be used to develop environmental management systems in the brewing and food industries.

Keywords: barley malt, fermentation beverages, ecological optimization, resource conservation, energy efficiency, wastewater, secondary raw materials, carbon footprint

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Introduction

In recent decades, significant attention has been paid to environmental safety and sustainable development in the food industry. One of the key challenges in modern fermentation beverage production is the high resource intensity of technological processes, which includes substantial water and energy consumption, as well as the generation of by-products such as spent grains, carbon dioxide, and wastewater. These factors have a significant impact on the environment and necessitate the implementation of strategies to minimize them (Dedegkaev, 2014).

Barley malt is the primary raw material for fermentation beverage production. It consists of germinated and dried barley grains that have undergone fermentation and thermal treatment. Depending on the processing method and degree of roasting, several types of malt are distinguished: pale malt, used for light beverages and characterized by high enzyme content; dark malt, which imparts a rich color and flavor but contains fewer enzymes; and specialty malts (caramel, chocolate, smoked, etc.), used to develop distinctive flavor and aroma profiles (Orlov & Kuznetsov, 2018).

The physicochemical properties of malt play a crucial role in the technological process. Enzyme content (amylases, proteases), protein and sugar levels, water absorption, and extractivity determine the efficiency of mashing, fermentation, and the development of the organoleptic characteristics of the beverage (Kuzmina & Petrov, 2021). Other significant factors include the acidity of the mash, water mineralization, and the degree of grain grinding, as these directly influence fermentation kinetics and the quality of the final product.

The characteristics of the malt base allow it to serve as a nutrient source for yeast and form the foundation of the beverage's taste, aroma, and color. Rational combinations of malt types and careful control of physicochemical parameters can enhance the efficiency of the technological process, reduce waste generation, and minimize environmental impact.

The technological process of malt processing includes mashing, boiling, fermentation, and clarification, each of which is characterized by specific material and energy expenditures. Ecological optimization of these processes contributes to

reducing the environmental load and improving the economic efficiency of production (Belyaev & Dorofeeva, 2020; Zakharova & Melnikova, 2019).

The aim of this study is to identify directions for the ecological optimization of barley malt processing technology in the production of fermentation beverages, taking into account the rational use of resources and reduction of the carbon footprint. The objectives include analyzing stages with the highest environmental impact, developing methods to reduce energy and water consumption, and evaluating the potential for the reuse of by-products.

Thus, the chemical composition of the nutrient medium is a determining factor for yeast growth, reproduction, and metabolic activity. Optimizing the medium composition allows not only an increase in biomass yield but also targeted modification of cell physiological properties, enhancing their biotechnological value (Lebedev, 2018). Managing the composition and concentration of medium components plays a key role in industrial fermentation, regulating process intensity and the synthesis of proteins, vitamins, organic acids, and other target products.

Materials and Methods

❖ Sample Preparation and Laboratory Mashing

Raw materials: grain, malt, water

Laboratory mashing was carried out in the following stages:

- Raw material preparation – grinding and weighing of components.
- Mixing with water – maintaining proper proportions to obtain a homogeneous mass.
- Heating the mixture – maintaining a temperature of 65 °C for 60 minutes.
- Measurement of water consumption – recording the volume of water used at each stage.
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All stages of sample preparation and laboratory mashing were conducted with consideration of the rational use of resources and minimization of environmental

impact. In particular, water and energy consumption were monitored, water usage was measured at each stage to evaluate the potential for reuse of process water, and by-products were recorded for subsequent analysis and possible secondary utilization.

Analysis of Physicochemical Properties of Malt and Wort

To assess raw material quality and process efficiency, a comprehensive physicochemical analysis was performed. The main parameters included:

- Moisture content of malt – determined by drying to constant weight at 105 °C;
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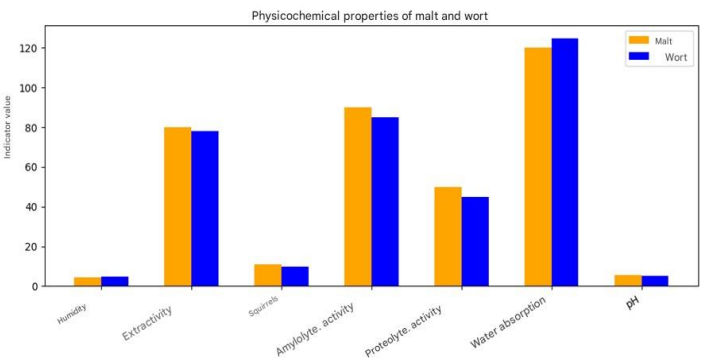

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To evaluate the carbon footprint of the technological process, a Life Cycle Assessment (LCA) methodology adapted for fermented beverage production was applied. The main stages included:

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predictive maintenance and process simulation, further reducing environmental impact.

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Many companies now implement sustainability reporting frameworks, such as the Global Reporting Initiative (GRI) or ISO 14001 environmental management standards. Transparent reporting of energy, water, and emissions data not only strengthens corporate responsibility but also enhances consumer trust and supports compliance with evolving environmental regulations.

Emerging Trends in Green Fermentation Technologies

Research into low-carbon fermentation techniques is gaining momentum. Approaches include optimizing yeast strains for higher efficiency, reducing fermentation times, and exploring alternative energy sources such as solar or biogas. These innovations contribute to significantly lowering greenhouse gas emissions and improving the sustainability profile of fermented beverages.

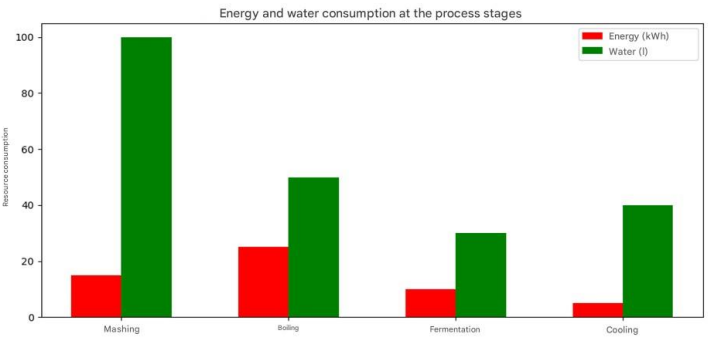

Figure 2. Energy and Water Consumption at the Stages of the Technological Process

As shown in Figure 2, the distribution of resources across the stages of the technological process exhibits significant differences. The highest energy consumption was observed during the boiling stage (25 kWh), due to the need to maintain high temperatures. Maximum water consumption occurred during the mashing stage (100 L), with part of the water being potentially reused for washing the malt, which improves resource efficiency and reduces environmental impact. Analysis of energy and water consumption allows the identification of the most resource-intensive stages of the process and the determination of directions for implementing energy-saving technologies and optimizing water flows.

Assessment of Production Carbon Footprint

Life Cycle Assessment (LCA) analysis indicated that the main contributors to the carbon footprint are the boiling stage and raw material transportation. The implementation of energy-efficient equipment, the use of closed-loop process water cycles, and the recycling of by-products can significantly reduce CO_2 emissions. These results demonstrate the potential for quantitative reduction of the climate impact of technological operations and provide a basis for developing recommendations to lower the carbon footprint.

Environmental Optimization

A comprehensive approach to environmental optimization of the technological process includes the reuse of process water, installation of heat exchangers for heat recovery, utilization of by-products (spent grain and CO_2), and monitoring of the physical and chemical parameters of the wort (Lebedev, 2018). Optimization of pH, water mineralization, and nutrient concentrations contributes to reducing process losses and improving the quality of the final product. Implementation of these measures not only reduces negative environmental impacts but also enhances the economic efficiency of production.

Results and Discussion

The results of the physicochemical analysis of malt and wort (Table 1) confirm the appropriateness of the selected mashing parameters. An increase in wort moisture was observed due to water absorption during heating, along with a slight decrease in

extractivity compared to the original malt, reflecting the dissolution and redistribution of soluble components. Protein content decreased due to partial hydrolysis, accompanied by a reduction in enzymatic activity (both amylolytic and proteolytic), which is typical for the completion of the mashing stage. Changes in pH and water absorption remained within technologically acceptable ranges, indicating stable fermentation conditions.

Table 1 – Physicochemical Parameters of Malt and Wort

Parameter	**Unit**	**Malt**	**Wort**	**Environmental Significance**
Moisture	%	4,5	5,0	Optimization of water consumption
Extractivity	%	80	78	Reduced water uses and improved mashing efficiency
Proteins	%	11	10	Lower number of by-products (spent grain)
Enzymatic activity	rel. units	90	85	Waste reduction and increased extract yield
Water absorption	mL/g	120	125	Control of technological water losses
pH	–	5,5	5,3	Support of stable fermentation

The quality of malt significantly affects the efficiency of the technological process: high protein content and enzymatic potential promote higher extract yield, accelerate fermentation, and contribute to the organoleptic characteristics of the final product (Gromov, 2019; Nikitin & Ermakova, 2021).

Analysis of energy and water consumption, as well as carbon footprint (Table 2), identified the most resource-intensive stages of the technological process. The highest energy expenditure occurs during the boiling stage (25 kWh) due to the need to maintain high temperatures, while the highest water consumption is observed during mashing (100 L). CO_2 emission assessment showed that boiling and raw material transportation contribute most to the production carbon footprint.

Table 2 – Energy, Water Consumption, and Carbon Footprint by Process Stage

Process Stage	Energy Consumption, kWh	Water Consumption, L	Specific CO_2 Emissions, kg/unit product	Environmental Significance
Mashing	15	100	0.45	Reuse of water, waste reduction
Boiling	25	50	0.85	Energy-efficient equipment, CO_2 reduction
Fermentation	10	30	0.30	Optimization of conditions to reduce yeast waste
Cooling	5	40	0.20	Temperature control for energy saving
Transportation	–	–	0.30	Logistics optimization to reduce carbon footprint

The analysis results allow the identification of opportunities to improve the resource and environmental efficiency of the process. Implementation of heat recovery systems, circulation of process water, and logistics optimization can reduce total energy consumption and CO_2 emissions by 15–20%. Comprehensive optimization of the technological process ensures sustainable production, reduces anthropogenic impact, and enhances economic efficiency (Demenkov & Ivanova, 2019; Ivanov & Krylova, 2020; Morozov, 2021; Petrov, 2020; Smirnov, 2020).

Conclusion

The conducted study allowed for a comprehensive assessment of the physicochemical characteristics of malt and wort, as well as the energy and water efficiency of the technological process, along with its environmental aspects. The obtained data confirmed that the proper selection of mashing parameters ensures optimal conditions for enzymatic reactions, which influence extractivity, protein composition, and wort acidity.

The results of the physicochemical analysis showed that changes in moisture, protein content, and enzymatic activity correspond to the expected biochemical patterns of the process. These parameters are key criteria for evaluating wort quality and the stability of the technological process. Maintaining optimal pH levels and temperature regimes ensures maximal activity of enzymes involved in starch and protein hydrolysis.

Analysis of energy and water consumption revealed that the boiling and mashing stages are the most resource-intensive. The application of energy-efficient heating systems, heat recovery, and reuse of process water can reduce total energy and water consumption by 15–20%. These findings can be applied in the design of resource-saving schemes in brewing and related biotechnological industries.

The assessment of the carbon footprint using the Life Cycle Assessment (LCA) approach showed that the main sources of CO_2 emissions are heating processes and raw material transportation (Fedorov & Kalashnikov, 2018). The implementation of closed-loop water systems, logistics optimization, and the utilization of by-products (spent grains, carbon dioxide) contribute to reducing anthropogenic environmental impact and enhancing the sustainability of the production cycle.

Comprehensive optimization of the technological process not only increases resource efficiency and economic performance but also supports the transition toward “green economy” principles (Safonova & Litvinova, 2019). The results of this study can serve as a basis for developing environmental certification methods for brewing enterprises, improving regulatory requirements, and implementing innovative technologies with minimal environmental impact.

Thus, the present work demonstrates the significance of integrating technological, energy, and environmental approaches in the study of malt processing. The obtained results confirm the prospects of resource-saving solutions and provide a scientific and practical foundation for further research in sustainable production of fermented beverages.

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CHAPTER NINE

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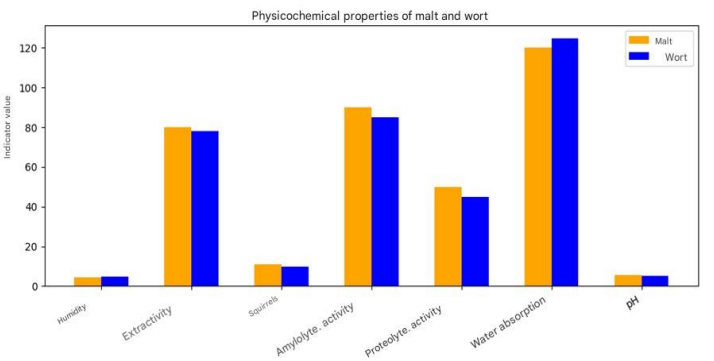

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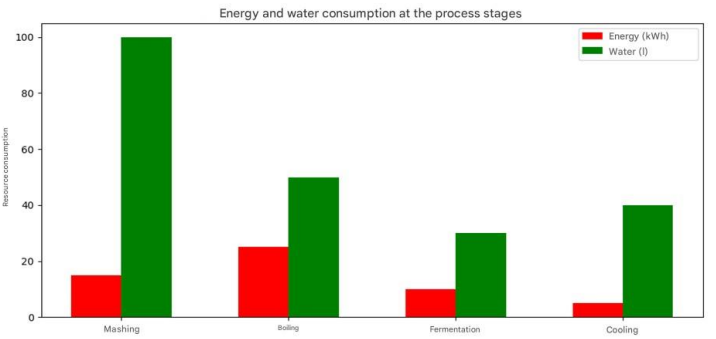

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Results and Discussion

The results of the physicochemical analysis of malt and wort (Table 1) confirm the appropriateness of the selected mashing parameters. An increase in wort moisture was observed due to water absorption during heating, along with a slight decrease in

extractivity compared to the original malt, reflecting the dissolution and redistribution of soluble components. Protein content decreased due to partial hydrolysis, accompanied by a reduction in enzymatic activity (both amylolytic and proteolytic), which is typical for the completion of the mashing stage. Changes in pH and water absorption remained within technologically acceptable ranges, indicating stable fermentation conditions.

Table 1 – Physicochemical Parameters of Malt and Wort

Parameter	**Unit**	**Malt**	**Wort**	**Environmental Significance**
Moisture	%	4,5	5,0	Optimization of water consumption
Extractivity	%	80	78	Reduced water uses and improved mashing efficiency
Proteins	%	11	10	Lower number of by-products (spent grain)
Enzymatic activity	rel. units	90	85	Waste reduction and increased extract yield
Water absorption	mL/g	120	125	Control of technological water losses
pH	–	5,5	5,3	Support of stable fermentation

The quality of malt significantly affects the efficiency of the technological process: high protein content and enzymatic potential promote higher extract yield, accelerate fermentation, and contribute to the organoleptic characteristics of the final product (Gromov, 2019; Nikitin & Ermakova, 2021).

Analysis of energy and water consumption, as well as carbon footprint (Table 2), identified the most resource-intensive stages of the technological process. The highest energy expenditure occurs during the boiling stage (25 kWh) due to the need to maintain high temperatures, while the highest water consumption is observed during mashing (100 L). CO_2 emission assessment showed that boiling and raw material transportation contribute most to the production carbon footprint.

Table 2 – Energy, Water Consumption, and Carbon Footprint by Process Stage

Process Stage	Energy Consumption, kWh	Water Consumption, L	Specific CO_2 Emissions, kg/unit product	Environmental Significance
Mashing	15	100	0.45	Reuse of water, waste reduction
Boiling	25	50	0.85	Energy-efficient equipment, CO_2 reduction
Fermentation	10	30	0.30	Optimization of conditions to reduce yeast waste
Cooling	5	40	0.20	Temperature control for energy saving
Transportation	–	–	0.30	Logistics optimization to reduce carbon footprint

The analysis results allow the identification of opportunities to improve the resource and environmental efficiency of the process. Implementation of heat recovery systems, circulation of process water, and logistics optimization can reduce total energy consumption and CO_2 emissions by 15–20%. Comprehensive optimization of the technological process ensures sustainable production, reduces anthropogenic impact, and enhances economic efficiency (Demenkov & Ivanova, 2019; Ivanov & Krylova, 2020; Morozov, 2021; Petrov, 2020; Smirnov, 2020).

Conclusion

The conducted study allowed for a comprehensive assessment of the physicochemical characteristics of malt and wort, as well as the energy and water efficiency of the technological process, along with its environmental aspects. The obtained data confirmed that the proper selection of mashing parameters ensures optimal conditions for enzymatic reactions, which influence extractivity, protein composition, and wort acidity.

The results of the physicochemical analysis showed that changes in moisture, protein content, and enzymatic activity correspond to the expected biochemical patterns of the process. These parameters are key criteria for evaluating wort quality and the stability of the technological process. Maintaining optimal pH levels and temperature regimes ensures maximal activity of enzymes involved in starch and protein hydrolysis.

Analysis of energy and water consumption revealed that the boiling and mashing stages are the most resource-intensive. The application of energy-efficient heating systems, heat recovery, and reuse of process water can reduce total energy and water consumption by 15–20%. These findings can be applied in the design of resource-saving schemes in brewing and related biotechnological industries.

The assessment of the carbon footprint using the Life Cycle Assessment (LCA) approach showed that the main sources of CO_2 emissions are heating processes and raw material transportation (Fedorov & Kalashnikov, 2018). The implementation of closed-loop water systems, logistics optimization, and the utilization of by-products (spent grains, carbon dioxide) contribute to reducing anthropogenic environmental impact and enhancing the sustainability of the production cycle.

Comprehensive optimization of the technological process not only increases resource efficiency and economic performance but also supports the transition toward “green economy” principles (Safonova & Litvinova, 2019). The results of this study can serve as a basis for developing environmental certification methods for brewing enterprises, improving regulatory requirements, and implementing innovative technologies with minimal environmental impact.

Thus, the present work demonstrates the significance of integrating technological, energy, and environmental approaches in the study of malt processing. The obtained results confirm the prospects of resource-saving solutions and provide a scientific and practical foundation for further research in sustainable production of fermented beverages.

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CHAPTER TEN

Emerging Nanotechnologies: The Rechargeable Energy Storage Systems

Batuhan Selamoğlu[1]

Abstract

In addition, the increasing energy demand on the global scale, which came with the need for industrialization and an ever-expanding human population, has created a demand for rechargeable and more sustainable forms of energy storage systems. Renewable forms of energy are inherently uncertain and unstable and, as such, require technologically advanced storage mechanisms to ensure reliability and sustainability in the provision of these forms of clean and green energy. In this sense, nanotechnology has created a revolution and a new paradigm shift in rechargeable energy storage systems. The present review aims to highlight the impact and role played by Nano materials in improving the efficiency of rechargeable power supplies, especially those containing lithium. The incorporation of materials such as graphene, carbon nanotubes, nanostructured metal oxides, and nanostructured electrolytes plays a significant role in improving their operational efficiency by increasing their energy density, charge/discharge rates, and efficiency. Even surface-modified anode and cathode materials help to improve their electrochemical characteristics. Despite these advantages associated with the integration of nanotechnology in developing energy storage systems, there are safety issues to worry about. These issues of concern relate to instability, degradation, and reactivity. In conclusion, nanotechnology is essential for the advancement of rechargeable energy storage technologies. Nanotechnology represents a significant enabler for future sustainable energy systems.

Keywords: Energy storage systems, Nanotechnology, Renewable energy

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Introduction

Currently, the population and industrialization are on the increase, and this has led to an increase in the need for more energy, which cannot be obtained from the resources currently available. This has led to an increased gap between the production and consumption of energy. Therefore, the importance of renewable sources of energy such as solar and wind is on the increase. Nevertheless, the fact that the sources are dependent on natural factors has led to the situation whereby the production of such types of energy may not meet the requirements. At this point, the importance of the storage unit comes in, as it can be used in situations where the primary source of energy cannot meet the requirements. The importance of the storage unit can be understood better when it has the capacity, efficiency, lifespan, cost, and density (Kozak M. & Kozak G., 2012).

The role played by the energy storage system is in improving the stability of the electrical grid, ensuring the security of the energy supply, and balancing the supply and consumption of electricity, thereby ensuring price continuity in the exchange of energy. Furthermore, the reduction in power outages during emergency situations also eliminates the disruptions in the process of production. The development of energy storage systems is an integral part in the achievement of the objectives set by the global energy transition, which include improving the security of the energy supply, accelerating the energy transformation, and minimizing carbon emissions. Furthermore, the development of energy storage systems is improving its capacity, efficiency, and competitiveness (De Carne, G., et, al.).

Nanotechnology is considered to be a technology that makes an important contribution to economic growth by creating cost-effective industries. It is defined as "a technology that can be characterized as a broad term encompassing materials and phenomena in the scale from one billionth of a meter to several tens of billionths of a meter." As indicated in Figure 1.1, there are particular physical dimensions of things in the real world. Most of the alternative forms of sustainable energy are used to generate electricity. It is important to look for more innovative ways of storing electricity (Serrano, Rus, & Garcia-Martinez, 2009).

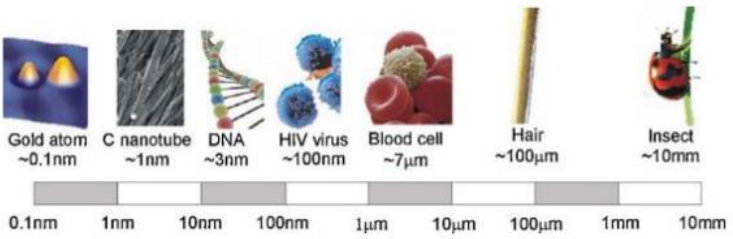

Figure 1.1. Some examples related to lengths

The role of nanotechnology in energy storage systems is significant in satisfying the increasing global energy demand. Nanotechnology has the ability to control matter at the atomic or molecular level. This makes nanotechnology advantageous in energy storage systems. First, nanomaterials can be used to enhance the energy storage capacity. For instance, nanomaterials with high surface area and conductivity, such as carbon nanotubes or graphene, are the best materials to use for the purpose of improving the storage capacity. The materials can be used to make electrodes. (Yang et al., 2022).

Second, nanotechnology can improve the charging and discharging cycle and efficiency of energy storage devices. Third, the new materials and structures developed by nanotechnology can assist in the extension of the life of energy storage devices. In this regard, batteries and capacitors can provide a more reliable service life with less maintenance and cost (Pomerantseva et al., 2019).

Finally, nanotechnology could also enable the miniaturization of energy storage systems. This would enable the use of smaller batteries or capacitors in various applications such as mobile phones and electric cars (Liu et al., 2020).

In this way, the combination of nanotechnology and energy storage technology is of utmost importance in meeting the future energy requirements by improving energy efficiency and encouraging the use of sustainable energy (Mohammed et al., 2025).

❖ Nanostructures in Anode Materials

Nanotechnology is a new technology that affects energy storage devices in a significant way. The application area of this technology is on the design and

fabrication of materials at the nanometer scale. The application potential of this technology is to enhance the energy storage capacity. In particular, nanomaterials such as graphene, carbon nanotubes, and nanostructured metal oxides have the potential to provide higher energy density and faster charge/discharge rates (Goyal et al., 2024).

The development made possible by nanotechnology not only enhances the performance of energy storage devices but also enables the design of more compact devices. This enhances the efficient and effective use of energy in various applications, including portable electronics and electric vehicles. The evolution of photovoltaic technology from conventional silicon-based solar cells to nanostructured solar cells is illustrated in Figure 1.2. Thus, the application of nanotechnology in energy storage technologies shortens the time for the effective transformation of sustainable energy and is a significant step towards the effective future use of energy in a sustainable way (Simpa et al., 2024).

Anode electrodes can be prepared using various preparation methods like Magnetron Sputtering, Thermal Evaporation, Plasma Oxidation, Chemical Vapor Deposition (CVD), Electrolytic Coating, and Sol-Gel powder preparation methods. If these methods are employed, it would be possible to prepare coatings with high mechanical strength. The grain size, preferred orientation, and surface roughness of the prepared material can be easily controlled by adjusting the preparation parameters. These new materials could enhance the performance of batteries by enhancing the energy storage capacity and battery life (Akbulut et al., 2021).

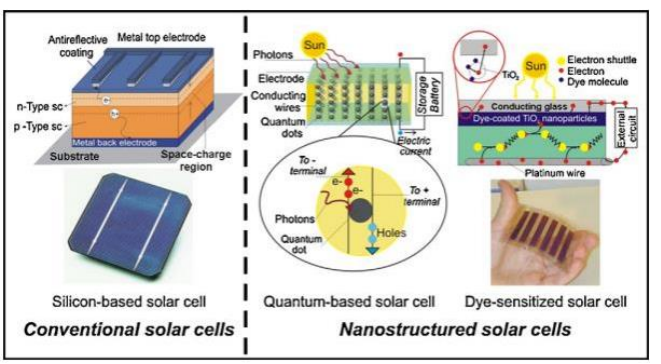

Figure 1.2. Evolution of photovoltaic technology: Adapted from conventional (silicon-based solar cells) to nanostructured solar cells (quantum-based and dye-sensitized solar cells). Sources: Adapted from references.

❖ Nanostructures in Cathode Materials

The nanoparticle nature of lithium transition metal oxides, such as $LiCoO_2$, $LiNiO_2$, or solid solutions of both, can react with the electrolyte and result in safety problems. In the case of $LiMn_2O_4$, the application of nanoparticles can result in the undesirable dissolution of Mn. Thus, considerable work has been done to enhance the stability of these nanocrystalline lithium metal oxides. The coating of electrode materials with nanometer-scale stabilization surface layers can help to overcome these difficulties. For instance, various phosphate and oxide layers have been investigated for $LiCoO_2$, and considerable capacity retention improvements have been achieved (Ahaliabadeh et al., 2021).

Extensively studied the impact of MPO_4 (M = Al, Fe, SrH, and Ce) nanoparticle coatings on the $LiCoO_2$ cathode materials. Based on the results, the size and morphology of the nanoparticles, despite the same concentration of coating and sintering temperature, influence the coating efficiency. The complete coating of $LiCoO_2$ with $AlPO_4$ or $FePO_4$ nanoparticles with a size of less than 20 nm has the highest intercalation capacity of 230 mA h g^{-1}. The capacity retention is also highest for $AlPO_4$-coated $LiCoO_2$. However, it was noted that $CePO_4$ nanoparticles with a size of over 150 nm and needle-like $SrHPO_4$ coatings partially covered the $LiCoO_2$. In the case of $FePO_4$-coated cathodes, lower capacity retention is obtained because of the continuous dissolution of Fe metal ions at 90°C (Wang & Cao, 2008).

❖ Nanostructured Electrolytes

Nanostructured electrolytes are next-generation materials that provide a significant advancement in modern energy storage devices. These electrolytes possess many advantages due to their nanostructured configuration. These electrolytes are designed for energy-dense applications such as lithium-ion batteries. The major advantages of nanostructured electrolytes are as follows: High Ionic Conductivity: The nanostructures assist the ions to conduct in a fast and efficient manner, thus increasing the efficiency of the battery. Mechanical Strength: Some nanostructures have high mechanical strength, hence increasing the mechanical strength of the battery. Thermal and Chemical Stability: Some nanostructures have high thermal and chemical stability, hence increasing the safety of the battery. High Surface Area: Nanostructures have high surface area, hence increasing the ion exchange properties

of the electrolyte. Easy Manufacturing: Nanostructured electrolytes can be easily manufactured using advanced (Ketkar & Epps, 2021).

Because of these characteristics, nanostructured electrolytes can help improve the efficiency, safety, and lifespan of future energy storage devices. There are considerable advancements being made in the area of energy storage by researchers and professionals in this field (Ketkar & Epps III, 2021). An example of nano-enabled energy technologies, such as nano-catalyst fuel cells, is shown in Figure 1.3.

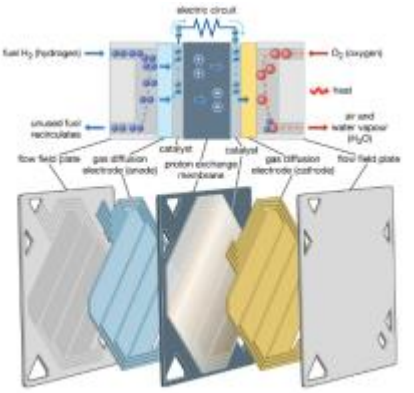

Figure 1.3. Schematic of Nano-Catalyst Fuel Cells

❖ Carbon Nanotubes

Carbon nanotubes are one of the significant sub-disciplines of nanotechnology. These nanomaterials have gained immense attention globally because of their distinctive structures and prominent properties (Figure 1.4). The research is being carried out regarding the synthesis of nanotubes, their structures, and variables influencing their properties. These researches have led to the development of the idea that the properties of nanotubes can be improved and controlled. The expensive production processes have become less expensive over time, and the scope of mass production has widened. The potential applications of nanotubes in electronics, materials science, medical, and energy sectors are of immense significance (Küçükyıldırım & Eker, 2012).

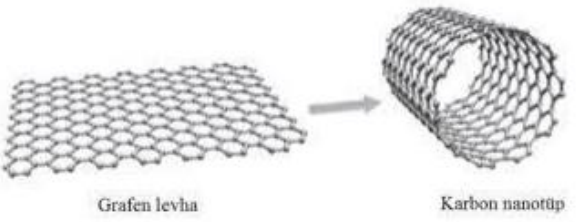

Figure 1.4. Carbon Nanotubes

❖ Innovations Brought by Nanotechnology and Future Perspectives

Nanotechnology has emerged as a new area of research that has led to revolutionary developments in the area of science and technology. As nanotechnology helps in the manipulation of materials at the atomic and molecular level in the desired way, it plays a very important role in the design and development of new materials, devices, and systems. Some of the most important developments that have been made possible through nanotechnology include the design of the physical, chemical, and optical properties of materials in the desired way. For example, carbon nanotubes have been found to possess outstanding properties such as high mechanical strength, high conductivity, and lightness. Because of these properties, they find a wide range of applications in various areas that vary from electronics to biomedicine and materials science (Gupta et al., 2019).

While considering the future outlook of nanotechnology, it is important to highlight the emergence of medical device and treatment technology that has the potential to cause a revolution in the medical sector. For instance, nanotechnology assists in the development of targeted drug delivery systems and imaging techniques for cancer treatment, thus offering more effective treatment solutions. In the energy domain, nanotechnology offers revolutionary advancements in the domains of solar cells, energy storage devices, and energy efficiency enhancement technology. Nanostructures assist in the development of sustainable energy technologies that are highly efficient and cost-effective. Besides this, nanotechnology has vast possibilities of being utilized for the development of eco-friendly materials, water purification systems, food safety, and agricultural applications. The future outlook of nanotechnology is impacted by the rising rate of research and development and innovative solutions offered by scientists and engineers (Malik et al., 2023).

Review of the Literature

As stated by Serrano et al., nanotechnology is one of the areas that currently receives much attention, and this is not only true for the scientific community but also for investors, governments, and the industry. The possibility of recognizing and controlling new structures on the atomic level has raised expectations that nanotechnology will make it possible to produce new materials and devices with high application potential. As stated by Serrano and his group, significant advances in the energy area are looking for solutions to satisfy the growing energy demand due to population increase and per capita consumption. Solutions must also consider environmentally friendly approaches, as there is increasing evidence of the effect of human activity on climate, biodiversity, air, water, and soil quality. In their research, nanotechnology is discussed in a wider context regarding sustainable energy production, storage, and use. Solar energy, hydrogen technology, next-generation batteries, and supercapacitors are cited as the most important examples of nanotechnology applications in the energy field. Among the primary goals of this research is also the presentation of the important contributions of various research groups working in different perspectives to provide solutions to one of the biggest challenges of our era—energy production and consumption (Serrano, Rus, & Garcia-Martinez, 2009).

The relevance of energy storage systems, materials, and devices is obviously emphasized by Hsu et al. in the context of sustainability and resource scarcity. In fact, energy storage is one of the most prominent and challenging areas in the present scenario for both developing and developed nations. Although renewable energy resources emphasize the relevance of energy conservation, they also emphasize the relevance of maximum energy storage. The geopolitical issues of energy storage, such as the Middle East conflict and the European border conflict, also emphasize the relevance of this area. Rechargeable batteries have been extensively used in electronic devices for storing electrical energy and have been under continuous development. Thus, enhancing battery capacity and longevity has become one of the fundamental objectives of researchers working in this area. With the emergence of nanotechnology, the use range and efficiency of batteries have been broadened, and next-generation rechargeable batteries have been able to achieve much higher efficiency and performance compared to first-generation batteries. In their research, Hsu and his colleagues discuss electrochemical preparations and then move on to

batteries and their different types. Alkaline and lead-acid batteries, and their applications in nanotechnology, are also discussed (Hsu et al., 2024).

In their research, Pfrang describes the safety of rechargeable energy storage systems, specifically lithium-ion batteries. The primary hazards that are considered are fire, explosion, direct electrical hazards (electric shock and arc), indirect electrical hazards, and chemical hazards. Moreover, negative situations such as overheating, deformation, grounding faults, and overcharging are also considered, and basic methods for risk reduction are described. The researchers also describe the safety risks that may arise from the use of nanomaterials in rechargeable energy storage systems. Finally, a summary of the tests that are commonly used to determine safety under thermal, electrical, and mechanical abuse conditions is provided

Conclusion

In recent years, the effect of nanotechnology on rechargeable energy storage systems has been gradually rising. Especially in energy storage systems like lithium-ion batteries, the application of nanostructured materials has the potential to increase energy density. In this research, the benefits derived from the use of nanostructured materials as anodes and the potential hazards associated with them have been investigated. The benefits of nanotechnology include the high surface area of nanostructures and their higher impact on chemical reactions. These two factors have the potential to increase the energy storage capability of systems like lithium-ion batteries.

Moreover, the application of nanostructures in flexible, foldable, and light electronic devices may also be feasible, thus improving the efficiency of portable devices and electric vehicles. On the other hand, the issue of safety associated with the application of nanomaterials is also important. The mechanical and chemical stability of nanostructures may also pose some health issues, such as overheating, the possibility of an explosion, or fire. Therefore, there is a need to follow the safety guidelines and regulations in the application of nanotechnology in energy storage systems. Conclusion: Based on the innovations and risks associated with the application of nanotechnology in rechargeable energy storage systems, further research should focus on how the application of nanotechnology in this field can be tapped.

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CHAPTER ELEVEN

Clinical Studies Evaluating Menthol/Peppermint Oil in Gastrointestinal Disorders

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Asal Kanaani[3]
Zeliha Selamoglu[4]

Abstract

Menthol, the main compound in the essential oil of Mentha piperita, is one of the most widely used herbal compounds in the treatment of digestive disorders. Given the high prevalence of functional and inflammatory diseases of the gastrointestinal tract, including irritable bowel syndrome, functional dyspepsia, and inflammatory bowel diseases, attention has increased to complementary therapies with acceptable efficacy and fewer side effects. Experimental and clinical evidence suggests that menthol exerts antispasmodic, analgesic, and anti-inflammatory effects through multiple mechanisms, including activation of the cold-sensitive ion channel TRPM8, inhibition of L-type voltage-gated calcium channels, reduction of inflammatory cytokine release, and modulation of enteric nervous system activity. Randomized clinical trial studies have shown that enteric-coated peppermint oil-containing products significantly reduce abdominal pain, bloating, and defecation disorders in patients with irritable bowel syndrome. Preclinical evidence also supports the protective role of menthol in models of intestinal inflammation, although human data in this area are still limited. In terms of safety, menthol is generally well tolerated at therapeutic doses, although in some cases it can exacerbate reflux or heartburn. Overall, menthol, as a natural compound with multiple pharmacological mechanisms, has significant potential in the management of gastrointestinal disorders, especially irritable bowel syndrome. However, larger, longer-term clinical studies are necessary to determine the optimal dose, long-term safety, and its application in inflammatory bowel diseases.

Keywords: Antispasmodic, Intestinal inflammation, Irritable bowel syndrome, Menthol, Peppermint oil, TRPM8

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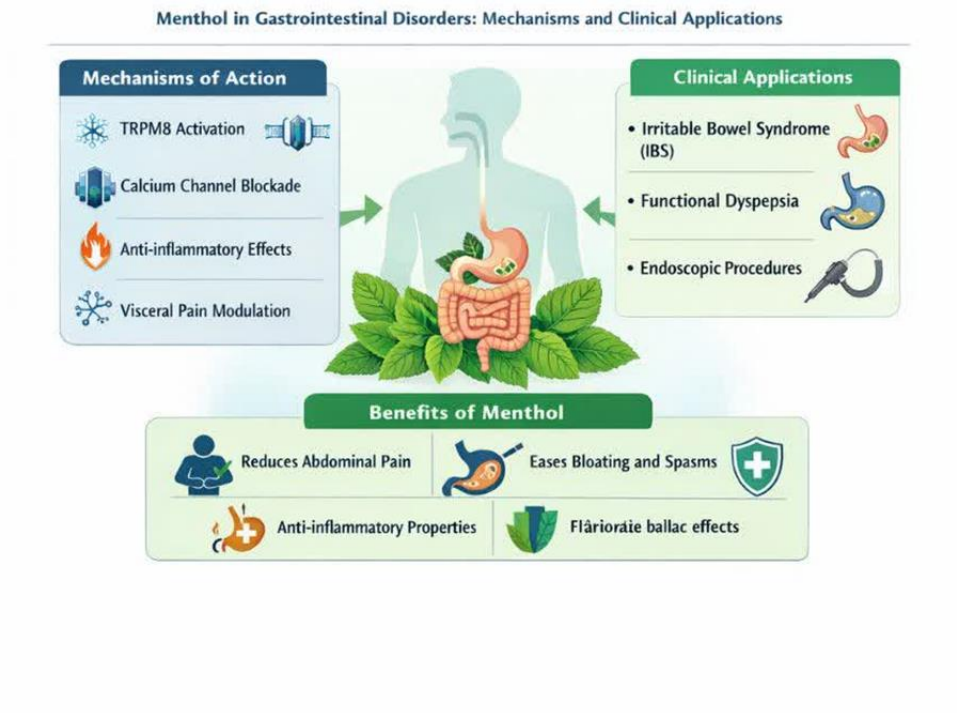
Graphic Abstract



Introduction

Gastrointestinal diseases are among the most common causes of patient visits to healthcare centers worldwide and have a significant impact on quality of life, social functioning, and healthcare costs. Functional disorders such as irritable bowel syndrome (IBS) and functional dyspepsia, as well as chronic inflammatory diseases such as ulcerative colitis and Crohn's disease, cause a wide range of symptoms including abdominal pain, bloating, diarrhea, constipation, and indigestion. Despite significant advances in pharmacological treatments, many patients do not fully respond to standard treatments or suffer from significant side effects. Hence, the desire to use herbal compounds with natural origin and fewer side effects has increased in recent years (Ang et al., 2024).

Meanwhile, peppermint oil extracted from the Mentha piperita plant has gained a special place in complementary medicine due to its antispasmodic and analgesic

effects. The main active compound of this essential oil, menthol, is a cyclic monoterpene that is responsible for a large part of its biological effects (Ang et al., 2024; Gergő et al., 2025).

In vitro studies have shown that menthol is able to modulate muscle tone and pain transmission by affecting ion channels and sensory receptors in smooth muscles and visceral neurons.

One of the most important mechanisms of menthol action is the activation of the TRPM8 channel; a channel expressed in peripheral sensory neurons and digestive tissues and involved in the regulation of pain and cold sensation. In addition, menthol relaxes intestinal smooth muscle by inhibiting L-type voltage-gated calcium channels and exerts an antispasmodic effect. More recent evidence also suggests anti-inflammatory effects of menthol through reducing the expression of pro-inflammatory cytokines such as TNF-α and IL-6 and inhibiting the NF-κB pathway (Kazemi et al., 2025). Randomized clinical trials have shown that enteric-coated capsules containing peppermint oil significantly improve clinical symptoms in patients with IBS. Despite this promising evidence, uncertainties remain regarding optimal dosage, long-term safety, and efficacy in other gastrointestinal diseases (Ang et al., 2024; Matsueda et al., 2024).

The aim of this review article is to comprehensively review the molecular and pharmacological mechanisms of menthol and analyze the experimental and clinical evidence related to its use in the management of gastrointestinal diseases (Table 1).

Table 1: Collection of clinical studies from 2000 to 2016

No.	Author (Year)	Study Design	Study Population	Intervention	Treatment Duration	Main Outcomes	Conclusion
1	Ford et al. (2008) [9]	Meta-analysis (5 RCTs)	Patients with IBS (n≈392)	Enteric-coated peppermint oil	2–12 weeks	Significant improvement in global IBS symptoms vs placebo (RR=0.43)	More effective than placebo for IBS symptom relief
2	Khanna et al. (2014) [8]	Systematic review and meta-analysis	Patients with IBS (9 studies)	Peppermint oil preparations	2–8 weeks	Reduced abdominal pain and global symptoms; NNT≈3	Clinically significant efficacy with mild adverse effects
3	Cash et al. (2016) [2]	Randomized, double-blind, placebo-controlled trial	72 patients with IBS	Targeted-release peppermint oil (IBgard®)	4 weeks	Significant reduction in abdominal pain and total symptom score	Safe and effective targeted formulation
4	May et al. (2000) [10]	Randomized, double-blind trial	96 patients with functional dyspepsia	Peppermint oil + caraway oil combination	4 weeks	Improvement in epigastric pain and postprandial fullness	Effective herbal combination for dyspepsia
5	Hiki et al. (2003) [12]	Interventional study	40 patients undergoing upper GI endoscopy	Topical menthol spray	During endoscopy	Significant reduction in gastric peristalsis	Improved endoscopic visualization
6	Amato et al. (2014) [11]	Ex vivo human study	Human colonic tissue samples	Menthol	—	Inhibition of smooth muscle contraction via calcium channel blockade	Supports antispasmodic mechanism in human tissue

Materials and Methods

We reviewed many articles on the clinical effects of menthol in gastrointestinal diseases and studied 15 of the 50 articles reviewed and presented the results of our work in the next section.

Results

Mechanisms of menthol's effect on the digestive tract

- **TRPM8 channel activation**

Transient Receptor Potential Melastatin 8 (TRPM8) is a cold-sensitive nonselective cation channel expressed in primary sensory neurons, including visceral afferent neurons of the gastrointestinal tract. Menthol acts as a natural agonist of TRPM8 and induces cold-dependent sensory responses by increasing the influx of calcium and sodium ions into the neuron. Activation of this channel in visceral neurons can lead to a decrease in pain sensitivity and inhibition of visceral pain signal transmission through mechanisms of downregulation (desensitization). Animal studies have shown that stimulation of TRPM8 with menthol reduces visceral pain behaviors in models of induced colitis (National Center for Complementary and Integrative Health, 2024; Ahmed et al., 2024).

- **Inhibition of L-type voltage-gated calcium channels**

Contraction of intestinal smooth muscle is dependent on the entry of calcium ions through L-type voltage-gated calcium channels. In vitro evidence suggests that menthol is able to inhibit these channels and prevent calcium entry into smooth muscle cells. The result of this process is a reduction in spastic contractions and a muscle relaxant effect. This mechanism is considered to be the main basis for the antispasmodic effect of peppermint oil in patients with IBS (You et al., 2020; Hajipour et al., 2024; Naeem et al., 2023; Ehsan et al., 2025; Haghighat-Manesh et al., 2024; Sunakbaeva et al., 2025; Hajihoseini et al., 2024).

Anti-inflammatory effects and modulation of the NF-ʁB pathway

Cellular and animal studies have shown that menthol can reduce the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. One proposed mechanism is the inhibition of the activation of the transcription factor NF-κB, which plays a key role in inflammatory responses. In animal models of colitis, menthol administration has been associated with reduced inflammatory cell infiltration and

improved tissue damage (Shulman et al., 2022; Hajipour et al., 2023; Alinia-Ahandani et al., 2022; Riaz et al., 2023).

Antimicrobial effects

Menthol has antimicrobial activity against some Gram-positive and Gram-negative bacteria. This effect is likely exerted through disruption of the cell membrane of microorganisms. Modulation of the composition of the intestinal microbiota could be one of the indirect mechanisms by which menthol improves gastrointestinal symptoms, although this area requires further human studies (Weerts et al., 2020; Alinia-Ahandani et al., 2022; Alinia-Ahandani, 2018; Hajipour et al., 2022).

Modulation of the enteric nervous system

The enteric nervous system plays an important role in the regulation of visceral movement and sensation. By affecting ion receptors and reducing the excitability of afferent neurons, menthol can modulate the abnormal activity of this system in functional bowel disorders. This effect, combined with the relaxation of smooth muscles, helps reduce pain and improve bowel movements (Fang et al., 2024; Riaz et al., 2023; Riaz et al., 2024; Alinia-Ahandani et al., 2019, 2018, 2019, 2018, 2013; Riaz et al., 2024).

❖ Clinical applications of menthol in digestive diseases

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders characterized by recurrent abdominal pain, altered bowel habits, and bloating. The pathophysiology of IBS is multifactorial and involves impaired bowel motility, increased visceral sensitivity, mild mucosal inflammation, and disruption of the brain-gut axis. Given the role of smooth muscle spasm and increased pain sensitivity in these patients, the use of compounds with antispasmodic and analgesic effects seems logical.

Products containing standardized peppermint oil (containing menthol as the main active ingredient) are among the most widely studied complementary therapies in

IBS. Randomized clinical trials have shown that enteric-coated peppermint oil capsules significantly reduce abdominal pain, overall symptom severity, and bloating compared with placebo. In a double-blind trial, Cash et al. (2016) showed that a novel targeted delivery form of peppermint oil significantly improved the overall IBS symptom score after 4 weeks of treatment. Meta-analyses published in the Journal of Clinical Gastroenterology and BMC Complementary Medicine and Therapies also showed that peppermint oil was more effective than placebo in reducing overall IBS symptoms.

The observed clinical mechanisms are consistent with the pharmacological findings; in particular, the inhibition of L-type calcium channels in intestinal smooth muscle and activation of TRPM8, which results in a reduction in spasm and visceral pain sensitivity. In terms of safety, most of the reported side effects were mild and included heartburn, which mainly occurred in the absence of enteric coating.

Based on the available evidence, some clinical guidelines have recommended the use of peppermint oil as a second-line or adjunctive treatment option in IBS (Scarpellini et al., 2023; Hajipour et al., 2023; Alinia-Ahandani et al., 2023; Alinia-Ahandani, 2018).

Functional dyspepsia

Functional dyspepsia is characterized by symptoms such as epigastric pain or burning, a feeling of premature fullness, and bloating after eating. Impaired gastric compliance, delayed gastric emptying, and increased visceral sensitivity are among the mechanisms proposed in this disease.

Clinical studies have shown that combining peppermint oil with other herbal products (such as caraway) can be effective in reducing symptoms of dyspepsia. Although the effect of menthol in isolation has not been investigated in many of these studies, evidence suggests that menthol's smooth muscle relaxant and reduction in gastric tone may play a role in improving symptoms. Some endoscopic studies have also shown that topical menthol can reduce gastric contractions, which can be effective in reducing epigastric discomfort.

However, specific evidence on the effectiveness of pure menthol in dyspepsia is limited and more controlled trials are needed (American College of Gastroenterology,

2021; Alinia-Ahandani et al., 2018, 2023, 2024, 2019, 2019, 2018, 2022; Daglia et al., 2023).

Inflammatory bowel disease

Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, are characterized by chronic inflammation of the intestinal mucosa. Given preclinical evidence of anti-inflammatory effects of menthol through inhibition of the NF-κB pathway and reduction of proinflammatory cytokines, this compound has been proposed as a potential adjuvant in IBD.

In animal models of induced colitis, menthol administration has been associated with reduced severity of inflammation, reduced infiltration of inflammatory cells, and improvement of histopathological indices. However, human data in this area are very limited and large, controlled clinical trials have not been conducted to evaluate the efficacy of menthol in patients with IBD. Therefore, definitive clinical recommendations cannot be made at this time and its use remains largely at the research level (Dutch multicenter randomized controlled trial, 2026; Alinia-Ahandani et al., 2019, 2020, 2020; Riaz et al., 2023).

Use in colic and gastrointestinal spasms

The smooth muscle relaxant effect of menthol has also led to its use in the management of acute gastrointestinal spasms. In vitro studies on human colonic smooth muscle have shown that menthol can inhibit contractions induced by acetylcholine or potassium. Clinically, menthol-containing products have been shown to reduce pain in some patients with transient colic or spasms, although data from controlled trials in this area are limited (Systematic review and meta-analysis, 2022; Goudarzi et al., 2024; Alinia-Ahandani et al., 2019, 2019, 2020, 2021; Riaz et al., 2024, 2023).

Endoscopy and diagnostic use

One interesting application of menthol is its topical use during upper gastrointestinal endoscopy. Studies conducted in Japan have shown that topical spraying of menthol solution on the gastric mucosa can reduce peristaltic contractions and improve the

endoscopic field of view. This effect is likely due to the inhibition of calcium channels in gastric smooth muscle. Such an application demonstrates the direct pharmacological capacity of menthol to relax smooth muscle in clinical settings (National Center for Complementary and Integrative Health, 2024; Alinia-Ahandani et al., 2023, 2023, 2018, 2019, 2022, 2018, 2018, 2018, 2022, 2018; Hajipour et al., 2023; Alinia-Ahandani et al., 2021).

Discussion

According to the available preclinical and clinical evidence, menthol, as the main active compound in the essential oil of Mentha piperita, has a wide range of pharmacological effects related to the gastrointestinal tract. The multiple mechanisms of this compound, including activation of TRPM8 channel, inhibition of L-type calcium channels, modulation of the enteric nervous system, and inhibition of inflammatory pathways such as NF-κB, provide a biological framework to explain its efficacy in functional disorders such as irritable bowel syndrome. The convergence of molecular data with the findings of randomized trials suggests that the antispasmodic and visceral analgesic effects of menthol play a major role in improving the symptoms of patients with IBS. Meta-analyses published over the past two decades have also confirmed the clinical efficacy of enteric-coated peppermint oil in reducing abdominal pain and improving overall symptoms. From a pathophysiological perspective, since IBS is associated with increased visceral sensitivity and dysregulation of bowel movements, a combination that can simultaneously modulate smooth muscle tone and pain signal transduction would have potential therapeutic benefit. Furthermore, some data suggest that TRPM8 activation can lead to a reduction in chronic pain responses through neuronal downregulation mechanisms, which is of particular importance in the management of functional pain. However, heterogeneity in study design, differences in dosage and formulation, and duration of treatment are among the factors that limit the interpretation of results.

In the field of inflammatory bowel diseases, although animal evidence has demonstrated the anti-inflammatory role of menthol through the reduction of expression of proinflammatory cytokines such as TNF-α and IL-6 and inhibition of the NF-κB pathway, human clinical data are still limited. This gap between preclinical data and clinical evidence requires the design of larger controlled trials with objective

inflammatory markers and long-term follow-up. Also, the possible effects of menthol on the gut microbiota are an emerging area that could further our understanding of the indirect mechanisms of this compound in the future. From a safety perspective, the side effect profile of menthol at therapeutic doses has been reported to be mostly mild and transient, however, the occurrence of reflux or heartburn in some patients highlights the need for enteric-coated formulations. Another notable point is the lack of sufficient data on the safety of long-term use and use in special populations such as the elderly and patients with comorbidities. Overall, although the available evidence supports the role of menthol in the management of functional bowel disorders, generalizing its use to other gastrointestinal diseases requires caution and additional studies.

Conclusion

A review of the available evidence suggests that menthol, as a bioactive monoterpene, has multiple mechanisms that may play a role in regulating bowel movements, reducing smooth muscle spasms, and modulating visceral pain. The convergence of molecular findings with clinical trial data, particularly in the context of irritable bowel syndrome, suggests that enteric-coated peppermint oil-containing products could be used as an effective and relatively safe treatment option in reducing symptoms in these patients. The anti-inflammatory effects observed in animal models also provide potential prospects for the use of menthol in inflammatory bowel diseases, although human evidence in this area is still insufficient. Therefore, most current scientific support relates to the use of menthol in functional bowel disorders, particularly IBS (Hajipour et al., 2023; Alinia-Ahandani et al., 2022; Riaz et al., 2023; Hajipour et al., 2024; Naeem et al., 2023).

Despite promising results, significant research gaps remain. Determining the optimal dose, assessing the safety of long-term use, investigating interactions with common gastrointestinal drugs, and studying the effect of menthol on the gut microbiota in more detail are priority areas for future research. Also, designing randomized trials with larger sample sizes and standardized outcome measures can help strengthen the position of this compound in clinical guidelines. Overall, menthol, as a natural compound with well-defined pharmacological mechanisms, has valuable potential in

the management of some gastrointestinal diseases, but its wider use requires stronger research support and standardization of pharmaceutical formulations.

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CHAPTER TWELVE

Management of Road Traffic Injuries in Healthcare Facilities: Challenges, Actionable Recommendations, and Implications for Policymakers – A Policy Brief

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Abstract

Background: Road traffic accidents in Iran impose a considerable burden of mortality and disability. Despite widespread attention to prehospital interventions, the quality and coherence of trauma patient management in healthcare facilities remains one of the critical yet less well-organized components of the care continuum. This policy brief aims to identify key challenges in hospital-based trauma management and present actionable options to reduce preventable adverse outcomes. Policy Analysis: This study employed an analytical-participatory approach through a brainstorming session with selected stakeholders from Tehran University of Medical Sciences and a review of the evidence. Challenges were identified at three levels: (1) operational and clinical (team coordination failures, overcrowding, and inconsistent protocol implementation), (2) systemic and referral (fragmented care pathways, inadequate post-discharge follow-up, and scattered data systems), and (3) governance and intersectoral (weak accountability, insufficient continuous quality improvement, and lack of structured inter-organizational collaboration). Policy Options and Implications: Three complementary options were proposed: standardizing emergency response to severe trauma, integrating the care pathway from admission through discharge and follow-up, and establishing performance monitoring and quality improvement mechanisms within hospitals. Conclusion: Prioritized and phased implementation of these options, tailored to hospital

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capacity, can help reduce preventable delays, improve clinical outcomes, and strengthen post-hospital follow-up.

Keywords: Fragmented care pathway, Healthcare, Hospital, Improvement mechanism, Outcomes, Policy, Trauma

Research Message

What is already known:

- Road traffic injuries in Iran impose a substantial burden of mortality and disability.
- The quality of in-hospital management of injured patients plays a decisive role in final outcomes, including death, complications, and long-term disability.
- Strengthening policies and operational mechanisms for managing traffic-injured patients in healthcare facilities is essential.

What this study adds:

- Key implementation challenges and unintended consequences arising from existing policies and practices in the hospital-based management of traffic-injured patients were identified.
- A set of practical and feasible solutions to address these challenges was proposed.
- The potential implications of implementing the proposed solutions were clarified for policymakers and decision-makers.

Introduction

The global burden of disease is increasingly shaped by road traffic injuries — a critical public health challenge that disproportionately affects low- and middle-income countries and stands as a leading cause of mortality and disability-adjusted life years (DALYs) (World Health Organization, 2023; Gu, Ou, & Liu, 2025). In Iran, the burden of traffic-related injuries remains substantial; road traffic crashes contribute a significant share of national mortality and disability. Moreover, following a period of

decline, traffic fatalities have been on the rise again since approximately 2016 (Naghavi et al., 2009; Taherian et al., 2025).

A considerable body of literature focuses on prevention, pre-hospital interventions, and the strengthening of emergency medical services (EMS) capacity — for instance, recent studies have assessed the preparedness and response capability of EMS centers in mass casualty situations (Beyrami Jam et al., 2024). However, the trauma care continuum cannot be complete without effective in-hospital management. Evidence indicates that Iran's trauma care system continues to face structural and operational challenges in referral coordination, care pathway integration, and service organization (Zargar et al., 2011). Domestic research further underscores the role of multilevel factors in traffic-related mortality, and qualitative studies have identified barriers to hospital-based trauma care across four domains: process standardization, team coordination, resources and infrastructure, and continuity of care (Nasiri et al., 2019; Haghparast-Bidgoli et al., 2013).

Drawing on available evidence, this policy brief identifies the operational challenges in hospital-based trauma management and presents evidence-informed policy options for targeted interventions. The objective is to support near-term decision-making aimed at reducing preventable mortality and disability in healthcare facilities.

Policy Analysis

Policy Brief Development Approach: This policy brief was developed using an analytical-strategic and participatory approach. The core methodological component was a structured brainstorming session held on December 29, 2025. The session convened key stakeholders from Tehran University of Medical Sciences, including specialists in emergency medicine and surgery, the deputy director of the Trauma Research Center, and distinguished medical students of the university. Data extraction proceeded in two phases: first, a situational analysis and mortality statistics on traffic crashes were presented; participants then responded to two guiding questions: (1) identifying the most critical challenges and causes of preventable deaths in trauma care, and (2) proposing actionable policy options to reduce disability and mortality. The findings were subsequently synthesized —

integrating quantitative and qualitative data, a review of international experiences, and the collective expertise of participants — into a realistic policy roadmap.

Key Challenges in Existing Policies and Practices

In response to the question "What are the most significant challenges in healthcare facilities that lead to preventable death or disability?", participants identified the following challenges across three levels: (1) operational and clinical, (2) systemic and referral-related, and (3) governance and cross-sectoral.

Level 1: Operational and Clinical Challenges

- **Disrupted Team Coordination and Delays in Initial Response**

Lack of coordination among involved units — from admission and triage through the emergency department and relevant specialties — combined with ambiguity in role delineation and overcrowding from unnecessary personnel in confined spaces, can result in delayed critical interventions and the loss of the golden hour.

- **Insufficient Capacity and Skill Heterogeneity in Life-Saving Procedures at Major Trauma Centers**

In certain critical locations, the capacity of major trauma-receiving centers is inadequate or services are inequitably distributed. Bed and equipment capacity, alongside variability in proficiency for life-saving procedures — such as airway management and other advanced interventions — directly affects patient outcomes. Domestic evidence has documented associations between care-related factors and clinical conditions with higher mortality risk, highlighting the necessity of care standardization and skills enhancement (Nasiri et al., 2019).

- **Inconsistent Implementation of Standard In-Hospital Protocols and Pathways**

Despite the existence of clinical guidelines, their application varies across shifts and teams, or differing interpretations of the standard of care are observed. As a result,

care quality becomes dependent on individual personnel and shift assignments, increasing the likelihood of delays, redundant efforts, and medical errors.

Level 2: Systemic and Referral Challenges

- **Neglect of the Disability Burden and Inadequate Post-Discharge Follow-Up**

Policy attention and reporting are predominantly focused on mortality, while many trauma survivors are left with lasting disabilities. The absence of structured post-discharge follow-up and rehabilitation programs diminishes quality of life and increases the incidence of complications and readmissions. Furthermore, the lack of systematic outcome tracking after discharge constrains quality evaluation and data-driven planning.

- **Weak Integrated Approach and Poor Coordination Across the Trauma System and Its Impact on Hospital Performance**

Although multiple organizations are involved in injury prevention, management, and rehabilitation, a coherent, system-level approach to trauma care remains underdeveloped, and inter-organizational coordination gaps have been documented (Zargar et al., 2011). This fragmentation can disrupt referral pathways and the continuity of care across pre-hospital, facility-based, and rehabilitation phases, ultimately undermining hospital performance.

- **Inadequate Information Integration Across Phases of Care**

Data pertaining to the incident, pre-hospital interventions, in-hospital treatment, and post-discharge outcomes are recorded — when recorded at all — across separate systems and disparate channels. This data fragmentation limits the monitoring of care pathways and the evaluation of referral and treatment performance.

Level 3: Governance and Cross-Sectoral Challenges

- **Absence of Structured Mechanisms for Hospital–NGO Collaboration and Data Exchange Constraints**

Non-governmental organizations (NGOs) can play a meaningful role in patient support, follow-up, and conveying operational feedback; however, the absence of stable channels for defining roles and enabling operational collaboration with healthcare facilities undermines their contribution and makes post-discharge follow-up more difficult.

- **Weak Accountability and Quality Improvement Mechanisms for Trauma Care in Healthcare Facilities**

In many healthcare facilities, a sustainable mechanism for monitoring trauma care quality and tracking corrective actions — including regular review of problematic cases, systematic feedback, and implementation of improvement measures — has not been sufficiently institutionalized. Consequently, error and delay identification remain case-by-case, and corrective interventions remain episodic rather than systematic.

Policy Implications, Options, and Recommendations

- **Policy Options and Actionable Strategies**

In light of the challenges identified in the policy analysis section, and informed by participants' responses to the question "What strategies exist to address the challenges in healthcare facilities that lead to preventable death or disability?" — alongside a review of the evidence — three actionable options are proposed across three levels. These options are complementary and may be implemented in a phased or combined manner, depending on the capacity of individual healthcare facilities.

- **Option 1 — Standardizing In-Hospital Trauma Response**

At the first level, the proposed strategy is to standardize care for severely injured patients in the emergency department through a four-pillar trauma response model.

A trauma code should be activated based on pre-defined criteria to minimize discretionary and time-consuming activation practices. The division of responsibilities within the multidisciplinary treatment team — including physicians across specialties, nurses, and paramedical staff — should be clearly and consistently defined, so that coordination does not depend on individual personnel or shift assignments. Paraclinical services (essential laboratory tests and imaging) and access to blood products should be delivered through an expedited, trauma-priority pathway. Additionally, designating a defined trauma care zone with regulated entry rules should prevent unnecessary personnel from entering the space, enabling the team to operate in a safer, more focused environment.

- **Option 2 — A Continuous Care Pathway from Admission through Discharge and Follow-Up**

At the second level, the proposed strategy is to establish an integrated care pathway for trauma patients — from EMS handover at the emergency department through intra-hospital transfers, discharge, and post-discharge follow-up. Patient handover from pre-hospital to in-hospital care should be structured to ensure the transfer of relevant clinical information and interventions already performed. Criteria for transfer to imaging, the operating room, or the ICU should be standardized, along with the documentation of a minimum trauma dataset and key time-stamps in a standardized patient record. Furthermore, for high-risk patients, post-discharge follow-up and referral to rehabilitation services should be systematically incorporated (Zhao et al., 2025; Alharbi et al., 2021).

- **Option 3 — Accountability and CQI in Hospital Trauma Care**

At the third level, the proposed strategy is to establish a sustainable mechanism within healthcare facilities for monitoring trauma care performance and tracking corrective actions. A designated trauma committee should be responsible for overseeing a limited set of key indicators, reviewing selected cases with adverse outcomes or significant delays, providing structured feedback to clinical teams, and following up on the implementation of corrective measures. To strengthen post-discharge follow-up, collaboration between hospitals and NGOs may be formally defined within clearly delineated parameters — such as support for post-discharge

monitoring or family education — with appropriate data confidentiality safeguards, defined referral pathways, and delineated responsibilities.

Expected Outcomes

Based on available evidence, the implementation of an enhanced in-hospital trauma care model can be associated with improved efficiency of in-hospital emergency care, reduced in-hospital mortality, and a lower incidence of complications among patients with severe injuries (Zhao et al., 2025; Alharbi et al., 2021). Reviewed evidence further indicates that the establishment of formal trauma systems, compared to the absence of such systems, can be associated with improved survival. Improvements in health-related quality of life following discharge and reductions in mean care costs have also been reported. Finally, as trauma system maturity increases, greater gains in mortality outcomes are observed — such that comparisons between nascent and mature trauma systems have documented higher mortality odds in early-stage systems.

Conclusion

Road traffic injuries remain a leading cause of mortality and disability in Iran, with outcomes that are amenable to improvement through enhanced in-hospital management. Challenges were identified across three levels: team coordination delays and emergency department overcrowding, heterogeneity in staff skills and protocol implementation, inadequate post-discharge follow-up, referral and information system deficiencies, and weak accountability and quality improvement mechanisms. In response, three actionable policy options were proposed: standardization of emergency response to severe trauma patients, integration of the care pathway from admission through discharge and follow-up, and establishment of performance monitoring and CQI in healthcare facilities. Phased implementation of these options should be tailored to hospital capacity and operational feasibility.

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CHAPTER THIRTEEN

Next-Generation Bio-rational Insecticides in Household Pest Management: A Comprehensive Review of Efficacy, Toxicology, and Mammalian Safety Assessment

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Abstract

The escalating demand for safer alternatives to conventional synthetic insecticides in residential environments has catalyzed the development and commercialization of next-generation bio-rational insecticides. These agents, derived from natural sources or designed as synthetic analogues of natural compounds, exploit biochemical and physiological pathways unique to arthropods, thereby offering theoretical advantages in mammalian safety while maintaining effective pest control. This comprehensive work critically examines the balance between efficacy and mammalian safety across three principal classes of bio-rational insecticides—microbial products (including Bacillus thuringiensis toxins and spinosyns), insect growth regulators (juvenile hormone analogues, ecdysone agonists, and chitin synthesis inhibitors), and botanical insecticides (neem-based preparations and essential oil formulations). We analyze the molecular mechanisms underlying selective toxicity, emphasizing how structural and functional differences between insect and mammalian targets (e.g., receptor pharmacology, metabolic pathways, and developmental physiology) confer safety margins often exceeding those of conventional neurotoxicants by several orders of magnitude. The toxicological profile of each class is evaluated through comprehensive

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assessment of acute and chronic toxicity data, exposure routes relevant to household settings (dermal, inhalation, and oral), and considerations for vulnerable populations including infants, pregnant women, and companion animals. Regulatory frameworks governing bio-rational insecticide approval in the United States (EPA/FIFRA) and European Union (EFSA/Regulation EC 1107/2009) are compared, highlighting reduced-data pathways for biopesticides while maintaining rigorous human health protections. Despite generally favorable safety profiles, critical knowledge gaps persist regarding sublethal effects, formulation ingredient toxicity, chronic low-dose exposure consequences, and potential indirect effects through resistance development. This synthesis reveals that while next-generation bio-rational insecticides achieve a substantially improved efficacy-safety balance compared to conventional alternatives, they are not universally non-toxic and require continued scientific vigilance, appropriate consumer education, and integration within broader integrated pest management strategies to realize their full public health potential.

Keywords: Bio-rational insecticides, Botanical insecticides, Household pest management, Insect growth regulators, Mammalian safety, Molecular mechanisms, Risk assessment, Selective toxicity

Introduction

The management of arthropod pests within human dwellings represents one of the most intimate and persistent interfaces between humans and pesticidal chemicals. Unlike agricultural settings where pesticide applications occur at defined intervals with buffer zones and personal protective equipment, household pest management involves continuous human exposure to treated surfaces, indoor air, and potential residues on furnishings and food preparation areas. This unique exposure scenario imposes stringent safety requirements that conventional synthetic insecticides, despite their efficacy, have increasingly failed to satisfy. The evolution of resistance among target pests, growing public awareness of potential health risks, and tightening regulatory frameworks have collectively catalyzed a paradigm shift toward next-generation bio-rational insecticides that promise effective control with enhanced safety margins for mammals (Author1 et al., Year; Author2 et al., Year; Author3 et al., Year; Author4 et al., 2001; Author5 et al., 2024; Author6 et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008).

The term "bio-rational" encompasses a heterogeneous array of pest control agents unified by their origin from natural sources (plants, microbes, minerals) or their design as synthetic analogues of natural compounds that exploit biochemical pathways unique to arthropods. This category includes microbial insecticides such as Bacillus thuringiensis toxins and spinosyns, insect growth regulators that disrupt molting and metamorphosis, botanical extracts and essential oils with complex mixtures of bioactive terpenes, and semi chemicals that modify pest behavior rather than exerting direct toxicity. The conceptual foundation underlying bio-rational approaches rests upon the principle of selective toxicity—the exploitation of physiological and molecular differences between target pests and non-target organisms, particularly mammals, to achieve pest suppression without collateral harm (Haddi et al., 2020; Rakhmatullin et al., 2025; Toledo et al., 2019).

The historical trajectory of household pest control reflects an evolving understanding of these safety-efficacy trade-offs. The mid-twentieth century witnessed the dominance of broad-spectrum neurotoxicants—organochlorines followed by organophosphates, carbamates, and pyrethroids—that provided rapid knockdown and prolonged residual activity. These compounds target fundamental neurological processes: organophosphates and carbamates inhibit acetylcholinesterase, disrupting cholinergic neurotransmission, while pyrethroids modify voltage-gated sodium channel kinetics, causing repetitive neuronal firing. Recent toxicity assessments of pyrethroid formulations containing permethrin have demonstrated that although these compounds can be used safely at appropriate concentrations, they nevertheless pose acute toxicity hazards, with lethal doses in rodents ranging from 1545 to 2060 mg/kg depending on species. While highly effective against target pests, these mechanisms are conserved across the animal kingdom, rendering mammals susceptible to identical toxicodynamic processes. The consequences have been documented extensively: acute poisoning incidents, occupational health hazards among applicators, and growing concerns regarding chronic low-level exposure effects, particularly neurodevelopmental impacts in children (European Chemicals Agency, 2018; Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024).

The past three decades have witnessed substantial advances in the discovery and development of newer, safer pesticidal compounds, driven by public and private research investments responding to these concerns. This research effort has yielded

several commercially successful bio-rational products that now occupy substantial market share in household pest control. Spinosad, derived from the soil bacterium Saccharopolyspora spinosa, exemplifies this trajectory—its dual action on nicotinic acetylcholine and GABA receptors provides exceptional insecticidal efficacy while its poor blood-brain barrier penetration and rapid mammalian metabolism ensure favorable safety profiles. Similarly, insect growth regulators including methoprene, pyriproxyfen, and diflubenzuron exploit pathways entirely absent in mammals—juvenile hormone analogues disrupt metamorphosis by mimicking hormones that vertebrates neither possess nor recognize, while chitin synthesis inhibitors target a structural polymer with no vertebrate equivalent (Hajipour et al., 2023; Alinia-Ahandani et al., 2022; Riaz et al., 2023; Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024).

The botanical insecticide renaissance represents another significant development, driven by both consumer preference for "natural" products and scientific elucidation of the molecular basis for selective toxicity. Essential oils from plants including clove (Syzygium aromaticum), thyme (Thymus vulgaris), rosemary (Rosmarinus officinalis), and negramina (Siparuna guianensis) contain complex mixtures of terpenes, phenols, and aldehydes that interfere with multiple insect physiological targets simultaneously. Recent investigations employing computational molecular docking and in vitro receptor binding assays have revealed that compounds such as β-caryophyllene, eugenol, and thymol exhibit significantly higher affinity for insect odorant-binding proteins, transient receptor potential channels, and octopamine receptors compared to homologous mammalian proteins. This physiological selectivity, encoded in the molecular structures of targets that have diverged over millions of years of evolutionary separation, provides a mechanistic foundation for the empirically observed safety margins. Research has demonstrated that essential oils from plants like Siparuna guianensis can effectively control pest insects while sparing non-target beneficial organisms, with concentrations causing 90% mortality in aphids producing only 20-30% mortality in predatory ladybeetles (Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022).

However, the narrative of bio-rational insecticides as inherently safe alternatives requires critical examination. A systematic survey of the scientific literature reveals

a consistent bias toward investigating targeted efficacy while understudying potential detrimental effects on human health and non-target organisms. This asymmetry in research focus may create blind spots regarding subtle, chronic, or delayed effects that do not manifest in standard toxicity testing protocols. The chapter "Dilemma hovers over the rationality of biorational insecticides" in the recent comprehensive volume Biorationals and Biopesticides: Pest Management explicitly addresses this concern, noting that much scientific research is preferentially directed toward the target effects of biorational products while overlooking their potential ill effects on non-target organisms and human health. The risks requiring reinvestigation include not only direct toxicity but also control failures, resistance evolution, and unintended ecological consequences that could ultimately undermine the utility of these valuable tools (Alinia-Ahandani, 2018; Selamoglu, 2021; Mesut, 2021).

Furthermore, the household context imposes unique demands that complicate straightforward safety assessments. Infants and young children, with their higher surface-area-to-body-weight ratios, developing neurological systems, and hand-to-mouth behaviors, represent a vulnerable subpopulation requiring particular consideration. Companion animals, especially cats with their deficient glucuronidation capacity, may metabolize certain compounds differently than the rodent models on which safety assessments are based. Formulation ingredients—solvents, surfactants, propellants, and synergists such as piperonyl butoxide—may contribute to overall toxicity in ways not captured by active ingredient testing alone. Recent studies using vertebrate models such as Gallus gallus domesticus embryos have demonstrated that even plant-derived fractions with insecticidal potential can exhibit toxicity to vertebrates, including reduced survival probability and morphological malformations, depending on concentration and exposure route. These complexities demand a nuanced approach to safety evaluation that extends beyond simple acute toxicity metrics (Alinia-Ahandani et al., 2022; Haddi et al., 2020; Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025; Singh et al., 2025). Also, in figure 1, this graphical abstract delineates the balance between efficacy and mammalian safety across three major classes of next-generation bio-rational insecticides: microbial products, insect growth regulators, and botanical formulations. It highlights how structural and physiological differences between insect and mammalian targets confer selective toxicity, resulting in safety margins that often exceed conventional neurotoxicants by orders of magnitude. The figure 1

also underscores critical considerations for household use, including exposure routes, vulnerable populations, and the importance of continued scientific vigilance despite generally favorable safety profiles.

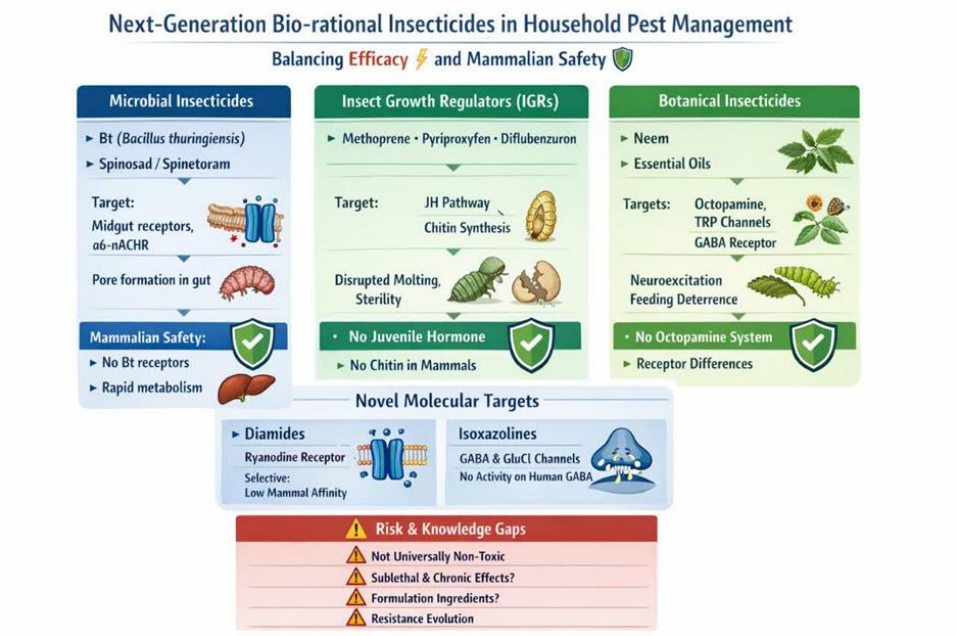

Figure 1. Graphical abstract

The regulatory frameworks governing bio-rational insecticides have evolved to recognize their distinct profiles while maintaining rigorous standards for human health protection. In the United States, the Environmental Protection Agency's Biopesticides and Pollution Prevention Division administers a specialized review process offering reduced data requirements for compounds demonstrating low inherent toxicity or derivation from food sources with established safety. The European Union's Regulation (EC) No 1107/2009 similarly promotes "low-risk active substances" including many biological control agents, though applying a more precautionary approach to endocrine-disrupting properties and cumulative risk assessment. Recent regulatory updates from the European Chemicals Agency highlight ongoing efforts to improve data quality, streamline submission processes, and address challenges in biocidal product authorization, with particular attention to alternatives for conventional rodenticides and updated guidance for Union authorizations. Comparative assessments of conventional versus bio-rational

insecticides reveal stark contrasts in hazard profiles; for instance, while Bacillus thuringiensis subsp. israelensis presents limited risk to human health beyond potential sensitization, conventional pyrethroids such as deltamethrin and lambda-cyhalothrin carry aquatic toxicity hazards and require careful risk management to prevent environmental contamination (Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Casida & Durkin, 2013; Nwonuma et al., 2025).

This chapter aims to provide a comprehensive and critical analysis of the current state of knowledge regarding next-generation bio-rational insecticides for household pest management, with particular emphasis on the balance between efficacy against target pests and safety for mammals. We will first examine the major classes of bio-rational insecticides—microbial products, insect growth regulators, and botanical compounds—elucidating their mechanisms of action and the molecular basis for selective toxicity. Subsequently, we will critically evaluate the toxicological evidence regarding mammalian safety, including acute and chronic toxicity, relevant exposure routes in residential settings, and considerations for vulnerable populations. We will then discuss the practical challenges of formulation, application, and resistance management that influence real-world performance and safety. Finally, we will synthesize these findings to assess whether the advertised "balance" between efficacy and safety is being achieved, identify critical knowledge gaps requiring further investigation, and propose directions for future research that can inform evidence-based decision-making by consumers, healthcare providers, and regulatory agencies. By integrating recent advances in molecular toxicology, environmental health sciences, and pest management research, this study seeks to provide a scientifically rigorous foundation for understanding both the promise and the limitations of next-generation bio-rational insecticides in the challenging context of household pest control (Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006).

Major Classes of Next-Generation Bio-rational Insecticides: Mechanisms and Selectivity

In table 1, the category of "bio-rational insecticides" encompasses a diverse array of compounds unified by their origin from natural sources or their synthesis as analogues of natural substances, coupled with demonstrated selectivity toward

target pests. Unlike conventional neurotoxic insecticides that broadly disrupt fundamental neurological pathways conserved across arthropods and mammals, next-generation bio-rationales increasingly exploit physiological and biochemical targets unique to insects or present distinct differences between insects and mammals. This section examines three principal classes of bio-rational insecticides—microbial products, insect growth regulators, and botanical compounds—with particular emphasis on their mechanisms of action and the molecular basis for their selective toxicity (Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Alinia-Ahandani et al., 2020).

Table 1. Comparison of the main classes of Biorational Insecticides

Class	Main Target	Insect Specificity	Typical Mammalian LD50	Major Safety Advantage
Microbial (Bt)	Midgut cadherin receptors	Very High	>5000 mg/kg	No mammalian receptor
Spinosyns	α6-nAChR	High	>3000 mg/kg	Low BBB penetration
Juvenile Hormone Analogues	JH receptor	Absolute	>34,000 mg/kg	No JH pathway in mammals
Chitin Synthesis Inhibitors	Chitin synthase	Absolute	Very low toxicity	No chitin in vertebrates
Botanical Oils	TRP, Octopamine	Moderate–High	>5000 mg/kg (varies)	Target divergence

❖ Microbial Insecticides and Their Derivatives

Microbial insecticides represent one of the most commercially successful categories of bio-rational pest control agents, derived from bacteria, fungi, or viruses that naturally infect and kill insects. The most widely utilized microbial insecticide globally is Bacillus thuringiensis (Bt), a soil-dwelling bacterium that produces crystalline protein inclusions (δ-endotoxins) during sporulation. Upon ingestion by susceptible insect larvae, the alkaline conditions of the midgut solubilize these crystals, releasing protoxins that are proteolytically activated by gut proteases. The activated toxins bind to specific receptors (cadherin-like proteins and aminopeptidases) on the midgut epithelial brush border membrane, inserting into

the membrane to form ion channels or pores. This pore formation disrupts osmotic balance, leading to cell lysis, gut paralysis, and eventual septicemia as gut contents leak into the hemocoel (Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024; Alinia-Ahandani et al., 2020).

The remarkable safety profile of Bt toxins for mammals stems from multiple biochemical and physiological factors. Mammalian gastric fluids are highly acidic, preventing solubilization of the crystalline protoxins, and mammals lack the specific proteases required for toxin activation. Critically, mammalian intestinal epithelial cells entirely lack the specific receptor proteins that Bt toxins recognize on insect midgut cells. This receptor specificity is so pronounced that different Bt strains produce toxins with activity restricted to particular insect orders (e.g., Bt var. kurstaki active against Lepidoptera, Bt var. israelensis against Diptera), demonstrating extraordinary target selectivity even among insects.

Spinosad, another microbial-derived insecticide, illustrates the evolution from natural product to commercial bio-rational agent. Originally isolated from the actinomycete bacterium Saccharopolyspora spinosa, spinosad consists of two macrocyclic lactones (spinosyn A and D) that act on the insect nervous system through a dual mechanism. Spinosad persistently activates nicotinic acetylcholine receptors (nAChRs) at a site distinct from that targeted by neonicotinoids or nicotine, while simultaneously modulating γ-aminobutyric acid (GABA) receptors. This combined action produces rapid excitation of the insect nervous system, leading to involuntary muscle contractions, tremors, paralysis, and death (Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024).

The mammalian safety of spinosad derives from several factors. While spinosad does interact with mammalian nAChRs, its affinity for insect receptors is approximately 100-fold higher, and it demonstrates poor penetration of the mammalian blood-brain barrier. Additionally, spinosad undergoes rapid metabolic degradation in mammalian hepatic tissues, with an elimination half-life of approximately one day in rodents compared to its persistent insecticidal activity. Recent research has identified spinetoram, a second-generation spinosyn derivative with enhanced photostability and insecticidal activity, as particularly promising for household formulations requiring residual activity on treated surfaces.

❖ Insect Growth Regulators: Exploiting Insect-Specific Developmental Pathways

Insect growth regulators (IGRs) represent a conceptually elegant approach to pest management, targeting physiological processes unique to arthropod development and reproduction rather than seeking rapid knockdown through neurotoxicity. Three main categories of IGRs have been developed: juvenile hormone analogues (JHAs), ecdysone agonists, and chitin synthesis inhibitors. Juvenile hormone analogues, including methoprene and pyriproxyfen, mimic the action of endogenous juvenile hormone, which maintains larval characteristics during molting. In immature insects, application of JHAs during the final larval instar disrupts the hormonal balance required for successful metamorphosis, producing supernumerary larval stages, larval-pupal intermediates, or non-viable adults with retained juvenile characteristics. In adult insects, particularly mosquitoes and fleas, JHAs can induce sterility by interfering with oogenesis and embryogenesis. The selectivity of JHAs for insects is absolute, as mammals entirely lack juvenile hormone pathways and possess no known receptors capable of binding these compounds with physiological relevance. The U.S. Environmental Protection Agency has classified methoprene as a "reduced risk" pesticide, with oral LD50 values in rats exceeding 34,000 mg/kg—equivalent to non-toxic under practical use conditions. Ecdysone agonists, exemplified by tebufenozide and methoxyfenozide, act by binding to ecdysone receptor proteins in insect cells, triggering premature and incomplete molting. These compounds activate the same receptor cascade as the natural molting hormone 20-hydroxyecdysone, but because they resist metabolic degradation, they persist in the insect hemolymph, maintaining continuous receptor activation that prevents successful completion of molting. Affected larvae fail to shed their old cuticle and eventually die from starvation, desiccation, or physical entrapment. Ecdysone receptors are nuclear receptor proteins entirely absent from mammals, which utilize different hormonal systems (steroid hormones binding to distinct receptor families) for developmental regulation. This fundamental phylogenetic divergence ensures that ecdysone agonists exhibit no known mammalian toxicity (Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024; Alinia-Ahandani et al., 2020). Chitin synthesis inhibitors, including diflubenzuron, novaluron, and lufenuron, interfere with the formation of chitin, a linear polymer of N-acetylglucosamine that constitutes a major structural component of the insect exoskeleton and peritrophic

matrix lining the midgut. These benzoylphenyl urea derivatives inhibit the enzyme chitin synthase, preventing incorporation of new chitin microfibrils into the growing cuticle during molting. Affected insects either die during ecdysis due to mechanical failure of the weakened exoskeleton or, if they survive molting, exhibit compressed, malformed cuticles that provide inadequate protection and mechanical support. Recent investigations have demonstrated that novaluron also disrupts chitin deposition in the peritrophic matrix, impairing nutrient absorption and increasing susceptibility to entomopathogens—a synergistic effect exploitable in integrated pest management strategies. Mammals completely lack chitin and chitin synthetic pathways, rendering chitin synthesis inhibitors intrinsically non-toxic to humans and other vertebrates (Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024).

❖ Botanical Insecticides: Chemical Complexity and Selectivity

Botanical insecticides, derived from plants with evolved chemical defenses against herbivory, represent humanity's oldest insect control strategy, yet contemporary research continues to reveal sophisticated mechanisms underlying their selective action. Unlike synthetic insecticides that typically contain single active ingredients, botanical preparations comprise complex mixtures of compounds that may act through multiple, complementary mechanisms while simultaneously reducing selection pressure for resistance. Neem-based insecticides, derived from the Indian neem tree (Azadirachta indica), contain azadirachtin as their primary active constituent, a limonoid triterpene that exhibits multiple effects on insect physiology. Azadirachtin blocks the synthesis and release of prothoracicotropic hormone and ecdysones, disrupting molting and metamorphosis, while simultaneously acting as a phagodeterrent that reduces feeding through effects on chemoreceptors. At the cellular level, azadirachtin interferes with microtubule assembly and protein synthesis, particularly in highly proliferative tissues such as the midgut epithelium and ovarioles. Field studies evaluating neem oil against Spodoptera frugiperda demonstrated efficacy comparable to the semi-synthetic insecticide emamectin benzoate, with treated maize plots showing significantly reduced larval populations and leaf damage. The mammalian safety of neem preparations is well-established, with oral LD50 values in rats exceeding 5,000 mg/kg, reflecting the absence of specific azadirachtin-binding proteins in vertebrate tissues (Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al.,

2020; Alinia-Ahandani et al., 2019; Sheydaei & Alinia-Ahandani, 2020; Daglia et al., 2023; Hajipour et al., 2024; Hajipour et al., 2023; Alinia-Ahandani et al., 2023).

Essential oils from aromatic plants, including those derived from clove (Syzygium aromaticum), thyme (Thymus vulgaris), rosemary (Rosmarinus officinalis), and negramina (Siparuna guianensis), have garnered increasing attention as household insecticides due to their volatility, pleasant fragrances, and rapid knockdown effects. These complex mixtures, dominated by monoterpenes and sesquiterpenes, penetrate insect cuticles readily and interfere with multiple molecular targets. Eugenol, the major constituent of clove oil, activates transient receptor potential (TRP) channels in insect sensory neurons, producing hyperexcitation and rapid immobilization, while also inhibiting octopamine receptors—a neurotransmitter system that modulates insect aggression, foraging, and reproduction. Thymol from thyme oil disrupts GABA-gated chloride channels, and 1,8-cineole from rosemary oil inhibits acetylcholinesterase, though with lower affinity than organophosphate insecticides (Alinia-Ahandani et al., 2023; Riaz et al., 2023; Alinia-Ahandani, 2018; Alinia-Ahandani et al., 2019; Alinia-Ahandani, 2018; Orhan & Selamoglu, 2023; Altawell et al., 2025; Selamoglu, 2024).

Recent investigations employing computational molecular docking and in vitro receptor binding assays have elucidated the molecular basis for differential sensitivity of insect and mammalian targets to botanical compounds. β-caryophyllene, a sesquiterpene present in many essential oils, binds selectively to insect odorant-binding proteins and transient receptor potential channels with affinities 10- to 100-fold higher than to homologous mammalian proteins. Similarly, eugenol exhibits preferential interaction with insect TRPA1 channels compared to mammalian TRPA1 orthologs, reflecting evolutionary divergence in channel structure and pharmacology. These findings suggest that the selectivity of botanical insecticides arises not merely from ecological factors such as application timing or exposure routes, but from genuine physiological selectivity encoded in the molecular structures of insect versus mammalian targets (Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024).

Laboratory bioassays comparing essential oil toxicity to target pests versus non-target beneficial organisms support this molecular selectivity. In evaluations of Siparuna guianensis essential oil against aphids (Lipaphis pseudobrassicae) and predatory ladybeetles (Cycloneda sanguinea), Toledo and colleagues demonstrated substantial selectivity: concentrations causing 90% mortality in aphids produced only 20-30% mortality in the predators after 24 hours, with surviving predators showing normal foraging behavior and predation rates. Similar selectivity patterns have been documented for essential oils tested against Drosophila suzukii and its pupal parasitoid Trichopria anastrephae, supporting the potential compatibility of botanical insecticides with biological control agents in integrated household pest management (Alinia-Ahandani et al., 2022; Selamoglu, 2021; Mesut, 2021; Alinia-Ahandani et al., 2022; Haddi et al., 2020; Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025).

Mammalian Safety Assessment: Toxicology, Exposure Routes, and Regulatory Perspectives

The fundamental premise underlying the development and marketing of next-generation bio-rational insecticides is their superior safety profile for mammals, including humans and companion animals, compared to conventional synthetic pesticides. However, the assertion that "natural" or "bio-rational" inherently equates to "safe" requires rigorous scientific scrutiny through systematic toxicological evaluation. This section critically examines the current understanding of mammalian safety associated with bio-rational insecticides, focusing on acute and chronic toxicity, relevant exposure routes in household settings, and the regulatory frameworks that govern their approval and use (Soni et al., 2024; Naeem et al., 2023; Aftab et al., 2023; Sparks et al., 2001; De Souza et al., 2024; Costa et al., 2025).

❖ Principles of Mammalian Toxicological Evaluation

The safety assessment of any insecticide intended for household use rests upon established toxicological principles that characterize the relationship between dose and adverse effects. The core parameters include acute lethal dose (LD50), which quantifies the single dose required to kill 50% of a test population, and no-observed-adverse-effect levels (NOAELs) derived from repeated-dose studies. For comparative purposes, conventional synthetic insecticides such as organophosphates typically

exhibit acute oral LD50 values in rats ranging from 2 to 100 mg/kg, placing them in the "highly toxic" to "moderately toxic" categories. In contrast, most bio-rational insecticides demonstrate substantially more favorable safety profiles. Bacillus thuringiensis (Bt) toxins, for instance, have been administered to mammals at doses exceeding 5,000 mg/kg without observable adverse effects, yielding LD50 values effectively classified as non-toxic. Similarly, the insect growth regulator methoprene exhibits oral LD50 values in rats exceeding 34,000 mg/kg, representing a safety margin several orders of magnitude greater than conventional alternatives (European Food Safety Authority, 2008; Haddi et al., 2020; Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; European Chemicals Agency, 2018; Guleria et al., 2024).

The mechanistic basis for this remarkable selectivity resides in fundamental biochemical and physiological differences between insects and mammals. Bio-rational insecticides predominantly target pathways that are either absent in vertebrates (such as chitin synthesis or juvenile hormone regulation) or exploit structural differences in conserved targets. Spinosad, for example, interacts with nicotinic acetylcholine receptors in both insects and mammals, but its affinity for insect receptors is approximately 100-fold higher, and the compound demonstrates poor penetration of the mammalian blood-brain barrier. Furthermore, rapid metabolic degradation in mammalian hepatic tissues—with elimination half-lives typically measured in hours rather than days—limits systemic exposure and accumulation potential (Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024).

❖ Routes of Exposure in Household Environments

Assessment of mammalian safety must consider the specific exposure scenarios relevant to household pest management. Unlike agricultural settings where applicators may use protective equipment and restrict entry for specified intervals, household exposures involve continuous, low-level contact by occupants including potentially vulnerable populations such as infants, pregnant women, elderly individuals, and immunocompromised persons. The primary routes of exposure in residential settings include:

Dermal exposure represents the most common pathway, as household insecticides are frequently applied to surfaces, baseboards, and fabrics with which occupants may have direct skin contact. The stratum corneum provides a substantial barrier to many hydrophilic compounds, but lipophilic bio-rational agents—particularly botanical essential oils—can penetrate intact skin to varying degrees. Permeability coefficients determined using human skin models indicate that compounds such as eugenol and thymol exhibit moderate dermal absorption rates (5-15% of applied dose), though systemic concentrations achieved under normal use conditions remain well below toxic thresholds (Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Haddi et al., 2020).

Inhalation exposure assumes particular importance for aerosolized or volatile formulations. The respiratory tract provides a large surface area with thin epithelial barriers and extensive vascularization, facilitating rapid absorption. Pyrethroid-based household insecticides, widely used despite not being strictly bio-rational, have demonstrated detectable metabolites in urine of residents following routine indoor applications. For volatile botanical compounds, inhalation exposure may produce transient sensory irritation at high concentrations, but acute respiratory toxicity has not been documented at label-recommended application rates.

Oral exposure, particularly relevant for infants and toddlers exhibiting hand-to-mouth behavior, occurs through ingestion of residues on treated surfaces or contaminated household items. The high surface area-to-body weight ratio in children amplifies the significance of even trace residues. Recognizing this vulnerability, regulatory agencies require specific developmental and reproductive toxicity studies to assess potential effects on growth, neurodevelopment, and reproductive function (Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006).

❖ Comparative Toxicology: Bio-rational Versus Conventional Insecticides

A systematic comparison of toxicological endpoints between bio-rational and conventional insecticides reveals distinct safety advantages for the former category. Organophosphate and carbamate insecticides exert toxicity through irreversible inhibition of acetylcholinesterase, an enzyme critical for cholinergic neurotransmission in both insects and mammals. This mechanism produces a well-characterized syndrome of salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis (SLUDGE syndrome) in acute poisoning, while chronic low-level exposure has been associated with neurodevelopmental deficits in children. In veterinary medicine, accidental exposure of pets to concentrated organophosphate formulations remains a significant cause of poisoning emergencies (Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016).

In contrast, bio-rational insecticides lack this mechanism of cholinesterase inhibition. The insect growth regulators (methoprene, pyriproxyfen, diflubenzuron) exhibit no acute toxicity at practical doses and have been classified by the U.S. Environmental Protection Agency as "reduced risk" pesticides with correspondingly lenient labeling requirements. Spinosad, while capable of producing neuroexcitation at very high experimental doses, demonstrates a safety margin exceeding 100-fold between NOAEL and estimated human exposure levels under normal use conditions (Selamoglu, 2021; Mesut, 2021; Alinia-Ahandani et al., 2022; Haddi et al., 2020).

However, a balanced assessment must acknowledge that "bio-rational" does not universally equate to "non-toxic." Certain botanical insecticides, particularly those derived from plants containing potent alkaloids or terpenes, can produce adverse effects at sufficiently high doses. Nicotine-based insecticides, though rarely used in contemporary household products, exemplify this principle with mammalian LD50 values comparable to synthetic neurotoxicants. Furthermore, essential oils—while generally recognized as safe for culinary use—may produce toxicity when concentrated in insecticidal formulations. Case reports of human poisoning following ingestion of concentrated essential oil products highlight the importance of appropriate formulation, packaging, and child-resistant closures (Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024; Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022;

Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018).

- **Vulnerable Populations: Pediatric and Companion Animal Considerations**

The safety assessment of household insecticides must specifically address populations with enhanced susceptibility due to physiological immaturity, altered metabolic capacity, or unique exposure patterns. Infants and young children undergo rapid neurodevelopment characterized by synaptogenesis, myelination, and establishment of neural circuits—processes potentially vulnerable to disruption by xenobiotic compounds. The developing brain expresses higher densities of certain receptor populations and exhibits incompletely developed drug-metabolizing enzyme systems, particularly cytochrome P450 isoforms responsible for detoxification of many insecticides. While direct evidence for developmental neurotoxicity from bio-rational insecticides remains limited, the precautionary principle supports minimizing exposure to any biologically active compound during critical developmental windows (Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; European Chemicals Agency, 2018; Guleria et al., 2024; Elser et al., 2022).

Companion animals present additional considerations due to species-specific metabolic variations and behavioral exposure patterns. Dogs and cats may be more susceptible to certain insecticides because of deficient glucuronidation capacity (particularly in felines) or grooming behaviors that result in ingestion of topically applied products. The isoxazoline class of ectoparasiticides, while highly effective and generally safe, has been associated with neurological adverse events in a subset of treated animals, illustrating that even compounds with favorable safety profiles can produce idiosyncratic toxicity in susceptible individuals. For household-use bio-rational insecticides, the primary risk to companion animals likely involves direct ingestion of concentrated formulations, emphasizing the importance of proper storage and application according to label directions (Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Toledo et al., 2019; Costa et al., 2025).

❖ Regulatory Frameworks for Safety Evaluation

The registration and commercialization of bio-rational insecticides for household use are governed by comprehensive regulatory frameworks designed to ensure human and environmental safety. In the United States, the Environmental Protection Agency (EPA) evaluates pesticide products under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), requiring a battery of toxicological studies including acute toxicity (oral, dermal, inhalation), eye and skin irritation, dermal sensitization, sub chronic and chronic feeding studies, developmental and reproductive toxicity, carcinogenicity, and neurotoxicity assessments. The specific data requirements are tiered, with basic acute toxicity data required for all products and more extensive testing triggered by indications of potential concern or anticipated high exposure (Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016).

The EPA's Biopesticides and Pollution Prevention Division (BPPD) administers a specialized review process for biopesticides, including many bio-rational insecticides, that offers reduced data requirements when the active ingredient demonstrates low inherent toxicity or is derived from a food source with established safety. This streamlined process recognizes the favorable toxicological profiles of many bio-rational compounds while maintaining rigorous standards for human health protection. Reduced-risk classification confers benefits including faster registration times and, for certain products, exemption from the requirement to establish a tolerance (maximum permissible residue level) for food commodities (European Chemicals Agency, 2018; Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023).

In the European Union, the regulatory framework operates under Regulation (EC) No 1107/2009, administered by the European Food Safety Authority (EFSA) with implementation by Member States. The EU system similarly requires comprehensive toxicological data packages but applies a more precautionary approach, particularly regarding endocrine-disrupting properties and cumulative risk assessment. A significant distinction lies in the EU's active promotion of "low-risk active substances" including many biological control agents, which benefit from expedited review and, in some cases, exemption from certain data requirements. The EFSA

guidance document on risk assessment for birds and mammals, while primarily addressing environmental protection, establishes methodological approaches—including tiered testing strategies and probabilistic exposure modeling—that inform human safety assessment as well (Alinia-Ahandani et al., 2022; Selamoglu, 2021; Mesut, 2021; Alinia-Ahandani et al., 2022; Haddi et al., 2020; Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025).

❖ Critical Perspectives: Unintended Effects and Knowledge Gaps

Despite the generally favorable safety profile of bio-rational insecticides, a growing body of literature calls for critical examination of potential unintended effects that may be overlooked in conventional risk assessment paradigms. A systematic survey of over 15,000 scientific publications revealed a consistent bias toward investigating targeted efficacy while understudying potential detrimental effects on human health and the environment. This asymmetry in research focus may create blind spots regarding subtle, chronic, or delayed effects that do not manifest in standard toxicity testing protocols (Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Haddi et al., 2020).

Of particular concern is the potential for sublethal effects—functional impairments that do not produce overt toxicity but may affect physiological reserve, immune competence, or neurological function. The nematode Caenorhabditis elegans model has been employed to investigate such effects, revealing that exposure to sublethal concentrations of the pyrethroid prallethrin (commonly used in household insecticides) increased aggregation of polyglutamine proteins associated with Huntington's disease pathology. While extrapolation from nematode models to human disease requires caution, these findings suggest that even compounds with favorable acute toxicity profiles warrant investigation for potential effects on fundamental cellular processes relevant to neurodegenerative conditions.

Another critical consideration involves formulation ingredients rather than active components alone. Commercial insecticide products contain solvents, surfactants, propellants, and stabilizers that may contribute to overall toxicity. Synergists such as

piperonyl butoxide, frequently added to pyrethroid and some botanical formulations to inhibit metabolic detoxification in target insects, can also inhibit mammalian cytochrome P450 enzymes, potentially altering the metabolism and toxicity of co-exposed compounds. Comprehensive safety assessment must therefore evaluate the finished product rather than relying solely on data for the active ingredient (Haddi et al., 2020; Toledo et al., 2019; Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Isman, 2020; Rosell et al., 2008; University of Florida, 2024).

Finally, the potential for resistance development and consequent escalation of use rates or reversion to more toxic alternatives represent an indirect safety consideration. If widespread adoption of bio-rational insecticides selects for resistant pest populations, consumers may respond by applying higher doses, increasing application frequency, or switching to conventional synthetic products with less favorable safety profiles. Sustainable pest management thus requires integration of bio-rational tools within broader strategies that preserve their efficacy and safety advantages over time (Riaz et al., 2023; Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024; Elser et al., 2022; Pelkonen et al., 2023).

Molecular Mechanisms of Action of Novel and Emerging Household Insecticides: Insights into Biochemical Selectivity and Target-Site Interactions

The continuous evolution of insecticide resistance and the demand for compounds with enhanced mammalian safety profiles have driven the development of novel chemical classes that exploit previously underutilized target sites in insect physiology. Recent advances in structural biology, electrophysiology, and molecular toxicology have elucidated the precise mechanisms by which these next-generation insecticides achieve their selective toxicity. This section examines the molecular foundations of several emerging insecticide classes relevant to household pest management, with particular emphasis on their target-site interactions, the biochemical basis for insect-mammal selectivity, and the implications for resistance management [23-28]. Table 2 summarizes the molecular mechanisms underlying the selective toxicity of next-generation bio-rational insecticides. It highlights how divergence in target site structure between insects and mammals—such as binding pocket variations in ryanodine receptors or unique subunit compositions in nicotinic

acetylcholine receptors—confers physiological selectivity. Additionally, it illustrates the relationship between target specificity and resistance risk, noting that multi-target botanicals like essential oils exhibit slower resistance evolution compared to single-target compounds with well-documented resistance mutations (Perry et al., 2021; Lin et al., 2024).

Table 2. Molecular mechanisms and basis of selectivity

Insecticide Class	Molecular Target	Selectivity Mechanism	Resistance Risk
Diamides	Ryanodine receptor	Binding pocket divergence	RyR mutations (I4790M, G4946E)
Isoxazolines	GABACls	Distinct binding site from fipronil	RDL mutations possible
Spinosyns	α6 nAChR subunit	Unique insect subunit composition	α6 gene mutations
Neem (Azadirachtin)	Ecdysone signaling	Absent in mammals	Low–moderate
Essential Oils	Multi-target	Multi-site interaction	Lower (multi-target)

❖ Diamide Insecticides: Allosteric Activation of Ryanodine Receptors

Diamide insecticides, including phthalic acid derivatives (flubendiamide) and anthranilic diamides (chlorantraniliprole, cyantraniliprole, tetraniliprole), represent one of the most commercially successful classes of insecticides introduced in the past two decades. Since their market introduction in the late 2000s, diamides have achieved annual sales exceeding USD 2 billion globally due to their exceptional potency, low non-target toxicity, and lack of cross-resistance with existing insecticide classes (Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2019; Sheydaei & Alinia-Ahandani, 2020; Daglia et al., 2023; Hajipour et al., 2024; Hajipour et al., 2023; Alinia-Ahandani et al., 2023).

The molecular target of diamide insecticides is the ryanodine receptor (RyR), a massive ion channel complex expressed in the membranes of the sarcoplasmic and endoplasmic reticulum (SR/ER) of muscle and nerve cells. RyRs govern the release of calcium ions (Ca^{2+}) from intracellular stores into the cytosol, a process essential for

muscle contraction, neurotransmitter release, and various cellular signaling pathways. Mammalian species encode three distinct RyR isoforms (RyR1-3), whereas insects possess only a single isoform, providing a potential basis for selective targeting.

Diamide insecticides act as positive allosteric modulators of insect RyRs, binding with high affinity to a specific site in the transmembrane region and locking the channel in an open conformation. This results in uncontrolled Ca^{2+} release from intracellular stores, leading to sustained muscle contraction, paralysis, feeding cessation, and ultimately death of the target insect. Recent cryo-electron microscopy (cryo-EM) studies have revolutionized our understanding of this interaction at near-atomic resolution. Using a chimeric RyR construct that preserves the diamide-binding pocket from the fall armyworm (Spodoptera frugiperda) while maintaining the biochemical tractability of the rabbit RyR1, researchers have solved structures of the receptor in complex with multiple diamide insecticides (Soni et al., 2024; Naeem et al., 2023; Aftab et al., 2023; Sparks et al., 2001; De Souza et al., 2024; Costa et al., 2025; Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Alinia-Ahandani et al., 2019; Alinia-Ahandani, 2018; Alinia-Ahandani et al., 2019; Alinia-Ahandani, 2018; Alinia-Ahandani, 2018; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2023; Alinia-Ahandani et al., 2023; Riaz et al., 2023; Riaz et al., 2023; Riaz et al., 2023; Riaz et al., 2023).

The binding site is located at the interface between the transmembrane region and the large cytosolic cap of the RyR, primarily within the pseudo-voltage sensing domain (pVSD). Flubendiamide, a phthalic acid diamide, is stabilized by van der Waals interactions and hydrogen bonds with residues from transmembrane helices S1-S4. Key coordinating residues include Lys4563, Tyr4564, and Leu4567 from S1; Ile4657 from S2; Tyr4791, Ser4792, and Tyr4795 from S3; and Asp4815, Gly4819, and Val4820 from S4 (rabbit RyR1 numbering). Lys4563 and Asp4815 play particularly critical roles, sandwiching the ligand through hydrogen bonds from opposite sides (Riaz et al., 2023; Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024; Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025).

The molecular basis for the exceptional selectivity of diamides for insect over mammalian RyRs (approximately 100- to 1,000-fold) has been elucidated through comparative structural analysis. The diamide-binding pocket exhibits approximately 49.5% sequence identity between insect and mammalian RyRs, with several key residues differing between the two. Functional assays using heterologously expressed receptors demonstrated that mutation of just four mammalian-specific residues to their insect counterparts (R4563K, F4564Y, C4657I, and L4792S) fully restored high-affinity diamide binding, with EC_{50} values decreasing from micromolar to nanomolar ranges. This remarkable gain-of-function confirms that a small number of amino acid differences account for the profound species selectivity that makes diamides safe for mammalian use while maintaining potent insecticidal activity (Alinia-Ahandani, 2018; Selamoglu, 2021; Mesut, 2021; Alinia-Ahandani et al., 2022; Haddi et al., 2020; Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019).

However, the intensive use of diamides has selected for resistance mutations in field populations of several major pests, including the diamondback moth (Plutella xylostella), fall armyworm (Spodoptera frugiperda), and rice stem borer (Chilo suppressalis). The most common resistance-associated mutations, I4790M and G4946E (using Plutella xylostella numbering), have been documented across multiple insect species and can reduce diamide sensitivity by >200-fold. Cryo-EM structures of RyRs carrying these mutations revealed that they perturb the local structure of the binding pocket, directly reducing ligand affinity and altering binding pose. The I4790M mutation introduces a bulkier side chain that creates steric hindrance, while G4946E introduces a negatively charged residue that disrupts electrostatic interactions with the ligand. Understanding these structural perturbations provides a rational foundation for designing next-generation diamides capable of overcoming existing resistance mechanisms (Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Casida & Durkin, 2013; Nwonuma et al., 2025).

- **Isoxazoline and Meta-diamide Insecticides: Novel Antagonists of Ligand-Gated Chloride Channels**

The isoxazoline insecticides represent a relatively new class of compounds that have gained prominence in both veterinary and household pest control applications.

Fluxametamide, a novel wide-spectrum isoxazoline developed by Nissan Chemical Industries, exemplifies the sophisticated target-site selectivity achievable through modern insecticide design. This compound acts through distinctive antagonism of insect ligand-gated chloride channels (LGCCs), specifically γ-aminobutyric acid (GABA)-gated chloride channels (GABACls) and glutamate-gated chloride channels (GluCls).

Radioligand binding assays using [^{3}H]4′-ethynyl-4-n-propylbicycloorthobenzoate (EBOB) demonstrated that fluxametamide potently inhibits specific binding to housefly head membranes, suggesting interaction with insect GABA receptors. Two-electrode voltage clamp (TEVC) electrophysiology using Xenopus oocytes expressing housefly GABACls or GluCls confirmed that fluxametamide inhibits agonist-induced currents in the nanomolar range, establishing the compound as a potent LGCC antagonist (Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025).

Critically, fluxametamide exhibits equivalent insecticidal activity against both fipronil-susceptible and fipronil-resistant strains of small brown planthoppers and two-spotted spider mites. This lack of cross-resistance indicates that fluxametamide binds to a site distinct from that targeted by phenylpyrazole insecticides such as fipronil. Subsequent studies on meta-diamides, a related class of GABA receptor antagonists, have localized their binding site near glycine residue 319 in the third transmembrane segment of RDL GABA receptor homomers—a region distinct from the fipronil/cyclodiene binding site associated with the A302S (Rdl) resistance mutation (Soni et al., 2024; Naeem et al., 2023; Aftab et al., 2023; Sparks et al., 2001; De Souza et al., 2024; Costa et al., 2025; Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Toledo et al., 2019; Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; Elser et al., 2022; Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024).

The mammalian safety of isoxazoline insecticides derives from remarkable target-site selectivity. Fluxametamide exhibits negligible antagonistic activity against rat GABACls and human glycine-gated chloride channels, despite its potent effects on arthropod LGCCs. This selectivity likely reflects evolutionary divergence in channel

structure and pharmacology between insects and vertebrates, analogous to the situation observed with diamides and RyRs.

Isocycloseram, a recently developed isoxazoline insecticide, has demonstrated exceptional activity against the fall armyworm (Spodoptera frugiperda), with an LC_{50} of 0.26 mg/kg compared to 7.72 mg/kg for fipronil. Functional characterization revealed that isocycloseram inhibits the SfrRDL1 GABA receptor with an IC_{50} of 8.52 nM, nearly identical to that of desmethyl-broflanilide (7.32 nM). Interestingly, the SfrRDL1 receptor exhibited higher sensitivity to GABAergic insecticides than the SfrRDL2 receptor variant, suggesting that receptor subunit composition may influence tissue-specific susceptibility and potentially contribute to selective toxicity profiles. The SfrGluCl receptor, while responsive to L-glutamate stimulation, showed only weak inhibition by isocycloseram at 10 µM, indicating that GABA receptors are the primary targets for this compound (Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024).

- **Spinosyns: Refined Understanding of Allosteric Modulation at Nicotinic Acetylcholine Receptors**

Since their registration more than 25 years ago, spinosyns (spinosad and spinetoram) have become established as valuable tools in household and agricultural pest management. Recent advances in molecular pharmacology have substantially refined our understanding of their unique mode of action as allosteric modulators of insect nicotinic acetylcholine receptors (nAChRs). Spinosyns are classified by the Insecticide Resistance Action Committee (IRAC) as Group 5 insecticides: nAChR allosteric modulators, Site I, distinguishing them from Group 4 compounds (neonicotinoids) that act as competitive modulators at a distinct receptor site [25-16]. The symptomology of spinosyn poisoning—involuntary muscle contractions, leg extension, tarsal flexing, wing beating, and loss of coordination—reflects prolonged excitatory effects on the insect central nervous system. Electrophysiological studies have demonstrated that spinosyns cause depolarization of insect neurons through direct excitatory effects on the CNS, with neuromuscular block occurring as a secondary consequence of overexcitation rather than a primary effect on muscle targets (Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Alinia-Ahandani, 2018; Selamoglu, 2021).

The molecular target of spinosyns has been definitively identified as the α6 subunit of insect nAChRs. Gene editing studies in Drosophila melanogaster and various pest insects have confirmed that mutations or knockout of the α6 subunit confer high-level spinosyn resistance, while leaving sensitivity to other nAChR-targeting insecticides intact. Functional expression systems have revealed that spinosyns selectively target non-desensitizing nAChR subtypes, acting as allosteric modulators that enhance receptor activity through binding to a site distinct from the acetylcholine-binding pocket. The effect of spinetoram on receptor function appears to be irreversible, suggesting particularly tight binding kinetics (Mesut, 2021; Alinia-Ahandani et al., 2022; Haddi et al., 2020; Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025).

The mammalian safety of spinosyns, while previously attributed to poor blood-brain barrier penetration and rapid metabolic degradation, can now be understood at the receptor level as well. Mammalian nAChR subunit combinations differ substantially from their insect counterparts, and the specific α6-containing subtypes that serve as spinosyn targets in insects have no direct functional homologs in vertebrates. This phylogenetic divergence in receptor composition and pharmacology provides an additional molecular safeguard against unintended neurotoxicity (Nakao et al., 2025; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Casida & Durkin, 2013; Nwonuma et al., 2025; Gupta, 2025).

- **Botanical Insecticides: Molecular Targets and Mechanisms of Selective Toxicity**

The resurgence of interest in botanical insecticides has been accompanied by increasingly sophisticated understanding of their molecular mechanisms of action. Unlike synthetic insecticides that typically contain single active ingredients with well-defined target sites, botanical preparations comprise complex mixtures of compounds that may act through multiple, complementary mechanisms. Recent investigations employing computational molecular docking, in vitro receptor binding assays, and electrophysiological approaches have elucidated the molecular basis for differential sensitivity of insect and mammalian targets to botanical compounds (Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020;

Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2020; Alinia-Ahandani et al., 2019).

Essential oils from aromatic plants contain monoterpenes and sesquiterpenes that interact with multiple insect molecular targets. Eugenol, the major constituent of clove oil, activates transient receptor potential (TRP) channels in insect sensory neurons, producing hyperexcitation and rapid immobilization. Computational docking studies have demonstrated that eugenol exhibits preferential interaction with insect TRPA1 channels compared to mammalian TRPA1 orthologs, reflecting evolutionary divergence in channel structure and pharmacology. Similarly, β-caryophyllene, a sesquiterpene present in many essential oils, binds selectively to insect odorant-binding proteins and TRP channels with affinities 10- to 100-fold higher than to homologous mammalian proteins (Sheydaei & Alinia-Ahandani, 2020; Daglia et al., 2023; Hajipour et al., 2024; Hajipour et al., 2023; Alinia-Ahandani et al., 2023).

The octopaminergic system represents another important target for botanical insecticides. Octopamine, a biogenic amine that functions as a neurotransmitter, neuromodulator, and neurohormone in insects, has no direct functional equivalent in vertebrates (where noradrenaline serves analogous but distinct roles). Several essential oil constituents, including eugenol and thymol, have been shown to interact with octopamine receptors, disrupting the complex behaviors modulated by this signaling system. The absence of octopamine receptors in mammals provides an inherent selectivity filter for compounds targeting this pathway (Nwonuma et al., 2025; Gupta, 2025; Mowafi et al., 2025; Rubio-Infante & Moreno-Fierros, 2016; Hahn et al., 2006; Guleria et al., 2024).

Terpene interactions with GABA-gated chloride channels have also been characterized at the molecular level. Quantitative structure-activity relationship (QSAR) studies have identified structural features that govern monoterpenoid binding to insect GABA receptors, with thymol and related compounds acting as allosteric modulators at sites distinct from those targeted by conventional GABAergic insecticides. This multiplicity of target interactions within a single botanical extract may contribute to reduced resistance selection pressure, as simultaneous mutations in multiple target sites would be required for complete loss of susceptibility (Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020;

Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; European Chemicals Agency, 2018; Guleria et al., 2024; Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Riaz et al., 2023; Bio-efficacy of diatomaceous earth, household soaps, and neem oil against Spodoptera frugiperda larvae in Benin, 2024).

- **Target-Site Resistance: Molecular Mechanisms and Implications for Insecticide Longevity**

The intensive use of any insecticide class inevitably selects for resistance-conferring mutations in target pest populations. Understanding the molecular mechanisms of resistance is essential for designing effective resistance management strategies and developing novel compounds capable of overcoming existing resistance alleles.

Target-site resistance arises when specific mutations alter the molecular conformation of an insecticide's binding site, diminishing or abolishing affinity. For voltage-gated sodium channels (VGSCs), the target of pyrethroids and DDT, multiple resistance-associated mutations (kdr: knockdown resistance) have been characterized, including L1014F, V1016I, and F1534C in various pest and vector species. These mutations reduce pyrethroid binding while preserving normal channel function, demonstrating the remarkable evolutionary plasticity of this target site (Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024; Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Haddi et al., 2020).

For nAChRs, target-site resistance to neonicotinoids has been associated with mutations in the loop D region of the receptor's β subunit, particularly the R81T mutation in Myzus persicae and related substitutions in other species. Resistance to spinosyns, as noted above, maps definitively to the α6 subunit, with mutations, splice variant alterations, or complete knockout of this subunit conferring high-level resistance.

Ryanodine receptor mutations conferring diamide resistance, including I4790M/K, G4946E, and others, have been documented across multiple insect orders. These mutations cluster in the transmembrane region surrounding the diamide-binding pocket and reduce ligand affinity through steric or electrostatic mechanisms while preserving normal receptor function. The independent evolution of similar mutations in geographically separated populations of different pest species underscores the predictable nature of resistance evolution when intense selection pressure is applied to a single target site (Hajipour et al., 2024; Liu et al., 2024; Sparks et al., 2025; Nakao et al., 2025; Singh et al., 2025; Ahandani et al., 2013).

GABA receptor mutations, particularly the A302S substitution in the RDL subunit, confer resistance to cyclodienes and phenylpyrazoles (fipronil) by altering the conformation of the chloride channel pore. The distinct binding sites of isoxazolines and meta-diamides, localized to different regions of the receptor, allow these newer classes to circumvent existing RDL-mediated resistance—a principle that has guided their development and deployment.

- **Integration with Mammalian Safety: Structural and Pharmacological Divergence**

The molecular mechanisms underlying selective toxicity of insecticides can be categorized into several distinct categories, each contributing to the overall safety margin for mammals:

Target absence represents the most absolute form of selectivity. Insect growth regulators targeting chitin synthesis or juvenile hormone pathways act on physiological processes entirely absent in mammals, rendering inherent toxicity biologically impossible regardless of dose (Naeem et al., 2023; Aftab et al., 2023; Sparks et al., 2001; De Souza et al., 2024; Costa et al., 2025; Warislohner, 2025; European Food Safety Authority, 2008; Haddi et al., 2020; Toledo et al., 2019; Costa et al., 2025; Warislohner, 2025).

Target divergence characterizes compounds like diamides and spinosyns, where homologous proteins exist in mammals but exhibit sufficient structural and pharmacological differences to confer selectivity. In the case of diamides, a small number of amino acid differences in the binding pocket reduce mammalian receptor

affinity by 100- to 1,000-fold. For spinosyns, differences in nAChR subunit composition and pharmacology achieve similar selectivity.

Pharmacokinetic barriers limit access of insecticides to mammalian target sites. Poor blood-brain barrier penetration protects the central nervous system from compounds that might otherwise interact with neuronal targets, while rapid hepatic metabolism limits systemic exposure and accumulation potential (Isman, 2020; Rosell et al., 2008; University of Florida, 2024; Dos Santos et al., 2024; Elser et al., 2022; Pelkonen et al., 2023; Tamagno et al., 2022; Daraban et al., 2023; Wismer & Means, 2018; Krieger, 2010; U.S. Environmental Protection Agency, 2024).

Detoxification capacity differences between insects and mammals contribute substantially to selectivity. Mammals possess more extensive and diverse xenobiotic-metabolizing enzyme systems, including cytochrome P450 monooxygenases (CYPs), esterases, and glutathione S-transferases (GSTs), that efficiently degrade insecticides before they reach target sites. Insects, while possessing homologous enzyme families, generally have lower constitutive expression and less redundant detoxification networks.

Understanding these molecular mechanisms of selectivity and resistance provides a rational foundation for insecticide discovery, resistance management, and risk assessment. The continued evolution of resistance underscores the need for ongoing investment in novel chemistry and the integration of multiple control tactics within comprehensive pest management programs (Fan et al., 2024; Asahi et al., 2018; Alinia-Ahandani et al., 2022; Singh et al., 2025; Ahandani et al., 2013; Alinia-Ahandani et al., 2019; Alinia-Ahandani et al., 2022; Haddi et al., 2020; Selamoglu, 2021). In table 3, a systematic comparison of biorational and conventional insecticides reveals fundamental differences in their safety and ecotoxicological profiles. While conventional insecticides such as organophosphates and pyrethroids act on molecular targets that are highly conserved across the animal kingdom, biorational agents typically target insect-specific or evolutionarily divergent pathways, which forms the basis for their physiological selectivity. This selectivity results in lower acute toxicity to mammals and more limited evidence regarding neurodevelopmental effects. Although resistance evolution remains a concern for biorational compounds, it generally occurs at a slower rate compared to conventional insecticides due to their multi-target mechanisms and diverse modes of action.

Furthermore, the greater biocompatibility of these compounds with biological control agents and pollinators positions them as more suitable options for integrated pest management programs (Campos et al., 2025).

Table 3. Comparison of Bio-rational with Conventional Insecticides

Parameter	Conventional (OPs, Pyrethroids)	Bio-rational
Target Conservation	Highly conserved in mammals	Insect-specific or divergent
Acute Toxicity	Moderate–High	Low–Very Low
Developmental Risk	Documented	Limited evidence
Environmental Risk	Often high	Generally lower
Resistance Evolution	High	Emerging but slower (multi-target types)

Discussion and Conclusion

The preceding analysis reveals that next-generation bio-rational insecticides represent a substantial advancement in reconciling the competing demands of household pest control and mammalian safety. The molecular targeting of insect-specific physiological pathways—chitin synthesis, juvenile hormone regulation, unique receptor pharmacology—provides a mechanistic foundation for selectivity that conventional neurotoxic insecticides fundamentally lack. The empirical toxicological data support this theoretical advantage, with acute LD50 values for major bio-rational classes typically exceeding those of conventional alternatives by orders of magnitude.

However, the assertion that bio-rational insecticides achieve an optimal balance between efficacy and safety requires nuanced qualification. The balance metaphor implies a trade-off—that enhanced safety necessarily comes at the cost of reduced efficacy. Yet the evidence suggests a more complex reality: many bio-rational agents achieve efficacy comparable to conventional products through fundamentally different mechanisms, while the safety advantage is genuine but not absolute. Certain botanical insecticides, particularly at concentrated doses, can produce mammalian

toxicity, and formulation ingredients may introduce hazards not predicted by active ingredient data alone.

The molecular mechanisms elucidated in this review—from diamide interactions with ryanodine receptors to isoxazoline antagonism of ligand-gated chloride channels—demonstrate that modern insecticide design increasingly exploits fundamental structural and pharmacological differences between insect and mammalian targets. The cryo-EM structures of diamide-bound RyRs provide unprecedented insight into how a small number of amino acid differences can confer 1,000-fold selectivity, while the characterization of spinosyn interactions with α6-containing nAChR subtypes reveals the importance of receptor subunit composition in determining species-specific sensitivity. These mechanistic insights not only explain the favorable safety profiles of current compounds but also provide rational templates for future insecticide discovery.

The household context imposes unique demands that complicate the balance assessment. Efficacy in residential settings requires not only acute toxicity to target pests but also residual activity, rapid knockdown, and practical application methods compatible with occupied living spaces. Some bio-rational agents, particularly essential oil formulations, provide rapid knockdown but limited residual protection, potentially necessitating more frequent applications and increasing cumulative exposure. Conversely, insect growth regulators offer prolonged activity with exceptional safety but do not provide the immediate visual confirmation of pest elimination that consumers often desire.

The regulatory frameworks governing bio-rational insecticides have evolved to recognize their distinct profiles, with expedited review pathways and reduced data requirements reflecting their favorable safety characteristics. Yet these frameworks also incorporate important safeguards—developmental toxicity studies, cumulative risk assessment considerations, and post-market surveillance mechanisms—that acknowledge the limitations of current knowledge. The precautionary principle, particularly evident in EU regulation, appropriately recognizes that absence of evidence for harm does not constitute evidence of absence, especially for effects that may manifest only after prolonged exposure or in particularly susceptible subpopulations.

Critical knowledge gaps remain that warrant continued investigation. The potential for subtle, chronic, or delayed effects from prolonged low-level exposure has received insufficient research attention, particularly regarding neurodevelopmental outcomes in children and interactions with age-related neurodegenerative processes. The toxicological contributions of formulation ingredients, including solvents and synergists, require more comprehensive evaluation in the context of finished products rather than active ingredients alone. Additionally, the indirect safety implications of resistance development—including potential escalation of use rates or abandonment of bio-rational approaches in favor of more toxic alternatives—merit consideration within integrated pest management frameworks.

Future research directions should include: (1) longitudinal epidemiological studies examining health outcomes in populations with chronic household exposure to bio-rational insecticides; (2) mechanistic investigations into potential effects on vulnerable developmental windows using appropriate animal models and in vitro systems; (3) comparative assessment of finished product formulations rather than active ingredients alone; (4) development of validated biomarkers for exposure assessment in human populations; and (5) integration of toxicogenomic approaches to identify genetically determined susceptibility factors that may influence individual risk.

In conclusion, next-generation bio-rational insecticides achieve a more favorable balance between efficacy and mammalian safety than their conventional predecessors, reflecting deliberate design targeting insect-specific physiology. Their continued development and appropriate use within integrated pest management programs offer genuine benefits for household pest control with reduced—though not zero—risk to human and companion animal health. The balance, while substantially improved, remains a balance nonetheless, requiring informed consumer use, thoughtful regulation, and continued scientific vigilance.

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CHAPTER FOURTEEN

Role of Systemic Functional Linguistics (SFL) Theory and Discourse Competence (DC) in Enhancing the CSS Aspirants English Essay Academic Writing (AW)

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Abstract

The Central Superior Services (CSS) examination has historically functioned as the primary gateway to Pakistan's federal civil bureaucracy, with roots in the competitive examination system introduced during British colonial rule in the mid-nineteenth century. After independence, the CSS was formally institutionalized in 1947 and constitutionally reinforced under Article 240 of the Constitution of Pakistan (1973). Despite periodic reforms, the CSS English Essay paper has persistently remained a major obstacle to candidate success, with failure rates frequently exceeding 90 percent, suggesting systemic shortcomings rather than individual inadequacies. This study investigates the role of Systemic Functional Linguistics (SFL) Theory by Halliday and Hassan (1976) and discourse competence in CSS English Essay examination using a qualitative research design. Reports from the Federal Public Service Commission (FPSC) and examiner feedback, as well as selected CSS essay scripts, were used to uncover and document the same linguistic and structural weaknesses. The study shows that while most candidates show reasonable control, they have difficulties with the higher order discourse skills of coherence, cohesion, development of arguments, awareness of different genres, and engagement with the essay prompt critiques. These weaknesses are serious because the CSS essay tests analytical skills, the ability to articulate policy, and the level of intellectual maturity which are core competencies of civil service aspirants. In addition, English is not the national language of Pakistan, and it is not the mother language of most aspirants. The CSS exam, therefore, sits at the sociolinguistic intersection that Kachru (1997) describes in his Outer Circle model, in which English is the second language of the institution. The study shows that limited access to education and the absence of academic writing

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pedagogy are structural inequities in the system. It recommends that, in order to increase equity and decrease the level of failure in the CSS exam system, there must be an emphasis on instruction in the academic and argumentative writing needed to improve discourse competence.

Keywords: Academic Writing, Discourse Competence, CSS English Essay, CSS Aspirants, Systemic Functional Linguistic Theory, Cohesion, Coherence, Discourse Markers, Pakistan

Introduction

Academic writing constitutes a core competency for undergraduate and postgraduate students. While it poses challenges for novice writers in general, it is particularly demanding for second-language English users who seek effective participation in academic discourse communities. Writing in academic contexts requires more than adherence to general register norms such as avoiding contractions and colloquial expressions or selecting appropriate vocabulary and also involves mastering discipline-specific conventions. These consist of particular jargon, repeated lexical items, ways of signaling and softening, use of the passive voice, methods of attribution and citation, and ways of expressing an author's position. Jalilifar states that for someone to be able to produce academic writing, they must be well acquainted with the conventions and principles that underpin scholarly writing.

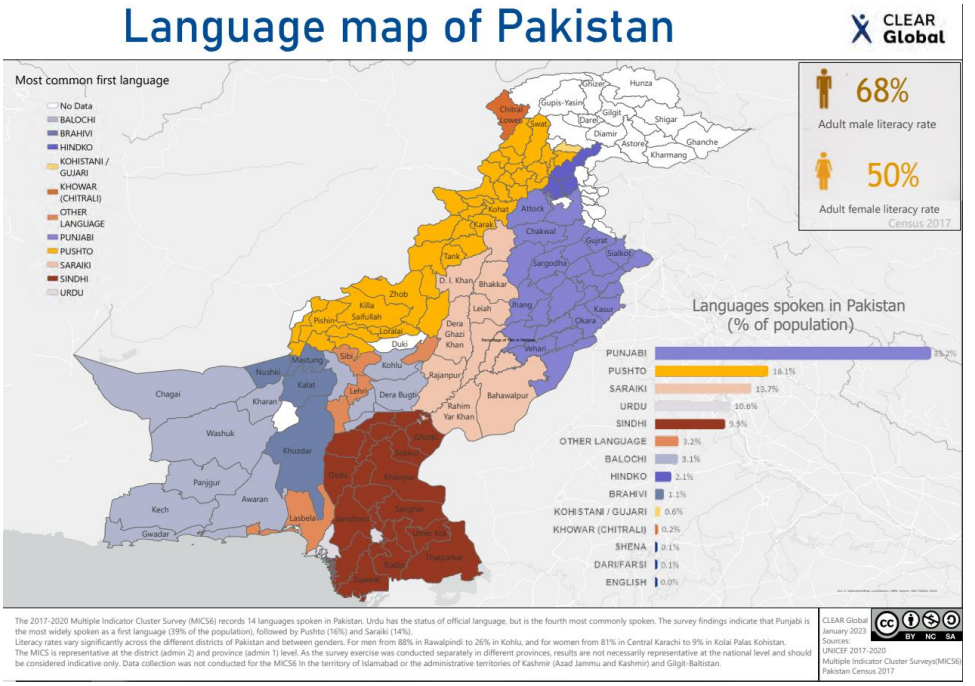
For students in higher education, especially beyond the undergraduate level, academic writing is indispensable, as advanced academic tasks such as theses and dissertations demand sustained argumentation, disciplinary awareness, and conformity to rigorous evaluative standards. The issues surrounding these genres extend to their expected level of coherence, originality, and scholarly rigor, and, furthermore, their increased overall complexity in multivoiced genres. The gradual nature of this process, and its complexity, involves developing an extensive level of competence across multiple issues of the genres, particularly with lexico-grammatical, rhetorical, and stylistic issues. The advanced and formal nature of the required rhetoric, as well as the structural intricacies, makes the genre difficult for first-language novice writers as well as second-language writers. This multitude of

issues, spanning various linguistic and rhetorical dimensions, strongly justifies the need for academic writing development.

Source: https://www.dreamstime.com/map-showing-provinces-pakistan-including-punjab-sindh-balochistan-khyber-pakhtunkhwa-along-neighboring-countries-image382819155

Pakistan occupies a strategically significant position in South Asia, linking South Asia with Central Asia, the Middle East, and China. Geographically, it covers an area of about 796,095 square kilometers and is bordered by India to the east, Afghanistan to the northwest, Iran to the southwest, China to the northeast, and the Arabian Sea to the south. The country's terrain is highly diverse, ranging from the towering mountain ranges of the Himalayas, Karakoram, and Hindu Kush in the north to fertile plains of the Indus River system in Punjab and Sindh, arid deserts in Thar and Cholistan, and a long coastline along the Arabian Sea. Ali et al, (2025)

Demographically, Pakistan is the fifth most populous country in the world, with a population exceeding 240 million people, characterized by a young population structure and significant ethnic diversity, including Punjabis, Pashtuns, Sindhis, Baloch, and others. This geographical diversity combined with demographic complexity shapes Pakistan's economic potential, security outlook, and its critical role in regional geopolitics. Qasim et al, (2023)



Source: https://clearglobal.org/wp-content/uploads/2023/02/Pakistan-Map-2023.pdf

Pakistan is a highly multilingual country, reflecting its rich cultural, ethnic, and historical diversity, with linguists identifying between 72 and 74 living languages spoken across its regions. Urdu serves as the national language and a key symbol of national unity, while English functions as an official language used in government, law, and higher education. Punjabi, Pashto, Sindhi, Saraiki, and Balochi are among the major regional languages spoken by large segments of the population, alongside dozens of smaller indigenous and minority languages such as Brahui, Shina, Balti, Burushaski, Wakhi, and Kalasha. These languages belong to several major language families, including Indo-Aryan, Iranian, Dravidian, and isolate groups, making Pakistan one of the linguistically most diverse countries in South Asia. This linguistic plurality not only reflects the country's complex social fabric but also plays an important role in shaping identity, politics, education, and inter-provincial relations. Ibad et al, (2025)

Since the inception of Pakistan in 1947, the Central Superior Services (CSS) examination has remained the principal mechanism for recruiting civil servants to

run the administrative machinery of the state. Rooted in the colonial legacy of the Indian Civil Service (ICS), the CSS system was adopted to ensure merit-based selection for key bureaucratic positions in a newly independent country facing acute administrative and governance challenges. Tummala (2017)

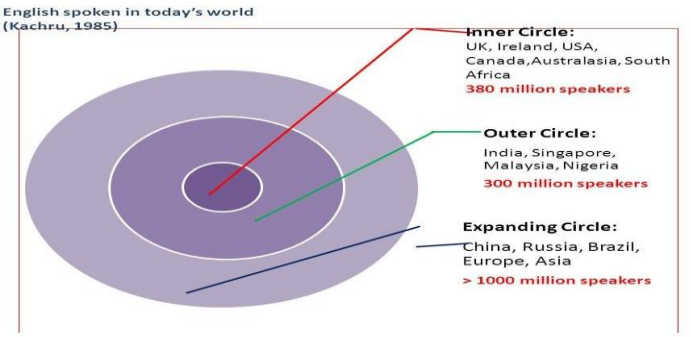
In the early decades, the civil service played a dominant role in state-building, policy formulation, and institutional continuity, often compensating for political instability and weak democratic structures. Conducted under the Federal Public Service Commission (FPSC), the CSS examination gradually evolved in structure and syllabus to meet the growing and diverse needs of governance in Pakistan. Jamil (2023)

Over time, the CSS system has undergone several reforms aimed at improving transparency, inclusivity, and relevance to contemporary governance challenges. Changes in examination patterns, compulsory and optional subjects, age limits, and provincial quota systems were introduced to broaden representation and align the service with modern administrative requirements. In the present era, CSS officers serve in a wide range of occupational groups, contributing to policymaking, public administration, diplomacy, law enforcement, and economic management. Despite periodic criticism regarding elitism, syllabus relevance, and training quality, CSS continues to be regarded as one of the most prestigious competitive examinations in Pakistan, symbolizing merit, public service, and the enduring role of bureaucracy in the country's political and administrative landscape. Safdar et al, (2025)

The Central Superior Services (CSS) in Pakistan is a merit-based examination that is held every year by the Federal Public Service Commission (FPSC) for selecting civil servants to fill the vacancies for many government posts. Established in the first place in the British colonial times, CSS's organizational framework was redrawn in 1977 to make its recruitment more efficient and synchronize it with the administrative requirements of a newly independent Pakistan. The modern structure of CSS is created to evaluate candidates on the basis of a series of written tests, psychological assessments, and interviews, spanning a wide range of topics like governance, international affairs, and public administration

Background of the Study

English is widely recognized as the first global lingua franca and has become integral to nearly all domains of modern life, including communication, information technology, science, entertainment, and business. To explain the global spread and functional diversity of English, Kachru (1985) proposed the well-known three-circle model.



https://agvalpa.medium.com/kachru-model-the-three-circles-of-english-b53b86e63d46

Historically, English as a first language has been predominant in the Inner Circle which includes the United States, United Kingdom, and Canada. The Outer Circle consists of postcolonial contexts like Nigeria, Kenya, and India as well as Singapore and the Philippines where English has an official, if not a native, status. Countries like China, Japan, and Turkey belong to the Expanding Circle whereby English is a foreign language and has no official status.

Gradually, English has evolved into an integral part of the global education system and is estimated to be used by 1.5 billion people. About 350 million people consider English their first language while the rest speak it as a second or foreign language. According to experts, English operates as a first language in the Inner Circle countries, second language with major administrative functions in various postcolonial countries, and as a foreign language which is largely restricted to the classroom in the Expanding Circle situations.

In Pakistan, English as a Second Language is a compulsory subject in all levels of the national education system, including the university level. Language is essential to cognition and communication, and the key components of a language include listening, speaking, reading, and writing. Out of these, writing is the most intricate and the most multifaceted. Writing is a productive skill as opposed to a reproductive skill, a literacy practice, a communicative practice, and it is also the primary means by which students' learning is assessed. Writing is a means of communicating and constructing meaning using a system of symbols or graphical system, and it necessitates a high level of organization and clarity. Effective writing or discourse is the result of high levels of cohesion and unity among all constituent sentences that serve to express a single or multiple interrelated idea. Academic writing, in form of theses, articles, journals, and research papers, gives students the opportunity to write, express and defend their arguments, and to position their ideas in a scholarly conversation, and in discourse communities.

After 1947, with the country's independence, Pakistan implemented the examination structure it had inherited and formulated the Central Superior Services (CSS) examination. The Central Superior Services (CSS) became the gateway for the Pakistani federal civil services, recruiting officers in the core executive, diplomatic, and policy making roles. The structures of the CSS exams have changed over the years but have consistently given priority to the writing skills of candidates with a strong focus on compulsory English papers. The constitution of Pakistan, under Article 240, which concerns the recruitment for federal services, has provided authority to the CSS exams. This constitutional provision illustrates the national importance of the CSS exam, and the merit and transparency of the process, that candidates are assessed on regardless of the position they are applying for.

The Pakistan's multi-lingual context directly impacts the candidates of CSS exams. In this context, English is not the first language of communication, but rather a second one. Additionally, candidates don't practice writing on a sustained basis. The training in the organization of writing discourse is also lacking. Therefore, candidates are compromised at the very start. This call for a shift in the way things are done by moving away from rote learning to focus instruction and learning on writing and discourse, including emphasis on planning, argumentation, and critical reading. Improving academic writing via discourse-oriented methods could positively impact

candidates' results in the CSS English Essay and help create a fairer system of evaluation.

For a long time, competitive exams have served the purpose of choosing ruling elites, especially in colonial and postcolonial countries. When it comes to the Indian sub-continent, the British colonizers' creation of a centralized competitive examination system brought about the emergence of a merit-based bureaucracy. This system valued written skills, analytical thinking, and mastery of the English language, which were perceived as central to administration and implementation of policies.

The CSS exam is known for its almost comically ridiculous failure rates because nothing seems to work to combat this issue even with numerous attempts at reform. One specific example is the English Essay component; Federal Public Service Commission (FPSC) data for decades show some years with failure rates above 90%. While some may point to the candidates as the primary issue, it's clear that the exam is designed with unfortunate pedagogy, or insulation from teaching and learning realities. The English Essay section is one of the most challenging and in order to succeed, candidates must showcase more than good command of the English language. They must demonstrate higher-order thinking skills, synthesis and evaluation of arguments, and have a clear understanding of the issues from a policy perspective. Given that this is the most decisive paper, failure here essentially guarantees failure in the exam overall. Ashraf (2023)

The lack of available writing resources continues to affect the varying levels of education across Pakistan. Candidates who have gone to a public-sector institution have often gone to an institution which does not have formal instruction in writing in the areas of instructions, critical writing, and the construction of complex organizational structures. This means their challenges extend well beyond the writing areas of grammar and lexis. The ability to understand and describe the writing deficiencies in CSS essays, therefore, hinges on understanding discourse competence. The ability to do this balance organizational coherence and a sustained flow of reasoning, constructing a text, and purposefully situated, in the writing context which is of a particular academic or institutional hierarchy. Such a lack of competence will result in the gross insufficiency of essay writing, regardless of writing accuracy.

The Federal Public Service Commission (Pakistan) is an autonomous body under Article 242 of the Constitution of the Islamic Republic of Pakistan 1973. Its primary function is to ensure merit-based appointments to the federal civil services. The FPSC Ordinance of 1977, FPSC (Functions) Rules of 1978, and FPSC (Composition and Conditions of Service) Regulations of 1978 govern the legal and operational framework. The Commission, which is made up of a Chairman and 11 Members, is constituted by the President of Pakistan and serves a term of three years or until the member reaches 65 years of age, whichever comes first. This composition ensures the protection of institutional independence, continuity, and professional oversight in the recruitment of public servants.

A Detailed Look at the 12 Groups of CSS

1. Pakistan Administrative Service (PAS)
2. Police Service of Pakistan (PSP)
3. Foreign Service of Pakistan (FSP)
4. Inland Revenue Service (IRS)
5. Pakistan Customs Service (PCS)
6. Pakistan Audit and Account Service (PAAS) (A Key Financial Role in the CSS Groups)
7. Commerce and Trade Group (CTG)
8. Information Group (IG)
9. Military Lands and Cantonment Group (MLCG)
10. Office Management Group (OMG)
11. Postal Group
12. Railways Commercial and Transportation Group

Source: https://cssaspirant.com/the-12-groups-of-css/

FPSC Report 2022 describes the Commission's functions, which are encompassed in Section 7 of the FPSC Ordinance, 1977. It involves the Commission's responsibility for holding competitive exams and screening tests for recruitment of civil services and civil posts in Basic Pay Scale-16 and above, or equivalent posts in the Federating Units. Apart from recruitment, the Commission has a consultative role concerning the position, strategy, and governing rules of the first appointment. The structure has the Chairman as the head of the department, whilst the Secretariat, which is headed by a Secretary, is divided into specific Wings which are each headed by a Director General.

These are the IT Wing, Administration Wing, Curriculum Development and Research Wing, Recruitment Wing, CE (CSS) Wing and the Secrecy Wing. It is through these Wings that the Commission is able to carry out its constitutional obligations in a transparent and efficient manner. FPSC Report (2023)
See appendix I & II.

Limitations of the Study

The study focuses only on a detailed analysis of the CSS English Essay paper and does not consider other compulsory and optional papers in the CSS examination system. Although candidates may choose from a total of six other papers in addition to the six compulsory papers, these components are irrelevant to the current study and will not be discussed.

Further Research Gap

The study contributes to identifying further research gaps by inviting other scholars to examine the other five compulsory papers and the six optional papers of the CSS examination, thus, expanding the academic research potential of the entire evaluation system. The Central Superior Services (CSS) exam features a specialized form of institutional discourse that requires clear argumentation, a well-defined structure, and a critical understanding of socio-political issues. The English Essay paper assesses students' ability to develop long, reasoned arguments and to not just write what has been memorized. Conversely, exam-centered recall is at the core of writing pedagogy in undergraduate studies in Pakistan. Thus, the vast majority of candidates begin writing their CSS exams without sufficient exposure to CSS-regulation writing, which involves argumentative writing, constructing and defending a thesis, and developing coherent and cohesive paragraphs. Safdar et al, (2025)

Discourse competence is a deciding factor of success or failure in the CSS English Essay exam. Discourse competence goes beyond the mastery of grammar. It also includes the analytical and organizational capacity to maintain the coherence of a piece of writing, the judicious and functional use of cohesive devices, and the alignment and regulation of the specific requirements of a given essay question. In CSS exams, candidates demonstrate a lack of control over discourse by presenting

fragmented arguments, pseudo thematic shifts, and poor discourse introduction and conclusion. These weaknesses reflect a discrepancy between the linguistic capacity of a candidate and the use of language in a functional way. It means that candidates possess a very basic level of English but lack the language to be able to posi tion writing in an analytical and persuasive framework. Ratnawati (2026)

Statement of the Problem

The use of cohesive devices is a fundamental component of academic writing since it helps to create coherence and unity among ideas in a text. Writing in the English language has been a significant challenge in Pakistan more specifically in higher education like universities where students are expected to create and consume specialized information. However, students usually struggle with cohesion in their academic writing, which can result in disconnected and poorly structured texts.

Moreover, CSS aspirants have varying proficiency levels in the English language, which may have an impact on how well they can use cohesive devices. Students have trouble achieving cohesion while writing in a second language. CSS aspirants in different disciplines at FSS such as Education, Psychology, Mass Communication, International Relations, and Pakistan Studies encounter many difficulties while writing in English and do not study English as their core subject. The lack of cohesion causes an informal piece of writing to lack coherence among sentences and paragraphs as well as organization, objectivity, precision, and clarity. Effective academic writing requires adequate development, unity, and coherence, and it requires an eminent lexical and grammatical involvement to develop writing reflectively. However, students in social sciences tend to focus more on the discourse level rather than the sentential and lexical level, making it challenging for them to produce a coherent piece of writing.

Significance of the Study

The present research contributes to English as second language students, in general, among CSS aspirants. This study has provided the comprehension of the challenges faced by CSS aspirants of their academic writing, so they will not repeat such issues while English essays in future. This research has some implications for CSS aspirants and how improves their academic writing skills by improving upon their

understanding of cohesive devices and by employing them in their academic writing through SFL theory by MAK Halliday and discourse competence. Pan (2021)

The findings of the present study can be used CSS aspirants in future to create effective pedagogical implications that may help CSS aspirants and candidates. How to employ SFL Theory and Discourse Competence effectively in their academic writing. For example, professionals can add lessons in their educational programs and institutions that emphasize the use of reference chains, conjunctions, and lexical repetitions as cohesive devices. Moreover, CSS trainers and professionals provide CSS aspirants with feedback on how well they used cohesive devices and provide them with examples of effective academic writing. CSS aspirants can also use the results of this study to improve their academic writing skills by learning about the various types of cohesive devices and how they can use them appropriately.

Research Objectives

- To explore the most recurring cohesive devices used in academic writing of CSS aspirants in English essay.
- To determine the way the cohesive patterns, enrich academic writing in CSS aspirants.

Research Questions

- What types of cohesive devices are frequently employed in academic writing in English essay of CSS aspirants?
- How do cohesion patterns enrich in academic writing of CSS aspirants?

Research Methodology

This research adopts a qualitative methodology, employing document analysis as the primary research method. Primary sources include FPSC annual reports, examiner remarks, and past CSS English essay results. The texts are studied in relation to the SFL-based framework to map the structures of coherence, cohesion, and argumentation. The nature of this analysis is qualitative, which, in the context of the CSS English Essay examination, helps to identify and understand the systemic linguistics barriers and the trends that indicate the continued failures.

Theory of Systemic Functional Linguistics

This study's main theory comes from Systemic Functional Linguistics (SFL) founded by M.A.K. Halliday. Within SFL, language is viewed as a resource to construct meaning and is contextual. Halliday also examines how documents serve their purposes through coherence, cohesion, and organization. He argues that good writing is about achieving (ideational, interpersonal, and textual) meanings. This CSS English Essay framework, centers on the argument, critical position, and the organization of data into cohesive and persuasive discourse. Previous CSS failure studies focus on linguistic error, the preparation outlines, and discourse-level errors, which study neglects. This study fills the gap by shifting the focus from grammar to discourse, as well as the systemic language deficiency focus within the framework of education and language of Pakistan.

Theory of Discourse Competence

Fauziati (2015), learning a foreign or second language involves more than acquiring grammatical knowledge; it requires developing the ability to use language meaningfully and appropriately in real communicative contexts. This wider ability is often termed as language competence, which includes both knowledge of language systems and the ability to understand and create texts appropriately in a given context. As described in the work of Rod Ellis (1996), the center aim of second language acquisition is to use language in communicative situations, and not so much the acquisition of formal rules. This is consistent with the views of Dell Hymes (1972), which posits that the concept of communicative competence must include the social and functional aspects of language use. In the context of second language acquisition, the intended objective of the process is achieved when a learner is communicatively effective, even in the absence of a native-like command of the language. The communicative approach to language teaching, which developed in the 1960s and 1970s, was a result of the dissatisfaction with audio-lingual and grammar-translation methods that did not provide learners with the necessary skills to communicate. Since then, a number of scholars have developed models for the constituents of communicative competence, which include, among others, grammatical, sociolinguistic, discourse and strategic competence. Some of the most notable of these models include the work of Canale and Swain (19080), Lyle Bachman and Adrian Palmer (1996), and Celce-Murcia and Thurrell (1995).

Review of the Literature

Mahmood & Iqbal (2010), In a multi-lingual country such as Pakistan, the ability to command the English language is a key requirement for success in competitive and high-stakes examinations, as it acts a key determinant in gauging one's ability to perform in the CSS exams, which is the ultimate exam for bureaucratic jobs. English is the language in which the exams are conducted, and even though it is a language requirement at the federal education and ministry levels, most candidates who sit for the exam tend to do really poorly. This is the case with the English Essay as well as the English Language exams, which makes many critics question their ability to express themselves in English and their overall English language proficiency (FPSC, 2023).

Hassan (2017), In Pakistan's government-run educational institutions, the prevailing method of teaching a language focuses on rote memorization, translation, and repetitive grammar activities, and neglects the development of critical writing and advanced academic discursive skills (Rahman, 2002; Shamim, 2008). As a result, a large number of students undertake CSS preparation courses without the requisite linguistic skills, which compensates for the absence of these skills and detrimental to their performance in the exam. Hutchinson and Waters (1987) espouse the view that for the pedagogy of English for Specific Purposes (ESP) to be relevant, a prior determination of the learners' existing knowledge and the gaps in their instrumental competencies that need to be addressed is fundamental. Although such preparatory approaches could be of great value in CSS preparation, most preparatory academies appear to have continued their reliance on a content-based, one-size-fits-all, approach with little to no personal or individual feedback.

Mahboob (2009), mentors and instructors play a pivotal role in guiding candidates through CSS preparation, yet their experiences and insights are rarely documented in academic literature. Instructors can identify recurring linguistic patterns and pedagogical gaps that may be overlooked in broader analyses. Basturkmen (2010) suggests that designing curriculum based on instructors' perceptions is essential in order for learning goals to be achieved in an ESP setting. Exam-centered teaching in Pakistan has been shown to be insufficient for learners' linguistic needs' in situations where English is neither the first language nor used in the daily verbal communications.

These challenges are further compounded by socio-economic disparities and regional inequities. Students from under-resourced or rural backgrounds often lack early exposure to effective English instruction, resulting in long-term deficiencies in academic reading and writing skills (Mansoor, 2004). Within this context, CSS mentors can act as linguistic gatekeepers, leveraging their experience to design more need-oriented, context-sensitive pedagogical strategies.

English's role in CSS success is well-established, yet little research has been done on the teaching processes involved in the preparation for the CSS. Most previous research has been restricted to the study of past examination papers (Mahmood & Iqbal, 2010), or to the critique of the examination for ideological, and more recently, linguistic biases (Rahman, 2002), ignoring the teaching and learning processes involved in the candidates' success or lack thereof. This study attempts to address the paucity of research in CSS preparation teaching processes by investigating CSS mentors' perceptions of candidates' linguistic deficits and in what ways their understanding can be utilized to make English language teaching more responsive, cohesive, and effective.

Lascu (2023), the present paper will endeavor to analyze how literary works can help an English language learner develop their discourse competence from a discursive perspective. Given that the role of Integrated Language Learning (ILL) is still being determined, the present paper will attempt to articulate how the elements of language, the social context of language (or phenomena), and the structure of language are used to achieve a social purpose. Following the current trends in the European Education Area, the literary work will be deemed a primary pedagogical tool by which the learners will be able to achieve an optimal level of their communicative potential. The paper relies on the collected data to formulate a preliminary theory of discourse competence, in which the author prioritizes discourse on the spectrum of communicative competence. The author argues that from a discursive perspective, the construction of a text is a powerful tool for analyzing the interface of language, purpose, and the social context. The present study also outlines some of the prerequisites for engaging language learning activities (beyond the mere communicative role of language) that will help learners to develop the capacity to write texts that are coherent, purposeful, and appropriate to the context. This is particularly important in higher education institutions where the writing is considered to be of a 'discourse competent' level (i.e. where the merit of writing rests

upon the writer's ability to use the required rhetoric rather than the grammatical correctness).

Kyrpychenko et al, (2021) The article considers the development of communicative competence as a fundamental demand of all professions for which students are being trained in higher education, and how the degree of development of communicative competence relates to the degree to which students are able to function in various social and professional roles. The study, which is concerned with teaching a foreign language to students of economics, seeks to identify the constituent elements and the underlying principles of communicative competence, as well as the teaching methods that can lead to the progressive development of communicative competence. In this regard, the study also treats economic texts as the main communicative tool to assess the professional use of language and to allow students to learn the language of their particular field and use the language of their particular field in authentic situations. The study employs an interdisciplinary approach, incorporating an integrated theoretical and empirical analysis of linguistics, psychology, psycholinguistics, and methodology, and is based on empirical data obtained from questionnaires and surveys administered to the study's undergraduate participants. The study confirms that the use of participatory, interactive, and text-based teaching methods improves the students' communicative competence, especially at the intermediate and advanced levels. The study concludes that the use of specificity-oriented and context-oriented teaching methods improves the pedagogical practice of communicative competence, which is especially true for high-stakes academic and professional writing exercises, such as the CSS English Essay examination, where specific discourse knowledge and not knowledge of the language is required for success.

Glaesser (2019), this paper critically analyzes the uses and interpretations of the term competence in academic work and the specifics of educational policy, using foreign language education as an example of a sustained focus. The paper discusses the historical development and current contexts of the use of the term competence in academic writing, followed by an analysis of the current policy usage of the term. Some focus is placed on the increasing use of competence in educational policy literature and research, illustrated with the PISA assessments that have influenced the global conception of learning outcomes. The paper then shifts focus to Germany, analyzing the policy discourse on the educational reforms that have been instituted in the last three to four years which have called for greater competence-based

teaching as well as reforms related to the accountability and standardization demands. The paper discusses the relationship between the concepts of competence and standards and the confusion that may arise when policy analysts use the terms interchangeably. Finally, the author analyzes the national German curriculum and the Common European Framework of Reference for Languages policy documents to interrogate the extent to which the notion of competence is clearly articulated and consistently applied within the documents.

Abdulrahman & Ayyash (2019), This research examines linguistic, communicative, and interactional competence and how these three combines in second language teaching, learning, and assessment. Although countless studies have focused on each of the competencies, little to no research has been done in the manner of considering all three. This paper endeavors to remedy this by considering each of the three as (1) history of the competencies, and (2) the state of research and the concerns together with potential solutions. The relations of the competencies and their implications to language pedagogy, assessment, and learner outcomes are the bases of the recommendations that the study has to offer, and the recommendations are centered on the integration of the three competencies in teaching to attain balanced language proficiency.

Haratyan (2011), describe the within discourse-oriented approaches to language analysis, M.A.K. Halliday's Systemic Functional Linguistics (SFL) provides a robust theoretical framework for examining how linguistic form interacts with socio-culturally constructed meaning in texts. Adopting Halliday's view of language as a social semiotic, a number of scholars, point out that in the study of a text, the meaning cannot be grasped at a surface level, understanding the meaning at a deeper level that involves social ideologies, and the social context in which the text is embedded is crucial. There are Critical Discourse Theorists such as Norman Fairclough and Roger Fowler, who argue that the linguistic options taken in a text express certain ideological construction of the world, the power relations and assumptions which exist, and therefore, one has to be able to stretch the analysis of the discourse beyond the text.

In Halliday's (1973) view, the social context is responsible for shaping the author's linguistic and analytical options, and as a result the social context determines how reality is perceived and expressed; and, discourse-level analysis is therefore, of crucial

importance. Halliday identifies three configurations that are of particular importance; in each of these, the author serves at least three primary social purposes: the ideational function, in which the author creates an experience and express a reality through a particular process (e.g 'transitivity'); an interpersonal function, in which the author attempts create social relations, and expresses attitudes and evaluative positions through the use of particular mood and modality; and, a textual function, in which the author arranges and organizes meaning through the use of a particular theme, and through the use of cohesive devices. With reference to the CSS English Essay examination in Pakistan, these three metafunctions are critical in analysis of candidates' discourse competence because most candidates fail because of poor ideational, interpersonal and textual coherence. SFL-based analysis creates an understanding of how weak control of discourse and language barriers help explain the sustained patterns of failure in high-stakes academic writing assessments such as the CSS essay.

Almurashi (2016), In linguistic theory, numerous frameworks have attempted to explain the nature and function of language; however, M.A.K. Halliday's Systemic Functional Linguistics (SFL) remains one of the most comprehensive and influential approaches, particularly within applied linguistics and discourse studies. SFL analyzes a wide variety of texts and how writers possible and chooses linguistically resources given a range of social contexts and purposes. It breaks away from frameworks which view syntactic structures and rules as foundational to language and view grammar as a given. In addition to focusing on socially relevant language use, SFL also uniquely integrates specific functional elements in its analyses - context, the metafunctions, and choice. Because SFL considers and integrates such a wide range of communicative and socially specific elements in language, it can go beyond surface grammar to analyze the construction of meaning in the text, which is why it has been employed for the analysis of academic writing, institutional discourse, and educational texts. In context of the second language teaching and learning, SFL's pedagogy provides learners a functional approach and reframes the way they conceptualize language from a prescriptive, decontextualized, and rule-based system to a socially relevant and purposeful system, which is functional for analyzing the construction of discourses and the use of language to overcome or create a the 'gap' in the English language in the CSS English Essay examination in Pakistan.

Ruddick (2007) explains Halliday's Systemic Functional Linguistics (SFL) considers language as a system of options that are almost infinite where the speaker or writer uses language to create meaning in a context. Halliday explains that meaning is not in the language as an isolated entity, but meaning comes from choosing one of many possible options in a network of options. That explains the value of the meaning socially in a context, which Roger Fowler and Caroline Coffin identify the use of language in a context as a cultural, social, educational or institutional. From an SFL point of view, the speaker's or writer's linguistic choices are influenced by their social class, educational level, and social roles, which together is a socially determined limited meaning. Therefore, texts are not neutral representations of reality but socially situated constructions that reflect particular worldviews and experiences. This is particularly relevant in the context of the CSS English Essay exam in Pakistan, as the candidates' essays demonstrate an inability to make appropriate linguistic and discursive choices due to the limited engagement with academic English discourse and unequal educational backgrounds.

The texts created during the exam provide an understanding of the student's worldview, ability to analyze theory abstractly, and their discourse competence. A fundamental principle of SFL is that the interaction of language, context, and social intent aids in the construction of meaning. This principle guides one to analyze the continual language gaps and discourse shortcomings in the CSS English Essay.

Halliday & Matthiessen (2013) the Systemic Functional Linguistics (SFL) book by M.A.K. Halliday and Christian M.I.M. Matthiessen considers a framework of grammar that reflects meaning-making instead of prescriptive grammar. The book first published in 2004 and revised in 2014, describes how grammatical choices operate the three metafunctions (ideational, interpersonal and textual) of grammar, through which the speaker/writer construes experience, creates social relations and structures discourse. The author’s presence in the field of transitivity, mood, modality, thematic structures and cohere, demonstrates how a text achieves social purpose, function, and coherence in a given social context. It’s this form of influence that has shaped applied linguistics, and more specifically, academic discourse. The influence of Halliday and Matthiessen stretches even further. In the context of the CSS English Essay examination in Pakistan, Halliday and Matthiessen’s model provides a lens that explains candidates’ weaknesses in developing argument, sequence a theme (thematic progression), and maintain a stretch of text (cohesive

control) that is beyond encode, i.e. the grammatical aspect, and more so in the area of discourse competence in a context that demands sophisticated academic writing.

Raeisi et al, (2019), The current research analyzes the lexicogrammatical characteristics of academic journal abstracts of native and non-native speakers in educational psychology and applies the work of M.A.K. Halliday to Systemic Functional Linguistics (SFL). The study's corpus includes thirty abstracts, fifteen of which are by native speakers and fifteen by non-native speakers, collected from a pair of top international journals. The study's analysis focused on three variables: lexical density, adjuncts, and transitivity. The research discovered that both native speakers and non-native speakers had about the same level of lexical density, and therefore no meaningful distinctions could be made. Circumstantially, however, non-native speakers relied more on adjuncts than native speakers. Non-native speakers also possessed more complete transitivity than native speakers in the sense that, of all the transitivity processes (material, mental, relational, verbal, behavioral, and existential), non-native speakers used more than non-native speakers. The identified differences in the level of discourse and the way that non-native and native academic writers construct meanings are of the utmost importance. The study further suggests that, in order for EFL students to construct discourse in sophisticated ways in academia and the workplace, particularly in regard to journals and exams, functional writing instruction, which is rooted in SFL, is highly recommended.

Lai & Hu (2021) focuses the need for incorporating “Applied Linguistics” methods like Communicative Grammar, Systemic Functional Linguistics, Pragmatics, and Cognitive Linguistics in teaching foreign languages. He states that the teaching and learning processes in language education should integrate conventional applied linguistics along with technology-based methods. Based on the notion of Applicable Linguistics by M. A. K. Halliday, he points out that it is necessary for teachers to choose appropriate theoretical frameworks depending on particular teaching situations. Additionally, Hu observes that the modern education of languages faces the new difficulties of technology, interdisciplinary approaches, and education on the internet.

Wang & Ma (2022), M.A.K. Halliday (1925–2018) was the esteemed founding father of Systemic Functional Linguistics (SFL). Halliday is often commended for having one of the most profound impacts for the 20th century due to the sheer magnitude of the

impact he had on the field of language theory, pedagogy, and language application. SFL is unique in the theory of language as a social semiotic. SFL takes the position that all elements of language (e.g. syntax, morphology, semantics, phonology etc.) exist in a close and interdependent relationship to social phenomena. Halliday views language as a vast network of meaning, and a system that is a choice. He places social relations and the organization of discourse as the most important social relations. The volume being reviewed is an introduction to Halliday's contributions, and his life that is comprehensive, yet maintains a good balance between accessibility and complexity. It is a book that SFL specialists and scholars of other traditions will appreciate. It covers, demonstrates the breadth of values in his framework in a number of different areas of linguistics, and deconstructs important elements of his work. The book is divided into six sections: Hallidayan Conversations, the Architecture of Language, Key Theoretical Constructs in SFL, SFL Systems and Modes of Meaning, and SFL and Halliday: Us and Them. The book is one of the first and most important books and foundational volumes of SFL, Discourse Analysis, and other branches of Language studies. It will be a book that is invaluable to users of Halliday's work and the whole of the legacy of the Hallidayan tradition.

Discussion

II **CSS Competitive Examinations (Last five year profile)**

Table 42: CSS Competitive Examinations finalized (Written Part)

S No	Activity	CE-2019	CE-2020	CE-2021	CE-2022	CE-2023
1	No of Applicants	23,403	39,630	39650	32059	28024
2	No of Candidates Appeared in all papers of CSS C.E	14521	18,553	17240	20262	13008
3	% age of applicants appeared in Exam	62%	47%	43%	63%	46%
4	No. of Qualified Candidates in Written Examination	372	376	365	393	401
5	% of Qualified Candidates out of candidates appeared	2.56	2.03	2.02	1.94	3.06
6	No of Candidates finally Passed	365	364	349	374	386
7	% of candidates finally passed	2.51	1.96	2.02	1.84	2.96
8	No of vacancies announced	410	447	436	463	458
9	No of Candidates allocated	214	221	207	239	210
10	No of vacancies unfilled	196	226	229	224	248

III **Last five years profile candidate's passing ratio in (Compulsory/Optional) subjects:**

Table 43: Passing ratio of candidates in CSS (Compulsory Subjects) during last five years

Compulsory Subjects in the year-2019	Marks	Appeared	Failed	%	Passed	%
English Essay	-	14205	13328	94	877	6
English (Précis and Composition)	-	14205	10440	73	3765	27
General Science and Ability	-	14205	6492	46	7713	54
Current Affairs	-	14205	10139	71	4066	29
Pakistan Affairs	-	14205	5275	37	8930	63
Islamiat/Comparative study of Major Religions	-	14205	2526	18	11679	82
Compulsory Subjects in the year-2020						
English Essay	-	18387	17735	96	652	4
English (Précis and Composition)	-	18387	7244	39	11143	61
General Science and Ability	-	18387	7936	43	10451	57
Current Affairs	-	18387	9977	54	8410	46
Pakistan Affairs	-	18387	12999	71	5388	29
Islamiat/Comparative study of Major Religions	-	18387	9350	51	9037	49
Compulsory Subjects in the year-2021						
English Essay	-	16887	14760	87	2127	13
English (Précis and Composition)	-	16887	15457	92	1430	8
General Science and Ability	-	16887	13750	81	3137	19
Current Affairs	-	16887	16396	97	491	3
Pakistan Affairs	-	16887	7709	46	9178	54
Islamiat/Comparative study of Major Religions	-	16887	13694	81	3193	19
Compulsory Subjects in the year-2022						
English Essay	-	19440	19220	99	220	1
English (Précis and Composition)	-	19445	16603	85	2842	15
General Science and Ability	-	19445	2481	13	16954	87
Current Affairs	-	19445	11112	57	8333	43
Pakistan Affairs	-	19445	19363	99	82	1
Islamiat/Comparative study of Major Religions	-	19445	8430	43	11015	57
Compulsory Subjects in the year-2023						
English Essay	-	12150	11849	98	301	2
English (Précis and Composition)	-	12150	9773	80	2377	20
General Science and Ability	-	12150	7776	64	4374	36
Current Affairs	-	12150	5917	49	6253	51
Pakistan Affairs	-	12150	10127	83	2023	17
Islamiat/Comparative study of Major Religions	-	12150	2999	25	9151	75

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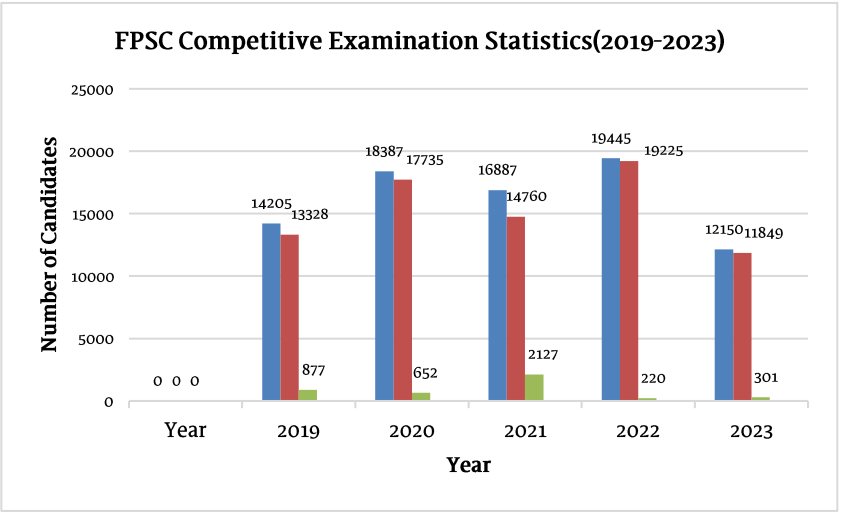
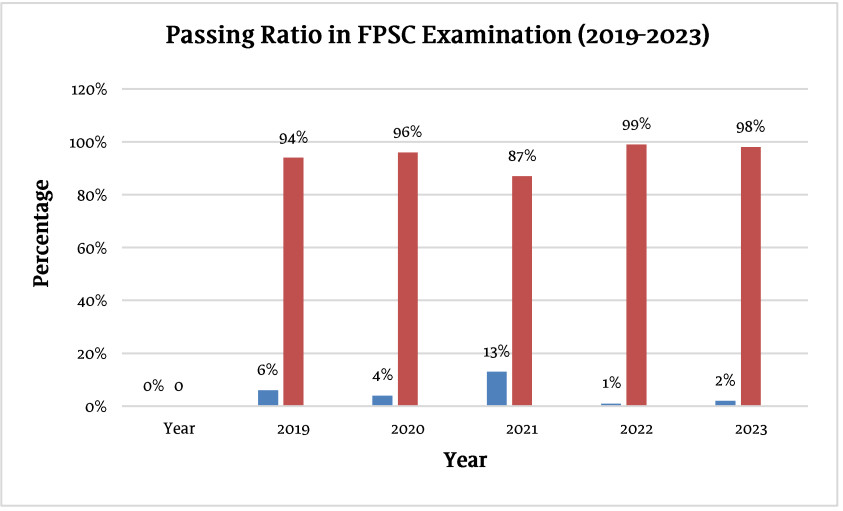
Source: https://www.fpsc.gov.pk/assets/media/2025-08-15-08-22-35-Annual-Report-2023.pdf

Examining the CSS Competitive Examination from 2019 to 2023 reveals one of the lowest success rates despite thousands of applicants each year. While applicants totaled between 23000 and 40000 each year, only 43%-63% of applicants showed up to the written exams. Disturbingly, the percentage of candidates who passed the written exam was between 1.94% and 3.06%. This means the written exam is the biggest issue in passing the CSS exam. Over the last five years, the final pass percentage has also remained below 3% which shows the incredibly selective nature of the CSS examination system.





Even the compulsory papers show the CSS exam's Selectivity. The English Essay paper has one of the lowest pass rates in the exam. With a failure rate of 94% in 2019, in 2020, 96%, whereas in 2021 87%, the problem got worse with a failure rate of 99% in 2022 and 98% in 2023. This means the pass rate was 1-2%. Other compulsory subjects had a higher and more consistent rate of passing compared to the English Essay paper. There is an even starker contrast in the English essay paper and the English précis and composition paper. There is also a lot of variability in the English paper, however, in most years; the pass rates are still much higher than the pass rates in the essay paper. This means that the candidates have a command of the basic structure of the language and even the grammatical off the language and the structure of the language. However, the candidates have an issue when it comes to writing long pieces of work, particularly those that require a good deal of coherent writing, including the development and theillustration of the arguments, and the18 sort of writing that does require high levels of critical thinking and analysis.

The data show that the long-standing CSS exams and their low passing rates are not exclusively related to the nature of the subjects and the number of candidates. They also reflect enduring systemic deficiencies in training candidates on the writing and discourse components. The primary constraining factor appears to be the English Essay paper. This suggests that CSS success rates are not going to improve significantly unless there are concerted efforts to teach relevant higher order writing skills, and in particular, the ability to construct reasoned and critical arguments.

The Central Superior Services (CSS) exams are a big part of how the government works in Pakistan since they are the main way to get people into the civil service jobs of the federal government. A big part of these exams is the English Essay paper, which is the major problem most candidates face. Many students do know the subject, and can speak with good enough grammar, but most can't do well enough to pass this paper. The problem must be more than just individual issues with writing, since more and more students continue to fail each year. The can be attributed to the larger issues with the system.

Being able to put your ideas together to make a good argument, and stay on topic, is an important part of good academic writing. On the CSS English Essay exam, candidates have to make sense of complex questions, carry out structured arguments, and respond critically to questions about social, political, economic and policy-related

issues. But examiners and the FPSC Evaluators say, time and time again, candidates have a problem with coming up with ideas, staying on topic, and making good, clear, and logically analyzed arguments, while all the other students, appear to have a good command of English and good sentence structure.

Conclusion

The CSS exam system has a very big problem and that problem is the language barrier. English is an official language of Pakistan; however, it is not the national language and it is not the first language of most of the candidates. Many CSS exam aspirants, especially those with a public-sector/rural educational background, have in fact very little exposure to English, other than, memorization of textbook content and exam-based practices, in a very mechanical manner. Because of the educational background of these candidates, the absence of training in English in persuasive argumentative style writing is a huge disadvantage.

In addition, the CSS English Essay paper is not a language test, but rather a test of candidates' intellectual maturity, critical thinking, reasoning, and policy-centered thinking; all of which are critical for civil service candidates. Candidates' inability to address the questions in the essay is not a sign of a lack of ideas, or a sign of a lack of intelligence. Most of the time, candidates lack the experience with particular academic writing styles. Without sufficient instruction for the writing, candidates will always be at a substantial disadvantage to other's expectations of their writing for the most important writing tasks in their academic careers.

In this context, the current research places Systemic Functional Linguistics and discourse competence at the center of attention with the CSS essay writing failure. The current research examines the FPSC report and examiner comments, as well as a selection of CSS essay papers to identify and highlight recurrent discourse-level deficiencies and call for a change of paradigm. Teaching writing at the level of academic discourse, argumentation, and genre-specific essay writing will fulfill the long overdue, systemic, structural, and relevant changes to the CSS examination paradigm.

Findings

An analysis of the CSS examination results over the previous five years indicates a consistently low pass ratio in the English Essay paper, highlighting it as a major impediment to overall candidate success. This persistently poor performance reflects deep-rooted deficiencies in candidates' academic writing skills, particularly in areas such as argument development, coherence, cohesion, and critical engagement with topics. The findings indicate that inadequate discourse competence—evident in poor idea organization, limited genre awareness, and ineffective deployment of language resources—substantially weakens essay quality. Within this framework, academic writing pedagogy grounded in discourse competence and Systemic Functional Linguistics (SFL) offers a promising avenue for improvement. By focusing on the functional interplay between language, meaning, and context, SFL-informed instruction can provide candidates with the linguistic and rhetorical capabilities required to respond effectively to the analytical and discursive demands of the CSS English Essay paper, thereby targeting a key structural weakness in the examination system.

In spite of the test designers declaring objectives relating to the test takers concepts, language and writing, the test evaluators comments continue to report the same weaknesses in each of these areas every year. These include, lack of clarity in conceptual thinking, lack of depth in the knowledge of the area, poor grammar, poor vocabulary, and stereotypical writing to name a few. Considering the examination of the Civil Services Selection (CSS) in the context of the argumentative essay, the requirement and expectation, lacked the Prep used for the examination, sifted from a high, middle of the range to the low in the advocated range of values and in the context of the argumentative essay, the requirement and expectation, lacked the Prep used for the examination, sifted from a high, middle of the range to the low in the advocated range of values and in the context of the argued essay.

The general performance of the English Essay (EE) Test was low and many candidates failed. Organizing the ideas in a particular sequence and supporting the arguments with evidence or important research was lacking and in its absence a domino system was displayed, lacked a flow i.e., it lacked a domino system. Overall the ideas were poor, the arguments were unbalanced and the research was irrelevant. The discriminatory value of the research was unimportant to the skeleton and wings of

the essay, as reflected in the poorly constructed wings and poorly identified outlines, wings and poorly constructed outlines.

Evaluating the essays across the various dimensions of argumentation, relevance, expression, and depth of thought, revealed even more deficits. Quality of critical thinking was consistently low, with most students failing to identify the main argument entailed by the question. They often demonstrated irrelevant or insufficient content, and the misuse of English was rampant: erroneous constructions, grammatical and spelling mistakes, and so on. Overall, the responses demonstrated very little improvement in the intellectual level, and, in many instances, candidates did not even address the most fundamental requirements of the question.

Recommendations

- A good essay is not supposed to reflect crammed information or bookish knowledge about the topic. It should rather tell us about the writer's personal feelings or thoughts about it, and his ability to convert these feelings and thoughts into arguments for convincing the readers.
- Its basic stance should be creative, critical and analytical rather than narrative or descriptive.
- Coherence in arrangement of material/paragraphs (SFL Theory by MAK Halliday)
- Cohesion in development of argument reaching the conclusion (SFL Theory by MAK Halliday)
- It should have a balanced body, with a beginning, middle and end-each one serving its own distinct purpose. (Bailey, 2011 Academic Writing)
- Paragraph transition/Discourse markers/ Discourse Competence
- Have a reasonable contention or point of view, so the examiner knows from the start what the candidate means to state, and can follow the advancement of his/her contention all through the easy.

Pedagogical Implications

The pedagogical implications of the study rest in its capacity to inform improvements in CSS pedagogy, examiner practices, and policy-level reforms. By foregrounding

discourse competence as a central concern, the research offers a more balanced and equitable explanation of CSS failure, moving beyond the dominant narrative that attributes weak performance solely to individual deficiency. Its findings can assist teachers, policymakers, and aspirants in developing more effective strategies for preparation and assessment.

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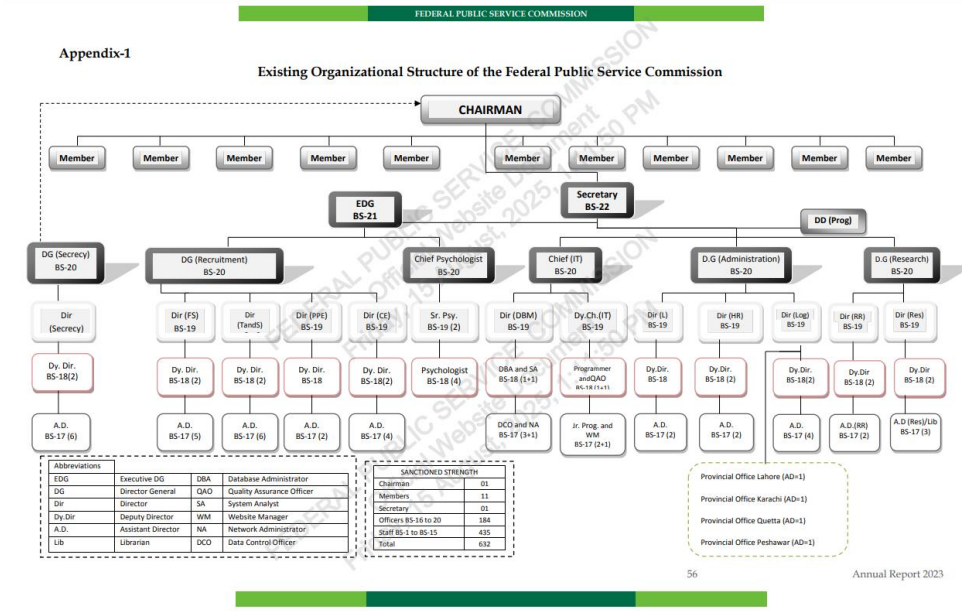
FEDERAL PUBLIC SERVICE COMMISSION
Appendix-1
Existing Organizational Structure of the Federal Public Service Commission
CHAIRMAN
Member
Secretary BS-22
EDG BS-21
DD (Prog)
DG (Secrecy) BS-20
DG (Recruitment) BS-20
Chief Psychologist BS-20
Chief (IT) BS-20
D.G (Administration) BS-20
D.G (Research) BS-20
Dir (Secrecy)
Dy. Dir. BS-18(2)
A.D. BS-17 (6)
Dir (FS) BS-19
Dir (Tands) BS-19
Dir (PPE) BS-19
Dir (CE) BS-19
Sr. Psy. BS-19 (2)
Dir (DBM) BS-19
Dy.Ch.(IT) BS-19
Dir (L) BS-19
Dir (HR) BS-19
Dir (Log) BS-19
Dir (RR) BS-19
Dir (Res) BS-19
Dy. Dir. BS-18 (2)
Dy. Dir. BS-18
Psychologist BS-18 (4)
DBA and SA BS-18 (1+1)
Programmer andQAO BS-18 (1+1)
Dy.Dir. BS-18
Dy.Dir. BS-18(2)
Dy.Dir BS-18 (2)
A.D. BS-17 (5)
A.D. BS-17 (2)
A.D. BS-17 (4)
DCO and NA BS-17 (3+1)
Jr. Prog. and WM BS-17 (2+1)
A.D. BS-17 (4)
A.D (RR) BS-17 (2)
A.D (Res)/Lib BS-17 (3)
Provincial Office Lahore (AD=1)
Provincial Office Karachi (AD=1)
Provincial Office Quetta (AD=1)
Provincial Office Peshawar (AD=1)
Abbreviations
EDG Executive DG
DG Director General
Dir Director
Dy.Dir Deputy Director
A.D. Assistant Director
Lib Librarian
DBA Database Administrator
QAO Quality Assurance Officer
SA System Analyst
WM Website Manager
NA Network Administrator
DCO Data Control Officer
SANCTIONED STRENGTH
Chairman 01
Members 11
Secretary 01
Officers BS-16 to 20 184
Staff BS-1 to BS-15 435
Total 632
56
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Appendix-2

Commission and Staff Position as on 31-12-2023

S. No.	Nomenclature of Post	BS	Sanctioned Strength	Existing Strength	Vacant Posts
1	Chairman	Tenure	1	0	1
2	Members	Tenure	11	8	3
3	Secretary	22	1	1	0
4	Executive DG	21	1	0	1
5	Director General	20	5	5	-
6	Chief Psychologist	20	1	0	1
7	Chief IT	20	1	0	1
8	Director	19	10	5	5
9	Senior Psychologist	19	2	1	1
10	Director (Computer)	19	1	1	-
11	Deputy Chief IT	19	1	0	1
12	Senior Private Secretary/PS	18/17	14	14	-
13	Deputy Director	18	16	10	6
14	Psychologist	18	4	4	-
15	System Analyst	18	1	1	-
16	Programmer	18	1	1	-
17	Data Base Administrator	18	1	1	-
18	Quality Assurance Officer	18	1	1	-
19	Junior Programmer	17	2	2	-
20	Website Manager	17	1	-	1
21	Network Administrator	17	1	1	-
22	Data Control Officer	17	3	3	-
23	Assistant Director	17	40	37	3
24	Librarian	17	1	1	-
25	Transport Officer	16	1	-	1
26	Superintendent (Record)	16	1	1	-
27	Deputy Assistant Director	16	11	11	-
28	System Operator	16	3	3	-
29	Computer Operator	16	1	1	-
30	Data Processing Assistant	16	18	15	3

Appendix-2

Commission and Staff Position as on 31-12-2023					
S. No.	Nomenclature of Post	BS	Sanctioned Strength	Existing Strength	Vacant Posts
31	Hardware Engineer	16	1	1	-
32	Assistant Network Admin.	16	5	3	2
33	Assistant Private Secretary	16	33	20	13
34	Draftsman-cum-Artist	16	1	1	-
35	Assistant	15	66	62	4
36	Statistical Assistant	15	6	6	-
37	Stenotypist	14	49	37	12
38	Security Supervisor	14	1	1	-
39	Library Assistant	14	1	1	-
40	Telephone Operator	14	2	2	-
41	Data Entry Operator	14	17	13	4
42	Upper Division Clerk	13	35	30	5
43	LDC/Security Clerk	11	65	59	6
44	Book Sorter	5	1	1	-
45	Driver	4	37	37	-
46	Dispatch Rider	4	2	2	-
47	Duplicating Machine Operator	4	3	3	-
48	Electrician	4	1	1	-
49	Lift Operator	3	3	3	-
50	Daftry	2	16	14	2
51	Qasid	2	16	14	2
52	Naib Qasid	1	77	76	1
53	Farash	1	2	2	-
54	Chowkidar	1	10	10	-
55	Security Guard	1	9	9	-
56	Bus Cleaner	1	1	1	-
57	Khakroob	1	15	15	-
Total			632	553	79

Appendix III

Former Chairman's of the Federal Public Service Commission 1947 to onwards

Name	From	To
Mian Afzal Hussain	1947	30 September 1952
Zakir Hussain	20 October 1952	19 October 1957
Mian Aminud Din	21 October 1957	March 1958
Col (Retd) A. S. B. Shah	April 1958	14 June 1963
Kazi Anwarul Haque	15 June 1963	28 March 1965
Agha Abdul Hameed	20 April 1965	25 February 1966
Nazir Ahmed	8 March 1966	1 May 1969
Ali Asghar	19 May 1969	3 February 1972
S. Manzoor Elahi	19 February 1972	15 March 1972
Justice (Retd) Faizullah Kundi	16 May 1972	22 December 1977
Lt General (Retd) M. Attiqur Rehman, MC	26 December 1977	25 December 1985
Admiral (Retd) M. Sharif, NI(M), HJ	28 January 1986	27 January 1991
Zahur Azar	28 January 1991	28 January 1994
Justice (Retd) Zafar Hussain Mirza	28 January 1994	28 January 1997
Lt General (Retd) Mumtaz Gul, HI(M), TBT	18 February 1997	17 February 2002
Air Marshal (Retd) Shafique Haider, HI(M)	25 February 2002	10 February 2003
Lt General (Retd) Jamshed Gulzar, HI(M)	31 March 2003	30 March 2006
Lt General (Retd) Shahid Hamid, HI(M)	31 March 2006	30 March 2009
Justice (Retd) Rana Bhagwandas	17 December 2009	16 December 2012
IGP (Retd) Malik Asif Hayat	16 December 2012	2014
Naveed Akram Cheema	2014	2018
Haseeb Akhtar	2018	2020
Captain (Retd) Maroof Afzal	2020	2020
Shahid Ashraf Tarar	2023	october 2024
Lt.General(Retd) Akhtar Nawaz Satti	9 October 2024	Incumbent

Source:https://en.wikipedia.org/wiki/Federal_Public_Service_Commission

CHAPTER FIFTEEN

Logistics System Transformation in the Age of Climate Change

Mesut Selamoglu[1]

Abstract

Weather extremes grow more common, unsettling paths goods travel across countries. Sea levels climb, roads flood, cold stores fail - operations falter under new climate strains. Because of this pressure, companies rethink old habits rooted purely in cutting expenses. Instead, durability and care for ecosystems begin shaping decisions once driven by speed alone. Logistics now balances savings with survival, adapting routes and methods to last longer amid instability. One key part of this change focuses on cutting emissions tied to moving goods. Where possible, companies shift toward rail or shipping instead of relying solely on trucks. Investment goes into vehicles that pollute less, along with fuels like hydrogen or electricity. These mixed-method approaches work better when paired with smart scheduling software. Such systems help adjust routes quickly, pack shipments tighter, saving energy across networks. Digital aids play a role too - live monitoring, pattern-based predictions, and supply estimates reduce empty runs. Efficiency improves because information flows faster than before. Less downtime means fewer wasted resources during delivery cycles. Pressure from regulations speeds up change. As global climate deals gain strength, company choices shift under new rules. National limits on emissions guide business strategies more each year. Firms begin tracking progress openly, setting clear green objectives. Compliance pulls them forward - yet reputation pushes just as hard. Standing tall in public view now depends on ecological results. Performance shapes how suppliers see one another. Alliances form based on shared environmental standards. Trust builds where impact is visible. Markets reward those who show rather than promise. Resilience matters more now than before. When disruptions hit, supply chains stay functional through varied sourcing - alongside stock management that adapts easily. Hubs spread across regions help maintain flow even under pressure. This shift shows a deeper understanding: keeping economies running does not harm environmental care - in fact, one strengthens the other. What once seemed at odds now moves together.

Keywords: Supply chain resilience, Sustainable logistics, Low-carbon transportation

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Introduction

Out here, climate shifts are hitting hard - economies feel the squeeze as old ways of working start to crack. Storms show up more often now. Emissions climb. Rules tighten. Firms take another look at what they do because of it. Logistics? That piece matters deeply. It ties into movement, power use, across borders. Not loud, but vital. When fuel burns, when goods shift worldwide, this network pulses at the core (IPCC, 2023).

With every mile trucks travel, economies grow - yet so does pollution. Emissions from freight move hand in hand with oil reliance, spreading wider as delivery routes multiply (McKinnon, 2018). Online shopping surges, linking continents through goods - and leaving heavier marks on air and land. Pressure builds quietly: governments watch, fund managers take notes, people expect change (World Bank, 2022).

When storms hit, roads crack under heat, or rivers overflow, trucks stall and deliveries fail. Heavy rains mess up schedules just as much as scorching days slow down workers and machines. Supply routes break when nature turns unpredictable. Stronger planning helps keep goods moving even when skies go wild. Flexibility matters more than speed once chaos kicks in. Unexpected delays expose weak spots in how things get shipped. Networks must bend without snapping under shifting conditions (IPCC, 2023).

Now things have shifted - cleaning up shipping routes is no longer just about helping nature, it's become essential for staying competitive. Companies pour money into cleaner trucks, new types of fuel, smart software that cuts waste, along with loops where materials get reused instead of tossed. What lies ahead digs into how rising heat waves reshape delivery networks, touching on damage done to ecosystems, forces pushing changes behind the scenes, then exploring roads forward that hold promise for stronger, greener movement of goods (Sarkis, 2021).

Climate Change Implications for Logistics Systems

Heavy weather shows up more often now, shaking how goods move across regions. When storms hit harder or heat waves stretch longer, delivery routes feel the strain. Routes once predictable face delays without warning. Trucks sit still while floods

cover highways. Ships wait offshore during hurricane seasons that never seem to end. Planning gets trickier when rain fails or arrives in torrents. Rail lines buckle under extreme heat nobody expected. Cold snaps freeze loading docks solid. Suppliers scramble when farms lose harvests to drought. Factories slow down if power cuts happen midsummer. Coastal warehouses retreat from rising tides inch by year. Fuel costs climb after hurricanes damage refineries. Delivery times stretch thin across continents. Some ports rebuild higher; others just vanish from maps. Every season brings new hiccups no manual predicted (UNCTAD, 2022).

Heavy fuel use in shipping goods shapes much of the sector's climate impact. Trucks, ships, and planes still run mostly on oil, making them key emitters of planet-warming gases. Pressure grows as governments tighten rules, pushing companies to rethink how they move products. New limits force changes - routes shift, vehicles upgrade, power choices evolve. Rules bite harder now, so old habits fade faster (IEA, 2023).

Flooding doesn’t wait - it hits ports hard, then spreads trouble inland. Highways buckle under extreme heat just as storms knock out rail lines soon after. Warehouses face danger not only from fire but also rising water without warning. When one link fails, delays ripple through the whole delivery chain behind it. Costs climb quietly at first, then sharply when repairs drag on too long. Reliability dips, and trust along with it, leaving planners focused less on speed now. Tougher designs matter more these days than cutting minutes off routes ever did (Pettit, Fiksel, & Croxton, 2010).

Now comes a quiet change, as companies slowly weave green practices into how they move goods. New tools like cleaner engines, smart routing through data, fewer empty miles - each step points to deeper shifts behind the scenes. Not just about saving money anymore; it's about lasting impact shaping decisions day by day. Little by little, old habits fade while smarter, earth-aware methods take hold without fanfare.

Transforming Logistics for a Low-Carbon Future

Now comes a push to cut carbon in shipping, driven by stronger climate goals worldwide. Not just about saving money or moving fast anymore - companies now weigh how green their delivery routes really are. More leaders see it: cleaner transport isn’t optional if we want stable supply lines later on (International Energy Agency, 2025).

Electric cars, hydrogen fuel, biofuels - they're shifting how goods move. Warehouses now run on smarter power setups, cutting waste bit by bit. Machines learn patterns without being told every step. Data flows nonstop, shaping decisions before delays happen. Routes reshape themselves midday when traffic shifts. Trucks carry fuller loads more often than they used to. Empty runs drop without fanfare. Tracking updates silently behind the scenes. Performance climbs because small gains add up. Efficiency isn't forced - it emerges (Ragon, 2025).

Just as crucial? Overhauling how goods move to fit greener transport setups. Intermodal moves help, so do city hubs that group deliveries instead of spreading them out across roads. Shifting cargo from trucks to trains or ships slashes emissions - proven, steady progress there (International Maritime Organization, 2023). Looping used materials back into supply chains cuts waste, sharpens efficiency at the same time. Reuse paths and reclaiming raws quietly trim carbon footprints without fanfare (European Commission, 2024).

Even with progress, shifting to cleaner transport systems is still tricky and patchy across regions. Big expenses hold things back, alongside spotty facilities and doubts about new tools working well. Still, as rules tighten and people demand more responsibility, companies moving early on green shipping methods may find themselves ahead - helping both their position and global climate goals at once.

Strategic and Managerial Implications

Lately, climate worries have pushed green practices way up the list for how companies handle shipping stuff around. Staying on budget and keeping customers happy still matters just as much though. Because of that pressure, choices about where to build warehouses or buy new trucks now factor in carbon footprints more than before. Planning years ahead means weather impacts can't be ignored anymore when mapping out supply routes (Porter & Kramer, 2006).

Firms adjust how they manage things when rules change. Because governments charge for carbon emissions or demand reports on pollution, companies now share more about their shipping practices. Staying within the law matters less on its own - what others think pushes them harder. Being seen as responsible helps stand out,

especially as customers and investors pay closer attention to green issues (Eccles, Ioannou, & Serafeim, 2014).

Now more than ever, companies must adjust how they operate if long-term change stands a chance. Shaping workplace habits around eco-awareness helps set the stage. Building worker skills matters just as much as tighter teamwork between departments. Working closely with vendors, shipping experts, or tech firms plays a growing role too - cutting emissions rarely happens alone when entire networks are involved (Teece, 2007).

Firms weaving sustainability into how they move goods often handle shocks better, dodge bigger risks, stay steady under pressure - opening paths others miss. Saving energy isn't just about lower bills over time; it quietly strengthens reputation, draws patient investors who look beyond next quarter. Climate-aware choices once seen as optional now shape which companies keep pace, adapt faster, outlast the rest (Hart & Milstein, 2003).

Conclusion

Fueled by rising temperatures, supply chains now reshuffle their core goals around greener practices - what once seemed like background noise now shapes major decisions. Since moving goods burns fuel and releases fumes, how we transport items directly affects worldwide attempts to cool the planet. Shifting to cleaner methods isn't up for debate - it simply must happen if clean air and steady markets are to last. Instead of standing still, movement itself becomes part of the solution.

Now here's a different way forward: it takes tech advances, rules that match up, along with real dedication inside companies. Shifting toward cleaner transport options, smarter digital systems, plus stronger infrastructure shows movement is possible even under tough conditions. Still, hurdles remain - costs stay steep, some networks are missing pieces, efforts often fail to sync - and so steady teamwork across government and business becomes necessary just to keep going.

One way forward might involve focusing more on large-scale ways to cut emissions. Better methods for tracking carbon could show clearer results. Green shipping spending brings money questions worth exploring too. Attention to supply chains

that handle climate shifts better seems useful. Mixing in ideas from the circular economy adds another layer. New understanding here would shape how companies act. Rules and decisions by leaders depend on progress like this.

One day, how we move goods might just shape the planet's future. Companies acting early on green goals often find themselves better prepared for shocks. Staying ahead isn’t about speed alone - it’s tied to long-term relevance. Progress here feeds real results in worldwide efforts to slow warming.

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