



REVIEW ARTICLE

Biological Activities of Isorhamnetin : A Review

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ABSTRACT

In recent years, flavonols have been a focus of research due to their important biological activities. Isorhamnetin is a flavonol. It belongs to a group of plant secondary metabolites known as flavonoids. It is present in man's daily diet and is known for its biological activities such as antioxidant, antiviral, anticancer, antimicrobial, anti-Tuberculosis and anti-inflammatory effects. It has been reported for its antioxidant and antiviral applications hence it is not only used as such, but it also has various derivatized forms which has potentials for development into drugs for the treatment of diseases caused by oxidative stress and lethal viruses.

Keywords: Isorhamnetin, Plants, Bioactivities.

INTRODUCTION

Flavonoids important secondary constituents and they are natural polyphenolic compounds that have two benzene rings linked with heterocyclic pyrone ring, recently attention have been focused on the antioxidative activities of several plant phenolics, especially flavonoids, because these compounds inhibited lipid peroxidation, and the significance of potential protective properties of flavonoids present in vegetables and fruits has become an important matter (Wattenberg, 1990; Mabry, 1980). They are a large group of secondary plant metabolites and also usual constituents of the human diet comprising in excess of six thousands identified compounds are characterized from a variety of plant sources. Until now, a huge number of biological and pharmacological effects have been ascribed to flavonoids, including anti-allergic, anti-antioxidant, antitumor, antiviral, and antimicrobial activities (Araujo *et al.* 2014; Burda & Oleszek, 2001; Ramos 2007). Flavonoids are mainly present in tea, red wine, aromatic plants, medical herbs, fruits, and vegetables (Rice-Evans, 2001). Epidemiological studies point out that use of foods rich in flavonoids may reduce the incidence of existence diseases (Steinberg *et al.* 1989; Katan, 1997).

Isorhamnetin, a flavonoid compound and it is well known for its anti-inflammatory, anti-oxidative, anti-adipogenic, anti-proliferative, and anti-tumor activities. However, the role of isorhamnetin in cardiac hypertrophy has not been reported (Lu Gao *et al.* 2017).

The flavonoid isorhamnetin is the metabolite of quercetin and it is naturally occurring O-methylated flavonol that is plentiful in apples, blackberries, cherries, and pears in medicinal herbs and plants, such as the sea buckthorn (*Hippophae rhamnoides* L. dropwort (*Oenanthe javani*) caused in the Greek and Danish traditional medicines for the prevention and treatment of a range of diseases (Boesch-Saadatmandi, 2011; Kobori, 2011). This review focuses on the pharmacological evidences of isorhamnetin.

BIOLOGICAL ACTIVITIES

Isorhamnetin Protects Against Cardiac Hypertrophy

We investigated the effects of isorhamnetin (100 mg/kg/day) on cardiac hypertrophy induced by aortic banding in mice. Cardiac hypertrophy was evaluated by echocardiographic, hemodynamic, pathological, and molecular analyses. Our data demonstrated that isorhamnetin could inhibit cardiac hypertrophy and fibrosis 8 weeks after aortic banding. The results further revealed that the effect of isorhamnetin on cardiac hypertrophy was mediated by blocking the activation of phosphatidylinositol 3-kinase-AKT signaling pathway. In

vitro studies performed in neonatal rat cardiomyocytes confirmed that isorhamnetin could attenuate cardiomyocyte hypertrophy induced by angiotensin II, which was associated with phosphatidylinositol 3-kinase-AKT signaling pathway. In conclusion, these data indicate for the first time that isorhamnetin has protective potential for targeting cardiac hypertrophy by blocking the phosphatidylinositol 3-kinase-AKT signaling pathway (Lu Gao *et al.* 2017).

Isorhamnetin Alleviates Lipopolysaccharide-Induced Inflammatory Responses in BV2

Present study investigated the inhibitory potential of isorhamnetin against inflammatory responses in lipopolysaccharide (LPS) stimulated BV2 microglia. To measure the effects of isorhamnetin on inflammatory mediators and cytokines, and reactive oxygen species (ROS) generation, the following methods were used: cell viability assay, griess assay, ELISA, reverse transcriptase polymerase chain reaction, flow cytometry, western blotting and immunofluorescence staining. The results revealed that isorhamnetin significantly suppressed LPS induced secretion of pro inflammatory mediators, including nitric oxide (NO) and prostaglandin E₂, without exhibiting significant cytotoxicity. Consistent with these results, isorhamnetin inhibited LPS stimulated expression of regulatory enzymes, including inducible NO synthase and cyclooxygenase 2 in BV2 cells.

Isorhamnetin also downregulated LPS induced production and expression of pro inflammatory cytokines, such as tumor necrosis factor α and interleukin 1β . The mechanism underlying the anti inflammatory effects of isorhamnetin was subsequently evaluated; this flavonoid inhibited the nuclear factor (NF) κ B signaling pathway by disrupting degradation and phosphorylation of inhibitor κ B α in the cytoplasm and blocking translocation of NF κ B p65 into the nucleus. In addition, isorhamnetin effectively suppressed LPS induced expression of Toll like receptor 4 (TLR4) and myeloid differentiation factor 88. It also suppressed the binding of LPS with TLR4 in BV2 cells. Furthermore, isorhamnetin markedly reduced LPS induced generation of ROS in BV2 cells, thus indicating a strong antioxidative effect. Collectively, these results suggested that isorhamnetin may suppress LPS mediated inflammatory action in BV2 microglia through inactivating the NF κ B signaling pathway, antagonizing TLR4 and eliminating ROS accumulation.

Further studies are required to fully understand the anti inflammatory effects associated with the antioxidant capacity of isorhamnetin; however, the findings of the present study suggested that isorhamnetin may have

potential benefits in inhibiting the onset and treatment of neuroinflammatory diseases (Shin Young Kim *et al.* 2019).

Isorhamnetin Exerts Neuroprotective Effects in STZ-Induced Diabetic Rats

A single dose of a freshly prepared solution of streptozotocin (STZ) (60 mg/kg body weight) was intraperitoneally injected to establish STZ-induced diabetic model in male Wistar rats. The animals were randomly divided into four groups: control, control + isorhamnetin, diabetic, diabetic + isorhamnetin. Isorhamnetin at a dose of 10 mg/kg body weight was intraperitoneally administered once a day for 12 weeks. Formalin and tail immersion tests were performed to evaluate the severity of pain. Astroglial markers such as GFAP and APO-E4, DNA fragments, MDA level, and TNF α expressions were evaluated using ELISA assay.

Neuronal density in the hippocampus region was evaluated using Nissl staining. The method of Ellman and fluorescent probe 2, 7-dichlorofluorescein diacetate (DCFH-DA) was used to measure brain acetyl-cholinesterase activity and detect reactive nitrogen and oxygen species (RNS and ROS), respectively. Isorhamnetin reduced pain, blood glucose levels, and increased body weight significantly compared to control. Moreover, isorhamnetin inhibited astroglial activation, acetyl-cholinesterase activity, oxidative stress, apoptosis, and inflammation, and isorhamnetin has potential effects as neuroprotective agents against diabetes-related changes in the brain (Nida Jamali-Raeufy *et al.* 2019).

Isorhamnetin: A Hepatoprotective Agent

The present study is in order to explore the hepatoprotective effect of isorhamnetin on concanavalin A (ConA)-induced acute fulminant hepatitis and the underlying mechanism. Mice were injected with ConA (25 mg/kg) to induce acute fulminant hepatitis, three doses of isorhamnetin (10/30/90 mg/kg) was intraperitoneally administered about 1 h previously. The serum and liver tissues were harvested at 2, 8, and 24 h after ConA injection.

The levels of serum liver enzymes and proinflammatory cytokines were significantly reduced in isorhamnetin administration groups. Besides, isorhamnetin improved pathological damage. Furthermore, isorhamnetin affected P38/PPAR- α pathway, and subsequently regulated the expression of apoptosis and autophagy related proteins. This study proved that isorhamnetin inhibits apoptosis and autophagy via P38/PPAR- α pathway in mice (Xiya Lu, *et al.* 2018).

Anti-tuberculosis Activity of Isorhamnetin

The present study proved that Isorhamnetin had antimycobacterial effects on *Mycobacterium tuberculosis* H37Rv, multi-drug- and extensively drug-resistant clinical isolates with minimum inhibitory concentrations of 158 and 316 μ M, respectively. Mycobacteria mainly affect the lungs, causing an intense local inflammatory response that is critical to the pathogenesis of tuberculosis. We investigated the effects of Isorhamnetin on interferon (IFN)- γ -stimulated human lung fibroblast MRC-5 cells. Isorhamnetin suppressed the release of tumor necrosis factor (TNF)- α and interleukin (IL)-12. A nontoxic dose of 1 reduced mRNA expression of TNF- α , IL-1 β , IL-6, IL-12, and matrix metalloproteinase-1 in IFN- γ -stimulated cells. Isorhamnetin inhibited IFN- γ -mediated stimulation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase and showed high-affinity binding to these kinases (binding constants: 4.46×10^6 M⁻¹ and 7.6×10^6 M⁻¹, respectively). The 4'-hydroxy group and the 3'-methoxy group of the B-ring and the 5-hydroxy group of the A-ring of 1 play key roles in these binding interactions. A mouse in vivo study of lipopolysaccharide-induced lung inflammation revealed that a nontoxic dose of 1 reduced the levels of IL-1 β , IL-6, IL-12, and INF- γ in lung tissue. These data provide the first evidence that 1 could be developed as a potent anti-tuberculosis drug (Hum Nath Jnawali, *et al.* 2016).

Anticancer activity

Isorhamnetin was reported that it is a potent anticancer agent during in vitro studies in various cancer cell lines and in vivo dies in rodents especially mice. Isorhamnetin been reported to show valuable effect on cancer inly it was suppresses colon cancer cell growth ough the PI3K-Akt-mTOR pathway (Chuan Li, *et al.* 2014).

Antioxidant Activity

Isorhamnetin has a potential as a natural antioxidant to alternate synthetic substances as food additives. Recently, in vivo study, it has been reported that isorhamnetin has antioxidative enzyme activities on the concentrations of cholesterol and lipoperoxide in the serum and liver (Masamichi, 1995).

Antimicrobial Activity

Isorhamnetin being a bacteriostatic and it is a good molecule for antibacterial drug research. The compound isorhamnetin extracted from leaf oil of *Ribes nigrum* proved a wide range of antimicrobial effect, it's used in the treatment of various bacterial and fungal infections could

be beneficial. These inhibitory effects are also interesting in relation to the prevention of contamination in many food products caused by micro-organisms such as *Staphylococcus* spp., *Salmonella* spp., *Bacillus* spp., *Pseudomonas fluorescens*, and *Clostridium botulinum* (Tatjana, *et. al.* 2010).

CONCLUSION

This review showed the pharmacological effects of Isorhamnetin.

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