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Isorhamnetin: A Phytochemical Powerhouse – Chemical Properties and Therapeutic Potential- A Review

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ABSTRACT:

Isorhamnetin, a flavonoid derived from various plant sources, has gained attention for its diverse pharmacological properties and therapeutic potential. It is known for antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective effects documented in the literature. This review aims to comprehensively examine the pharmacological profile of isorhamnetin, focusing on its various therapeutic effects including antioxidant activity, anti-inflammatory properties, anticancer mechanisms, neuroprotective effects, and cardioprotective actions. A literature review was conducted to gather evidence on the pharmacological activities of isorhamnetin. Studies investigating its antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective effects were analyzed to provide a comprehensive understanding of its therapeutic potential. Isorhamnetin exhibits potent antioxidant properties by scavenging free radicals and reducing oxidative stress, which is implicated in aging and chronic diseases. It modulates inflammatory pathways and cytokine production, suggesting therapeutic applications in inflammatory conditions. Additionally, isorhamnetin demonstrates anticancer effects through apoptosis induction, inhibition of proliferation, and suppression of angiogenesis in various cancer models. In neuroprotection, it protects neurons from oxidative stress, neuroinflammation, and excitotoxicity, showing promise in neurodegenerative disorders. Furthermore, isorhamnetin has shown cardioprotective effects by reducing cholesterol levels and enhancing endothelial function. Isorhamnetin exhibits a multifaceted pharmacological profile with significant therapeutic potential across multiple health conditions. While clinical trials and mechanistic studies support its safety and efficacy, challenges remain in optimizing its bioavailability and translating these findings into clinical practice. Future research should focus on addressing these challenges to fully harness the therapeutic benefits of isorhamnetin in human health.

1. Introduction

Flavonoids constitute a diverse group of phytochemicals ubiquitous in the plant kingdom, renowned for their manifold biological activities and therapeutic potential [1]. Isorhamnetin is a plant-derived secondary metabolite that belongs to the flavonoid family, specifically within

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the flavonol subgroup. Isorhamnetin, known as a 3′-O-methylated gut metabolite of quercetin, is also found in several plant species such as *Hippophae rhamnoides*, *Ginkgo biloba*, and *Opuntia stricta* var. *dilleni*, which have been used medicinally in various cultures [2,3]. Other dietary sources of isorhamnetin include onions, almonds, and various berries [4,5]. The methylation of isorhamnetin enhances its stability and bioavailability, thereby contributing to its pharmacological efficacy [6].

Flavonoids, including isorhamnetin, are known for their antioxidant, anti-inflammatory, and other health-promoting properties. The 3-hydroxyflavone backbone of flavonols, with various substitutions, is responsible for these beneficial effects [7]. Isorhamnetin's additional hydroxyl group at the 3'-position makes it a more stable and bioavailable compound, increasing its effectiveness as a therapeutic agent [6].

The beneficial effects of isorhamnetin on LPS-induced acute lung injury and collagen-induced arthritis mouse models are directly associated with its antioxidant effects [8,9]. In addition, the protective effects of isorhamnetin on oxidative stress-induced DNA damage and apoptosis are associated with blocking of ROS production [10,11].

The beneficial effects of isorhamnetin on LPS-induced acute lung injury and collagen-induced arthritis mouse models are directly associated with its antioxidant properties [9]. Additionally, the protective effects of isorhamnetin on oxidative stress-induced DNA damage and apoptosis are linked to its ability to block ROS production [12]. Isorhamnetin also shows potential in inhibiting carcinogenesis and protecting against neurodegenerative conditions [8,13,14]. These properties underscore its therapeutic relevance across a spectrum of diseases, including cardiovascular disorders and neurodegenerative diseases.

Isorhamnetin's antioxidant effects play a crucial role in mitigating inflammation and tissue damage in acute lung injury and arthritis models [8], highlighting its potential in managing inflammatory conditions [9]. By blocking the production of reactive oxygen species (ROS), isorhamnetin protects cells from oxidative stress-induced DNA damage and apoptosis, hepatoprotective [10] which is fundamental in preventing various chronic diseases [11, 12]. Moreover, isorhamnetin has demonstrated significant potential in cancer prevention. Its ability to inhibit carcinogenesis is attributed to its antioxidant properties and its role in modulating cell signaling pathways involved in cell proliferation and apoptosis [10,11,15]. In the context of neurodegenerative diseases, the neuroprotective effects of isorhamnetin are linked to its capacity to reduce oxidative stress and inflammation, key factors in the pathogenesis of conditions such as Alzheimer's and Parkinson's disease [14,15].

The objective of this review is to provide a comprehensive overview of the pharmacological properties of isorhamnetin, synthesizing current literature on its mechanisms of action, therapeutic potential, and clinical applications. By consolidating existing knowledge, this review aims to highlight the multifaceted roles of isorhamnetin in health and disease, thereby guiding future research endeavours and therapeutic developments.

2. Structural Characteristics of Isorhamnetin:

Isorhamnetin is a flavonol, specifically a methylated derivative of quercetin. Its structure is defined by a 3-hydroxyflavone backbone, which is a common feature among flavonols. This backbone comprises a chromone core (a benzopyran with a keto group at the 4-position) with a hydroxyl group attached at the 3-position.

What distinguishes isorhamnetin from other flavonols is its specific pattern of hydroxylation and methylation. It has an additional hydroxyl group at the 3'-position on the B ring, which enhances its antioxidant properties by providing an extra site for free radical scavenging [11].

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Furthermore, isorhamnetin has a methoxy group (-OCH3) at the 4'-position on the B ring, resulting from the methylation of the hydroxyl group found in quercetin at the same position. This methylation increases the molecule's stability and lipophilicity, improving its bioavailability and allowing it to better integrate into cell membranes, where it can exert its protective effects [7,12].

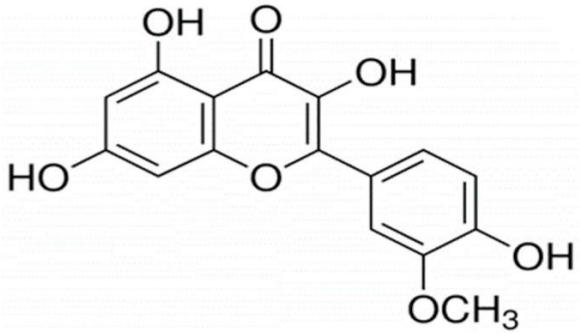

Figure 1. Structure of Isorhamnetin

3. Occurrence in Natural Sources:

Isorhamnetin is found in various plants, fruits, and vegetables, contributing to their antioxidant and health-promoting properties. This flavonol is particularly abundant in foods such as onions, apples, tomatoes, and various berries, including strawberries and grapes [16,17].

Onions (*Allium cepa*) are one of the richest dietary sources of isorhamnetin. The presence of this compound, along with other flavonoids like quercetin, enhances onions' antioxidant properties, which help in reducing oxidative stress and inflammation [18].

Apples (*Malus domestica*) contain isorhamnetin primarily in their peel. Regular consumption of apples has been associated with various health benefits, including reduced risk of cardiovascular diseases and certain cancers, largely due to their rich polyphenolic content, including isorhamnetin [19].

Tomatoes (*Solanum lycopersicum*), another source of isorhamnetin, are well-known for their high antioxidant content. The flavonoids in tomatoes, including isorhamnetin, contribute to their ability to neutralize free radicals, thus preventing cell damage and reducing the risk of chronic diseases [20].

Berries such as strawberries (*Fragaria ananassa*) and grapes (*Vitis vinifera*) are also significant sources of isorhamnetin. These fruits are celebrated for their potent antioxidant capacities, which help protect the body from oxidative stress and inflammation, contributing to their overall health benefits [21,22].

The presence of isorhamnetin in these dietary sources not only enhances their nutritional value but also provides a natural means to bolster the body's defense mechanisms against various diseases. The compound's bioavailability and stability, attributed to its methylated structure, ensure that it is effectively utilized in the body to exert its beneficial effects.

4. Mechanistic Insights into Therapeutic Effects:

- **Antioxidant Properties:** Isorhamnetin, a flavonol derived from various plant sources, exhibits potent antioxidant activity due to its chemical structure and functional groups. It functions by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby reducing oxidative stress within cells [16]. This scavenging activity helps to prevent oxidative damage to cellular components such as lipids, proteins, and DNA, which is implicated in the pathogenesis of numerous diseases, including cardiovascular disorders and neurodegenerative conditions [23,24].
- **Anti-inflammatory Effects:** In addition to its antioxidant properties, isorhamnetin exerts anti-inflammatory effects by modulating inflammatory pathways and reducing the production of pro-inflammatory cytokines and

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mediators. It inhibits the activation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in the expression of inflammatory genes [25,26]. By blocking NF-κB signaling, isorhamnetin suppresses the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [24].

2. Anticancer Potential of Isorhamnetin

Isorhamnetin, a flavonol found in various plant sources, has shown promising anticancer properties through multiple mechanisms:

- **Induction of Apoptosis:** Isorhamnetin induces programmed cell death (apoptosis) in cancer cells by activating intrinsic pathways that lead to DNA fragmentation, caspase activation, and mitochondrial dysfunction. This process helps to eliminate cancerous cells and inhibit tumor growth [27].
- **Inhibition of Cell Proliferation Pathways:** Isorhamnetin, an O-methylated flavonol, disrupts the PI3K-Akt-mTOR signaling pathway, which is crucial for cell proliferation and survival and often dysregulated in cancers. By inhibiting this pathway, isorhamnetin reduces abnormal cancer cell growth and division. Studies have shown that isorhamnetin significantly downregulates the phosphorylation of PI3K, Akt, and mTOR, leading to decreased cell viability and increased apoptosis in various cancer cell types, including ovarian, breast, and hepatocellular carcinoma cells [28].
- **Suppression of Metastasis:** Isorhamnetin has garnered attention for its potential as an antitumor agent across various cancers, including prostate cancer. In androgen-independent prostate cancer cells (DU145 and PC3), Isorhamnetin demonstrates selective cytotoxicity, induces apoptosis, and inhibits cell migration and invasion in a concentration- and time-dependent manner. This effect is mediated by the activation of the mitochondrial apoptosis pathway, involving key proteins such as Bax, Bcl-2, caspase-3, caspase-9, and cytochrome c. Additionally, Isorhamnetin suppresses the PI3K/Akt/mTOR signaling pathway, which is crucial in prostate cancer pathogenesis and therapy resistance. These findings suggest that Isorhamnetin could be a promising therapeutic agent for androgen-independent prostate cancer [29].

3. Neuroprotective Effects

Isorhamnetin exhibits significant neuroprotective effects through multiple mechanisms. It reduces oxidative stress by scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant enzyme activity, thus protecting neurons from oxidative damage. Its anti-inflammatory properties inhibit the activation of microglia and astrocytes, decreasing the release of pro-inflammatory cytokines and mediators. Isorhamnetin also protects against excitotoxicity by modulating glutamatergic neurotransmission, which is beneficial in neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. Additionally, it preserves mitochondrial function, ensuring adequate ATP production and reducing the release of apoptotic factors. Isorhamnetin's ability to activate the Nrf2 pathway and inhibit the NF-κB pathway further enhances its neuroprotective effects. These mechanisms highlight its potential as a therapeutic agent for neurodegenerative diseases [30-32].

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4.Cardioprotective Effects

Isorhamnetin has been shown to protect against myocardial injury in rats subjected to cardiac ischemia/reperfusion (I/R). It inhibited cardiomyocyte apoptosis in a dose-dependent manner by decreasing the protein expression of Bax and cleaved-caspase-3, while increasing Bcl-2 expression. Additionally, isorhamnetin mitigated I/R-induced oxidative stress, evidenced by reduced malondialdehyde (MDA) levels and enhanced activities of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). These findings indicate that isorhamnetin provides cardioprotection by reducing apoptosis and oxidative stress [33,34].

5. Conclusion

Isorhamnetin, a flavonoid with diverse pharmacological properties, holds significant therapeutic potential across various health conditions. Its potent antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective effects have been well-documented, highlighting its ability to mitigate oxidative stress, modulate inflammatory pathways, induce apoptosis in cancer cells, protect neurons, and enhance cardiovascular health. Despite its promising efficacy and safety profile, further research is needed to optimize its bioavailability and clinical application. Future studies should focus on advancing the clinical translation of isorhamnetin to fully harness its therapeutic benefits.

Conflict of interest

The authors declare that there are no conflicts of interest.

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