

## Review Article

# Pharmacological activities and pharmacokinetic study of hyperoside: A short review

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### Abstract

Hyperoside (quercetin-3-O-D-galactoside) is a flavonol glycoside which has been isolated from different plants. It has different pharmacological actions such as anti-inflammatory, anti-depressant, neuro-protective, cardio-protective, anti-diabetic, anti-cancer, anti-fungal, radio-protective, gastro-protective, and antioxidant activities. Studies on its pharmacokinetic (PK) properties revealed that it is a stable compound with no significant gender variation in its activities. Other significant details on its pharmacological properties and information for future investigations on its components are provided.

**Keywords:** Hyperoside; Anti-inflammatory, Antidepressant, Neuroprotective, Antidiabetic, Anticancer, Antioxidant, Cytochrome P450

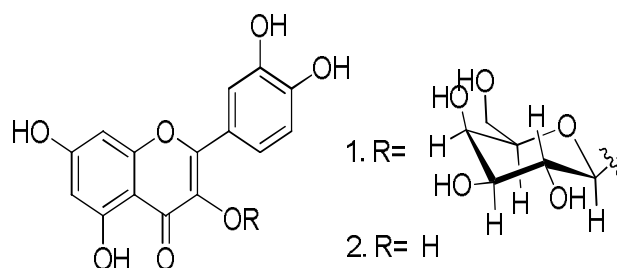
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## INTRODUCTION

Natural products have recently attracted much attention in drug discovery and food supplement research because they are frequently used due to their chemical diversity and potent bioactivities. Flavonoids are plant polyphenols found in herbs, vegetables and fruits. They are well known for their hepatoprotective, cardioprotective, antipyretic, analgesic, and anti-inflammatory activities [1]. Flavonoids comprise a large group of polyphenolic with a benzo- $\gamma$ -pyrone structure. They are synthesized by the phenylpropanoid pathway. Available reports show that secondary phenolic metabolites including flavonoids are responsible for a variety of pharmacological activities [2].

Hyperoside (Figure 1), also known as quercetin-3-O-D-galactoside, is a flavonol glycoside present in a variety of vegetables and fruits [3,4]. It has been isolated from various medicinal

plants such as *Hypericum perforatum* [5], *Ligularia fischeri* [6], *Crataegus davisii* [7], *Divaricate saposchnikovia* [8] and *Hypericum mysorense* [9]. Hyperoside is associated with several potent pharmacological activities which include anti-inflammatory, anti-thrombotic, anti-diabetic, anti-viral, anti-fungal, hepato-protective, and antioxidant protective effects [10-14] (Table 1).



**Figure 1:** Chemical structures of hyperoside(1) and quercetin (2)

**Table 1:** Pharmacological activities of hyperoside

Activities	References
Anti-inflammatory activity	[13], [14], [15], [16], [17]
Anti-nociceptive activity	[18], [14]
Anti-depressant activity	[19], [20], [21]
Neuro-protective effects	[22], [23], [24], [25], [26]
Protective activity on brain	[27], [28], [29], [30], [31], [26]
Cardio-protective activity	[32], [33], [34], [35], [11]
Anti-diabetic activity	[36], [37], [38], [16], [10], [39]
Anti-cancer activity	[40], [41], [42]
Anti-viral activity	[2], [43], [44]
Hepato-protective activity	[45]
Antioxidant activity	[46], [12], [1], [47], [48], [49]
Immuno-modulatory activity	[50], [43]
Cytochrome P <sub>450</sub> isoform inhibitory activity	[51]
Other activities	[9], [52], [53], [54], [55], [56]

## PHARMACOLOGICAL APPLICATIONS OF HYPEROSIDE

### Anti-inflammatory Activity

Hyperoside exhibited anti-inflammatory activity in mouse ear edema, with inhibition of arachidonic acid-induced edema by more than 15 %, and crotonoil-induced edema by 19-25 % [15]. When mixed with isoquercitrin it produced anti-inflammatory activity against carrageen-induced hind paw edema in albino mice, with 30 % inhibition for 6 h [16]. This phytochemical isolated from the leaves of *Tripodanthus acutifolius* has been reported to produce its anti-inflammatory effect by inhibiting cyclooxygenase-2 (COX-2) and hyaluronidase [17]. Hyperoside suppressed vascular inflammatory processes caused by high glucose level in the human umbilical vein endothelial cells (HUVECs) and in mice [18]. It suppresses the production of interleukin-6 (IL-6), tumor necrosis factor (TNF) and nitric oxide (NO) in lipopolysaccharide (LPS)-stimulated mouse peritoneal macrophages [17,19].

### Anti-nociceptive activity

Studies have shown that hyperoside exhibits analgesic activity by down regulating calcium (Ca<sup>2+</sup>) concentrations in afferent nerve endings [18,20]. It has anti-nociceptive activity in *p*-benzoquinone-induced abdominal constriction in mice with inhibition of 25 % [16].

### Anti-depressant effect

Hyperoside isolated from *Apocynum venetum* leaves has been shown to exhibit excellent anti-depressant activity. *In vitro* study confirmed that 2.5-10 µg/ml of the compound shielded PC12 cells from the lesions and high influx of

intracellular Ca<sup>2+</sup> induced by corticosteroid (10 µM). Its ability to boost brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB) has also been reported [21]. In mice orally administered hyperoside at doses of 10-30 mg/kg for 10 days, antidepressant-like activity was noticed in suspension test (TST) and forced swimming test (FST) that may be affected in their interaction with serotonergic (5-HT<sub>2A</sub> and 5-HT<sub>2</sub>) systems [20,22]. Antidepressant-like effects of hyperoside have also been observed in forced swimming tests in rats. The antidepressant effect in rats was prevented by the administration of sulpiride (D2-antagonist). Evidence indicates that the antidepressant effect of hyperoside is mediated through the dopaminergic system [21,23].

### Neuroprotective activity

*In vitro* studies have shown that pretreatment with hyperoside (0.01-1 µmol/L) for 4 h decreased apoptosis in PC12 cells induced by sodium azide (20 µM). This neuro-protective action has been attributed to inhibition of ROS production [22,24]. At 5-20 µM, hyperoside protected primary rat cortical neuron from neurotoxicity of β-amyloid protein (Aβ) induced by sodium azide at 20 µM for 24 h. Thus, hyperoside could be a useful therapeutic remedy for Alzheimer's disease (AD) and other neurodegenerative diseases [23,25]. Furthermore, in *in vitro* ischemic models of oxygen-glucose deprivation followed by reperfusion (OGD-R), it was observed that hyperoside offered protection from ischemic neuron damage by nitric oxide signaling process [26]. It has also been reported that hyperoside attenuates neuronal apoptosis triggered by L-glutamate through inhibition of NR2B-containing N-methyl-D-aspartate (NMDA) subtype of glutamate receptors [27]. At 16 µM it has been

shown to effectively reduce elevated levels of NO and  $\text{Ca}^{2+}$  from 34.4  $\mu\text{M}$  and 640 nM to 25.0  $\mu\text{M}$  and 331 nM in brain cells, respectively. Hyperoside also reduces the level of neuronal damage caused by anoxia as a result of increased concentration of NO and  $\text{Ca}^{2+}$  in brain cells [28].

### Protective activity on brain

Hyperoside at 1~10  $\mu\text{M}$  reduced the degree of cerebral injury induced by oxygen-glucose deprivation followed by reperfusion [29]. This provided protective effect on focal brain ischemia-reperfusion injury and restrained brain edema in rats [30]. Moreover, it was observed that hyperoside has protective effect on focal brain ischemia and reperfusion injury induced by oxidative damage in rats [31]. Furthermore, it was observed that brain tissues treated with this compound had lower water content [32]. Another study revealed that it shields rats from brain ischemia-reperfusion injury and protects them from cognitive disability [33].

### Cardiovascular protective activity

Hyperoside at 25 and 50 mg/kg protected rats from cardiomyocyte apoptosis caused by ischemia and perfusion, and at 0.50  $\mu\text{mol/L}$  protected cultured rat neonatal cardiomyocyte from apoptosis [34]. It was also reported that hyperoside suppressed levels of malondialdehyde (MDA) and NO in the myocardium, but increased the level of superoxide dismutase (SOD) [35]. It has also been reported that hyperoside protects cardiomyocytes from oxidative stress caused by ischemia and perfusion through significant up-regulation of extracellular signal-regulated protein kinase (ERK) [36]. Hyperoside inhibited vascular lesions produced in a carotid artery ligation rat model [37]. It also possesses anticoagulant effects, as demonstrated through its capacity to restrain the production of thrombin and activated factor X (FXa), and extension of activated partial thromboplastin time (aPTT) and prothrombin time (PT) as well as inhibition of thrombin and FXa in HUVECs [13].

### Antidiabetic activity

Hyperoside is well regarded for its anti-diabetic effects. It has been reported that hyperoside from *Rhododendron arboretum* and *Crataegus pinnatifida* exhibited anti-diabetic activity in streptozotocin-induced diabetic rats [38,39]. Methanolic extract of *Artemisia capillaris* which contains hyperoside has been reported to show

excellent  $\alpha$ -glucosidase inhibitory action [40]. In a molecular docking studies, it was shown that hyperoside could be an effective docking agent with targets of Type II diabetes mellitus [12,41].

### Anticancer activity

In an *in vitro* study on osteosarcoma cells, hyperoside was reported to restrain the growth of U2OS osteosarcoma cell lines ( $\text{IC}_{50}$  value 223.5  $\pm$  9.5  $\mu\text{g/ml}$  for 72 h) and MG63 ( $\text{IC}_{50}$  value 239  $\pm$  22.4  $\mu\text{g/ml}$  for 72 h) by revitalizing the  $\text{G}_0/\text{G}_1$  arrest in cell cycle [42]. In addition, hyperoside in combination with Quercetin produced anti-cancer effects in 786-O renal cancer cells ( $\text{IC}_{50}$  value 18.2, 18.7, 11.8  $\mu\text{g/ml}$  at 48, 72 and 96 h) [43].

### Antiviral activity

Hyperoside from *Abelmoschus manihot* (L) medik inhibited the production of HBeAg and HBsAg by hepatitis B virus (HBV)-producing 2.2.15 cells, and inhibited the duck hepatitis B virus (DHBV)-DNA levels in HBV- infected duck models [2]. Its antiviral activity was investigated in covalently-closed circular DNA (cccDNA) of duck hepatitis B virus [44]. *Yinqiaosan* powder which contains hyperoside is known to possess antiviral action against influenza virus [45].

### Hepatoprotective activity

Hyperoside isolated from *Artemisia Capillaris* has been reported to protect mice from liver damage induced by carbon tetrachloride ( $\text{CCl}_4$ ). Furthermore, it increased inducible nitric oxide synthase (iNOS), hemeoxygenase-1 (HO-1) and mRNA expression of tumor necrosis factor-R (TNF-R) [46].

### Antioxidant activity

Hyperoside protected PC12 cells against cytotoxicity induced by hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and *tert-butyl*hydroperoxide (*t*-BuOOH), and also protected lung fibroblast cells from oxidative stress induced by  $\text{H}_2\text{O}_2$  [47].

Moreover, hawthorn fruit extract containing hyperoside has been reported to attenuate oxidative damage by protecting mouse bone marrow cells from genotoxicity caused by cyclophosphamide [3]. It also protected hepatic L02 cells and HUVEC cells from oxidative damage induced by  $\text{H}_2\text{O}_2$  [48,49]. Recently hyperoside isolated from lotus seed epicarp showed significant DPPH and ABTS<sup>+</sup> radical scavenging activities [50].

### Immunomodulatory activity

Hyperoside has been shown to exhibit immunomodulatory activity in mice in non-specific, cellular and humoral immunity tests. In carbon clearance test (non-specific immunity), clearance index at doses of 12.5, 25 and 50 mg/kg was enhanced 34.6 %, 7.7 % and 7.7 %, respectively, and phagocytic index was increased by 18.3 %, 12.9 % and 2.1 % respectively when compared to normal group. In lymphocyte proliferation test, lymphocyte proliferation was elevated by hyperoside action [51]. It also raised the concentration of effector T helper cells secreting cytokines in mouse spleen lymphocytes [44].

### Inhibitory activity against cytochrome P<sub>450</sub>(CYP) isoform

It has been reported that hyperoside inhibits different isoforms of CYP, especially CYP2D6 [52].

### Other activities of hyperoside

Hyperoside has remarkable antifungal effect against *Pestalotia guepinii*, *Drechslera sp.* and *Fusarium avenaceum* [11]. It protected mice from gastric mucosal damage induced by ethanol via its anti-oxidant properties, as well as reduction of NO level in gastric mucosal tissues [53]. It decreased the formation of calcium oxalate stones in rat kidney [54] and diminished renal fibrosis *in vivo* [55]. Hyperoside also shielded hamster lung fibroblast cells from gamma ray radiation-stimulated apoptosis [56] and inhibited ultraviolet B (UVB) -stimulated transactivation of activator protein-1(AP-1), as well as mitogen-activated protein kinase signaling pathway(ERK1/2) in JB6 P+ mouse epidermal cells line [57].

### Pharmacokinetics of hyperoside

*In vitro* studies show that hyperoside is a stable compound. In an oral absorption study of this compound and isoquercitrin in rats, it was demonstrated that isoquercitrin was more easily hydrolyzed to its aglycone moiety in the gastrointestinal tract than hyperoside, and that *in vitro*, it was more stable than isoquercitrin [58]. In another study, binding interaction between hyperoside and bovine serum albumin (BSA) was investigated by fluorescence spectroscopy [59]. Fluorescence spectroscopy data was examined with the aid of Tachiya model and Stern–Volmer equation. Tachiya model equation revealed that the binding sites and binding constants were increased with increase in temperature. On the other hand, Stern-Volmer

equation showed that binding constants reduced with temperature elevation, although the binding sites were independent of temperature. The binding of hyperoside to bovine serum albumin was enhanced in the presence of Cu<sup>2+</sup>, Ca<sup>2+</sup>, Zn<sup>2+</sup> and K<sup>+</sup> but decreased when Mg<sup>2+</sup> was present [59]. When hyperoside and 3'-O-methyl-hyperoside were administered through gastric probe and intraperitoneal (i.p.) route to rats, it was observed that hyperoside and 3'-O-methyl-hyperoside were present in rat brain after i.p. administration, but were not detected when administered by gastric probe [60]. In another pharmacokinetic profile study of hyperoside in male and female dogs, it was shown that sex has no remarkable impact on its pharmacokinetic profile [61].

### CONCLUSION

For this review, a number of scientific databases (Science Direct, ISI Web of Knowledge, Google Scholar and China Knowledge Resource Integrated Database) were employed to access information. Research articles published in both English and Chinese languages were included. According to available information, hyperoside from different fruits and vegetables has become important due to its numerous pharmacological activities such as anti-inflammatory, anti-analgesic, neuro-protective, anti-coagulant, anti-diabetic, anti-cancer, anti-viral, anti-fungal, and anti-oxidant activities. The information presented in this review will assist in future studies on hyperoside.

### DECLARATIONS

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#### Conflict of Interest

No conflict of interest associated with this work.

#### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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