Review Article

The Molecular Pathways of Diosmetin: A Flavonoid's Role in Preventing Chronic Diseases

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ABSTRACT

Diosmetin is a flavonoid predominantly found in citrus fruits that has recently attracted research interest as a potential candidate for preventing chronic diseases such as diabetes, cardiovascular diseases, neurodegeneration, and inflammation. This review aimed to analyze the molecular mechanisms underlying diosmetin's anti-diabetic, anti-inflammatory, antioxidative, and neuroprotective activities. A comprehensive literature search was performed on studies published between 2000 and 2024 using databases including PubMed, Scopus, and Google Scholar. Diosmetin was found to improve insulin sensitivity by modulating the PI3K/Akt and AMPK pathways and to exert strong anti-inflammatory effects by inhibiting NF-κB and COX-2. As an antioxidant, diosmetin activates the Nrf2 pathway through the expression of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. Additionally, diosmetin protects neurons from oxidative stress and neuroinflammation by regulating multiple cell survival and inflammation pathways. Compared to other flavonoids such as quercetin and luteolin, diosmetin appears to provide enhanced benefits when combined with other compounds. The purpose of this review was to summarize the molecular mechanisms and therapeutic applications of diosmetin.

Keywords: *Diosmetin, Flavonoids, Anti-Diabetic, Anti-Inflammatory, Antioxidant, Neuroprotective, Molecular Pathways.*

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INTRODUCTION

Flavonoids are a group of chemical compounds characterized by a C6-C3-C6 structure linked by two benzene rings through three carbon atoms[1]. They represent a ubiquitous group of naturally occurring polyphenolic compounds characterized by the flavan nucleus and constitute one of the most prevalent classes of compounds in fruits, vegetables, and plant-derived beverages. More than 8,000 compounds with flavonoid structures have been identified, many of which are responsible for the attractive colors of flowers, fruits, and leaves. In plants, these compounds provide protection against ultraviolet radiation, pathogens, and herbivores[2,3]. Diosmetin is a flavonoid particularly abundant in citrus fruits that has attracted considerable research interest due to its broad bioactivity spectrum and potential therapeutic effects[4]. Diosmetin exhibits a variety of biological activities, with its anti-diabetic, anti-inflammatory, antioxidant, and neuroprotective properties being especially interesting to researchers investigating chronic disease prevention[5,6].

Chronic illnesses, including Type 2 diabetes (T2D), cardiovascular disease, and neurodegenerative diseases, are often associated with insulin resistance, chronic inflammation, oxidative stress, and neuroinflammation[7,8]. Therefore, therapeutic approaches using natural molecules like diosmetin that can modulate these underlying pathways may represent promising alternative treatments. Although the bioactive characteristics of diosmetin have been investigated in numerous studies, much of the literature has focused on evaluating its anti-inflammatory and antioxidant properties. The effects of its most active metabolites and their interactions with relevant signaling pathways are not well understood and require deeper investigation.

Despite growing interest in diosmetin due to its promising pharmacological properties—including

antioxidant, anti-inflammatory, and anticancer effects—several significant research gaps remain. Notably, there is a lack of well-designed clinical trials that evaluate its safety, efficacy, and therapeutic potential in human populations. Additionally, established dosing protocols have yet to be determined, limiting its translational potential. Diosmetin's low bioavailability, which restricts its usefulness as a therapeutic agent, also presents a significant obstacle. This review explores diosmetin's molecular mechanisms in chronic disease management while investigating its impact compared to other flavonoids, including quercetin, luteolin, apigenin, and kaempferol. It also examines the potential synergistic effects of combining these flavonoids with diosmetin. By integrating the current literature, this review explains the molecular mechanisms underlying the rational use of flavonoid combinations. This review aims to provide a more comprehensive understanding of diosmetin's preventive health benefits.

METHODOLOGY

This narrative review was conducted to explore and synthesize current knowledge regarding the molecular mechanisms underlying the anti-diabetic, anti-inflammatory, antioxidative, and neuroprotective activities of diosmetin. A comprehensive and systematic literature search was performed to identify relevant peer-reviewed articles published between January 2000 and March 2024. The databases used for the literature search included PubMed, Scopus, and Google Scholar. Keywords and Boolean operators were employed in various combinations, including "diosmetin," "flavonoid," "diabetes," "anti-inflammatory," "antioxidant," "neuroprotection," "PI3K/Akt," "AMPK," and "Nrf2," to ensure comprehensive article retrieval.

The selection process identified articles containing studies that investigated the biological activities and molecular pathways associated with diosmetin based on relevance to the topic and molecular and cellular studies conducted in vitro and in vivo. All study types were considered, including review articles, clinical studies, animal studies, and cell culture experiments, provided they offered mechanistic insights into the compound's therapeutic potential. Articles that were not in English, had incomplete text, or were not directly relevant to the molecular mechanisms associated with diosmetin were excluded.

Data extracted from the selected literature included study type, experimental model used, molecular pathways involved, metabolic effects, insulin sensitivity, inflammation, oxidative stress, and neuroprotection. Studies comparing diosmetin to other flavonoids such as quercetin and luteolin, as well as those discussing combination therapy and synergistic effects with other compounds, were also included.

LITERATURE REVIEW

Diosmetin, while pharmacologically promising, presents several pharmacokinetic challenges that limit its clinical applicability. Its oral bioavailability is notably low, reported to be less than 10% in several preclinical studies, primarily due to poor aqueous solubility and extensive first-pass metabolism. Diosmetin exhibits limited metabolic stability and undergoes rapid biotransformation, predominantly through phase I metabolism involving cytochrome P450 (CYP) enzymes. Specifically, CYP1A2 and CYP3A4 are involved in its hepatic metabolism, raising concerns about potential drug-drug interactions when co-administered with other substrates of these enzymes[4]. The compound also has a relatively short half-life, typically ranging from 1 to 2 hours, which further complicates sustained therapeutic exposure. Enzymatic conjugation of diosmetin to its relevant metabolite, 3-O-glucuronide, occurs at the systemic circulation level, followed by formation of 3,7-di-O-glucuronide[4]. These factors collectively underscore the need for advanced drug delivery systems or chemical modifications to enhance bioavailability, metabolic resistance, and overall pharmacokinetic profile.

Anti-diabetic Effects

Diabetes, particularly Type 2 diabetes (T2D), is a metabolic disease characterized by insulin resistance, chronic hyperglycemia, and systemic inflammation. The process of insulin resistance manifests as impaired glucose utilization by peripheral tissues (skeletal muscle and adipose tissue) and dysregulated hepatic glucose production[9]. Diosmetin has shown promise in alleviating these metabolic dysfunctions through multiple molecular mechanisms[10].

- **PI3K/Akt Signaling Pathway in Promoting Insulin Sensitivity**
  The PI3K/Akt signaling pathway is essential for regulating insulin signaling and glucose homeostasis. The activation of PI3K promotes the phosphorylation of Akt and downstream effectors involved in glucose transport, glycogen synthesis, and lipid metabolism[11]. Diosmetin enhances insulin sensitivity through activation of the PI3K/Akt signaling pathway[12]. Studies have reported that diosmetin enhanced insulin-mediated glucose uptake by activating PI3K and Akt in insulin-resistant hepatocyte cells, which subsequently led to increased GLUT4 expression in skeletal muscle and adipose tissue. This process is required to reduce blood glucose levels and restore glucose metabolic balance[13]. Moreover, diosmetin has been implicated in the regulation of important enzymes involved in glucose metabolism, particularly glycogen synthase kinase 3 beta (GSK3β), an enzyme involved in glycogen synthesis. By promoting glucose utilization, diosmetin may subsequently enhance insulin sensitivity[14]. We hypothesize that diosmetin influences PI3K/Akt signaling as a potential T2D therapeutic agent by restoring insulin sensitivity through modulation of these pathways.

- **AMP-Activated Protein Kinase (AMPK) Activation**
  AMPK acts as the principal cellular energy sensor and serves as a critical regulator of glucose homeostasis. AMPK activation induces fatty acid oxidation and glucose uptake while inhibiting gluconeogenesis[15]. Diosmetin activates AMPK, thereby improving glucose uptake and insulin sensitivity. Studies have demonstrated that diosmetin activates AMPK in both hepatocytes and skeletal muscle cells, increasing glucose uptake and inhibiting hepatic glucose production[16]. AMPK activation is critical for inhibiting gluconeogenic gene expression and preventing the progression of insulin resistance by suppressing the expression of key enzymes such as PEPCK and G6Pase. While other flavonoids, such as quercetin, also activate AMPK, diosmetin appears more specific to glucose metabolism and may provide a therapeutic advantage for T2D management[17]. By enhancing PI3K/Akt activity and restoring AMPK signaling, diosmetin offers a multifaceted approach to overcoming insulin resistance and restoring glucose homeostasis[18].

- **Inflammatory Pathways in Diabetes**
  Chronic inflammation is a key player in exacerbating insulin resistance and T2D onset. Pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, are associated with decreased insulin signaling and contribute to insulin resistance. Diosmetin exhibits anti-inflammatory effects that contribute to its anti-diabetic properties[19]. For instance, diosmetin can reduce pro-inflammatory cytokine levels by inhibiting the NF-κB signaling pathway, an important mediator of inflammation. Diosmetin can also reduce COX-2 expression, an enzyme involved in pro-inflammatory prostaglandin synthesis. These anti-inflammatory effects enhance insulin sensitivity and reduce insulin resistance[20].

Anti-inflammatory Effects

Chronic inflammation contributes to diseases including cancer, cardiovascular disease, and neurodegenerative diseases. Diosmetin exhibits powerful anti-inflammatory effects by modulating multiple essential inflammatory signaling pathways[19].

- **NF-κB and COX-2 Inhibition**
  NF-κB serves as a transcription factor that controls inflammation and immune responses. When activated by various signals, NF-κB translocates to the nucleus and initiates the expression of pro-inflammatory cytokines, adhesion molecules, and enzymes such as COX-2[21]. Diosmetin has been reported to inhibit NF-κB activation in both in vitro and in vivo models[22]. The inhibition of NF-κB activation reduces the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which are elevated in various inflammatory diseases. Diosmetin also suppresses COX-2 expression, an enzyme pivotal in the production of pro-inflammatory prostaglandins. This inflammatory pathway involvement is relevant to other diseases, including T2D, which is partly driven by chronic inflammation[23].

- **Nrf2 Pathway Activation**
  The Nrf2 pathway represents an important cellular defense mechanism against inflammation and oxidative damage. Nrf2 activates the expression of cytoprotective and antioxidant genes, including heme oxygenase-1 (HO-1), SOD, and GPx. Diosmetin activates Nrf2, resulting in increased expression of antioxidant enzymes and reduced oxidative stress. Research has shown that diosmetin significantly enhanced Nrf2 activity and antioxidant enzyme expression in liver cells exposed to elevated glucose, protecting the cells from oxidative damage[24]. Furthermore, diosmetin-induced Nrf2 activation also prevents NF-κB activation, creating a dual defense mechanism against oxidative stress and inflammation[25]. This dual activity makes diosmetin a strong candidate for treating conditions such as diabetes and cardiovascular disease that involve both oxidative stress and inflammation simultaneously.

Antioxidant Effects

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and their removal by antioxidant systems, has been linked to numerous chronic illnesses. Diosmetin exhibits potent antioxidant mechanisms through ROS scavenging and activation of cellular antioxidant defenses[24-26].

- **Nrf2-Mediated Antioxidant Response**
  As previously mentioned, diosmetin activates Nrf2, which regulates the expression of antioxidant genes. The Nrf2-dependent activation of antioxidant enzymes (SOD, GPx, and HO-1) represents a crucial defense against oxidative damage in response to oxidative stress. Studies have shown that diosmetin elevated these antioxidant enzymes in liver cells, thereby reducing oxidative stress caused by elevated glucose levels[25].

- **Synergistic Effects with Other Flavonoids**
  Diosmetin demonstrates synergistic enhancement of antioxidant activity, particularly when combined with other flavonoids such as luteolin and quercetin[27]. Studies have shown that flavonoid combinations activated Nrf2 more efficiently than individual flavonoids alone, resulting in higher levels of antioxidant enzymes than achieved by each flavonoid individually[28]. Therefore, these synergistic effects suggest that diosmetin may offer enhanced protection against oxidative stress when combined with other flavonoids, making it a potential component of polyphenol-based therapeutic approaches.

Neuroprotective Effects

Neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) are characterized by neuronal damage, oxidative stress, and neuroinflammation[29]. Diosmetin has demonstrated neuroprotective effects through its modulation of important molecular pathways involved in these processes[24].

- **The PI3K/Akt Pathway and Neuroprotection**
  The PI3K/Akt signaling system is essential for regulating neuroplasticity, cell survival, and neuronal protection. Diosmetin has been demonstrated to protect neurons by activating this pathway. Through PI3K/Akt signaling activation, diosmetin reduced neuronal death and enhanced cell survival in neurodegenerative models. This pathway is particularly important in neurodegenerative diseases such as AD and PD, where neuronal cell death is a key characteristic[30].

- **Microglial Activation Modulation**
  Neuroinflammation is a major factor in the pathophysiology of neurodegenerative disorders, where microglial and astrocyte activation play essential roles. Diosmetin inhibits microglial activation and reduces the production of pro-inflammatory mediators, including TNF-α, IL-1β, and nitric oxide. By modulating neuroinflammation, diosmetin helps protect neurons from chronic inflammation-induced damage, which is crucial for preventing neurodegeneration[31].

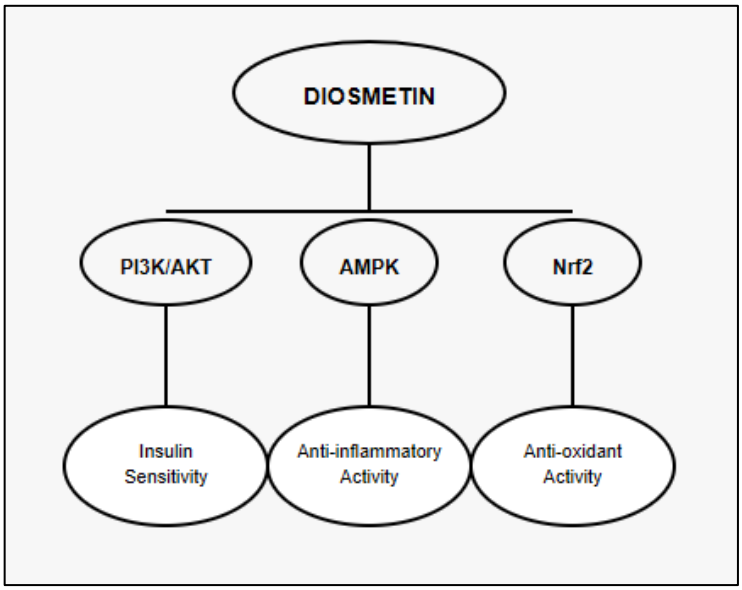

Figure 1: Biological Effect of Diosmetin

Table-1: Molecular Pathways of Diosmetin

Molecular Pathway	Mechanism of Action	Biological Effect	Health Benefits
NF-κB Inhibition	Suppresses NF-κB activation, decreasing the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)	Anti-inflammatory effects	Reduces chronic inflammation and decreases the risk of inflammatory diseases
PI3K/Akt Activation	Enhances insulin signaling and promotes cell survival	Metabolic and neuroprotective effects	Improves glucose metabolism (anti-diabetic) and supports brain function
Antioxidant Defense	Activates the Nrf2 signaling pathway, increasing antioxidant enzyme production and reducing ROS	Inhibition of oxidative stress	Provides protection from oxidative stress and slows the aging process
Neuroprotection	Reduces neuroinflammation, leading to prevention of neuronal cell death	Provides neuronal protection	Reduces the risk of neurodegenerative diseases (Alzheimer's, Parkinson's)

Comparative Studies with Other Flavonoids

Besides diosmetin, various flavonoids including quercetin, luteolin, kaempferol, and apigenin have shown comparable or even superior effects in specific diseases.

Quercetin

Recognized for its strong anti-inflammatory and antioxidant effects, quercetin efficiently blocks NF-κB activation and neutralizes ROS. It also enhances insulin sensitivity through AMPK activation. In contrast, while diosmetin influences inflammation and glucose metabolism, it may operate more specifically through the PI3K/Akt pathway[32-34].

Luteolin

This flavonoid is acknowledged for its anti-inflammatory and neuroprotective characteristics, particularly through blocking NF-κB signaling and reducing microglial activation.

Luteolin has demonstrated stronger neuroprotective effects in AD models, suggesting it may be more effective than diosmetin in addressing neuroinflammation[35,36]. However, diosmetin's dual functionality in addressing both inflammation and oxidative stress may render it a more versatile compound for simultaneously treating metabolic and neurological disorders.

Kaempferol

Like diosmetin, kaempferol has demonstrated the ability to activate Nrf2 and provide neuroprotective benefits[37]. However, kaempferol appears to exert a more significant effect on reducing oxidative stress, particularly in Parkinson's disease[38]. Although diosmetin demonstrates strong antioxidant effects, kaempferol's impact in Parkinson's models appears to be more pronounced.

Apigenin

Recognized for its neuroprotective and anxiolytic benefits, apigenin also displays significant anti-inflammatory properties[39]. Apigenin's capacity to modulate GABA receptors makes it more effective for anxiety and stress-related conditions, whereas diosmetin is more suitable for addressing chronic inflammation and metabolic disorders[40].

DISCUSSION

The evidence suggests that diosmetin offers multiple therapeutic benefits through various molecular mechanisms[41]. Its modulation of critical signaling pathways including PI3K/Akt, AMPK, NF-κB, and Nrf2 provides hope for its potential as a multi-target agent for chronic metabolic and neuro-inflammatory diseases. Diosmetin's enhancement of insulin sensitivity and reduction of inflammatory markers such as COX-2 and pro-inflammatory cytokines indicate its promise as an anti-diabetic and anti-inflammatory compound[42-43]. Additionally, the activation of Nrf2 signaling and the increase in antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) illustrate its protective action against oxidative stress, which significantly contributes to the development of neurodegenerative and metabolic diseases[25,44].

While diosmetin demonstrates significant therapeutic promise in preclinical models, its translation into clinical use faces several hurdles. One of the primary challenges is the absence of a standardized, clinical-grade formulation that ensures consistent quality, stability, and bioavailability[24]. Additionally, given its interactions with cytochrome P450 enzymes, particularly CYP1A2 and CYP3A4, there is considerable risk of drug-drug interactions, especially in patients concurrently taking medications such as anti-diabetics or antihypertensives, which are commonly metabolized by these pathways[45,46]. Careful pharmacovigilance and interaction studies are crucial before diosmetin can be safely integrated into therapeutic regimens. Despite these challenges, diosmetin holds considerable potential in the growing field of nutraceuticals, where its natural origin, antioxidant properties, and safety profile make it an attractive candidate for functional food and supplement development. Addressing formulation and safety concerns could pave the way for its broader application in preventive and adjunctive healthcare.

Although diosmetin is less extensively studied compared to other bioactive compounds, its combination with other flavonoids may produce synergistic interactions that potentiate its therapeutic effects, unlike individual flavonoids such as quercetin and luteolin used alone. Further preclinical analysis through in vivo experiments and clinical trials, alongside optimal dosing strategies, is necessary for validation. In conclusion, the versatile action of diosmetin against diabetes, inflammation, oxidative stress, and neurodegeneration demonstrates significant therapeutic potential.

Future Recommendations

Future studies should focus on initiating well-designed clinical trials to confirm diosmetin's safety and effectiveness in human populations, building on our current understanding of its pharmacological potential. These trials are essential for establishing evidence-based dosage guidelines and therapeutic indications. Simultaneously, improving the compound's low bioavailability remains a top priority; formulation techniques such as complexation with bioenhancers, prodrug approaches, and nanoparticle delivery systems should be thoroughly investigated. Furthermore, examining diosmetin in combination with currently available treatments may reveal synergistic benefits and increase its clinical relevance, particularly in chronic diseases such as diabetes and hypertension. A comprehensive focus on these areas will be essential to advance diosmetin from experimental promise to a viable therapeutic or nutraceutical agent.

- **Clinical Trials and Bioavailability Enhancement**
  While preclinical research shows promise, diosmetin's therapeutic effects in human

clinical trials remain limited. Future studies need to focus on carefully structured randomized controlled trials (RCTs) to assess efficacy, safety, and optimal dosage. Moreover, enhancing diosmetin's bioavailability through innovative delivery techniques, such as nanoformulations or conjugation with other bioactive compounds, may further improve its clinical relevance.

- **Mechanistic Investigations in Neurodegenerative Models**
  Further detailed research is required to examine the molecular mechanisms by which diosmetin demonstrates its neuroprotective properties. In vitro models, such as human neuronal cell lines and 3D organoids, will help understand how diosmetin interacts with important neuroprotective pathways including PI3K/Akt, MAPK, and Nrf2. These investigations will provide clearer insights into how diosmetin protects neurons against oxidative stress, inflammation, and apoptosis, particularly in Alzheimer's and Parkinson's diseases.

- **Synergistic Effects with Other Phytochemicals**
  The combination of diosmetin with various flavonoids, polyphenols, and natural compounds warrants further investigation. Exploring the combined effects of diosmetin with other bioactive substances may result in enhanced nutraceutical products and improved therapeutic outcomes by targeting multiple pathways simultaneously.

- **Long-Term Safety and Toxicity Profile**
  Given the interest in diosmetin as a treatment option, evaluating its long-term safety profile is essential. Research on prolonged exposure, including its effects on organ systems, metabolism, and potential interactions with other medications, is crucial to verify its safety for extended use.

CONCLUSION

Diosmetin is a flavonoid predominantly found in citrus fruits that possesses significant therapeutic potential, particularly for its anti-diabetic, anti-inflammatory, antioxidant, and neuroprotective properties. By modulating pathways such as PI3K/Akt, AMPK, NF-κB, COX-2, and Nrf2, diosmetin exhibits significant potential for the prevention and management of chronic diseases, including Type 2 diabetes, cardiovascular diseases, and neurodegenerative disorders. Moreover, diosmetin's combination with other flavonoids such as quercetin and luteolin further enhances its therapeutic effectiveness. Future clinical trials are necessary to validate the therapeutic potential of diosmetin, enhance its bioavailability, and assess its safety profile. Current evidence suggests that diosmetin is a promising natural agent for enhancing metabolic health and preventing chronic diseases, making it an attractive option for incorporation into functional foods or nutraceuticals.

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Author Contributions
Saviya Kashif and **Abdul Hameed** jointly contributed to the literature search, analysis, and synthesis of evidence. Both authors were involved in drafting, revising, and finalizing the manuscript, and approved the final version for publication.

Ethical Approval
Not applicable.

Conflict of Interests
None.

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