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**Review Article**

# Pharmacological Applications of Quercetin and its Derivatives: A Short Review

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## *Abstract*

*Quercetin (3,3',4',5,7-pentahydroxyl-flavone) is a flavonol, and it belongs to a class of plant secondary metabolites known as flavonoids. It is present in man's daily diet and is known for biological activities such as antioxidant, antiviral, anticancer, antimicrobial, anti-inflammatory and many more. Quercetin has been reported for its antioxidant and antiviral applications, hence, it is not only used as such but also its various derivatized forms have potentials for development into drugs for the treatment of diseases caused by oxidative stress and lethal viruses.*

*Keywords: Quercetin, Antioxidant, Pharmacological, Anticancer, Antimicrobial, Antiviral, Hepatoprotective*

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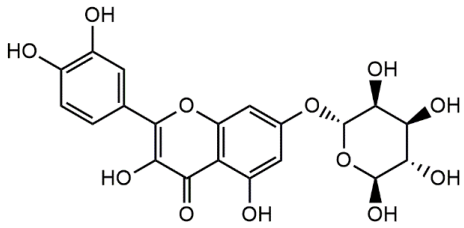
## INTRODUCTION

Quercetin is a plant pigment, abundantly occurs in many ethnic plants, especially onion and tea, therefore, a sufficient amount may be consumed daily [1]. Quercetin has importance in terms of ethnopharmacology such as its use as antioxidant, anticancer and neuroprotective [2]. It has been reported as an efficient free radical scavenger (antioxidant) [3]. In clinical trials (phase-I), quercetin has been reported to exhibit inhibitory effect on tyrosine kinase which suggests that it has antitumor therapeutic potentials [4].

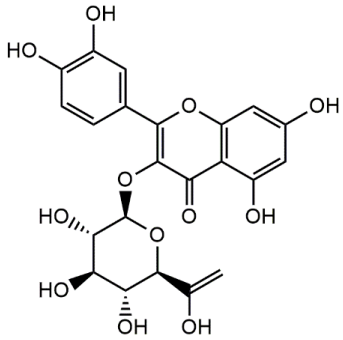
The review has been prepared using databases such as ISI Web of Knowledge, Science Direct, and Google Scholar, and covers the literature from the last decade. This article includes only original research articles published in English language; articles published in other languages are excluded.

### PHARMACOLOGICAL IMPORTANCE OF QUERCETIN

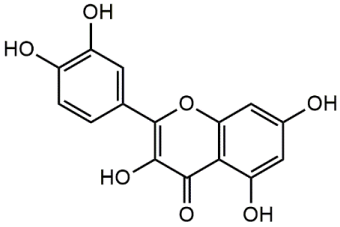
Quercetin is a versatile molecule (Figure 1) with many pharmacological properties including antioxidant, neurological, antiviral, anticancer, cardiovascular, antimicrobial, anti-inflammatory, hepatoprotective, protective of the reproductive system and anti-obesity agent. The literature available on these properties has been summarized here in this review (Table 1).



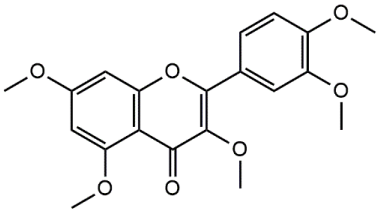
Quercetin 7-O-Rhamnoside



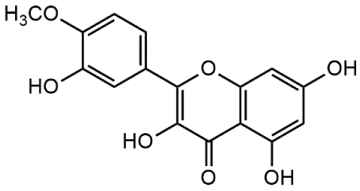
Quercetin 3-O-D-glucuronide



Quercetin



Quercetin pentamethylether



Quercetin 4'-methylether

**Figure 1:** Quercetin and some of its derivatives

**Table 1:** Pharmacological properties of quercetin

| Pharmacological property | References |
|---|---|
| Antioxidant activity | [4], [5], [6], [7], [8], [9], [10], [11] |
| Neurological effects | [12], [13], [14], [15] |
| Antiviral activity | [16], [17], [18], [19], [20], [21], [22] |
| Anticancer activity | [2], [23], [24], [25], [26] |
| Cardiovascular protection | [4], [27], [28], [29], [30] |
| Antimicrobial activity | [31], [32], [33] |
| Anti-inflammatory activity | [34], [35], [36], [37], [38], [39] |
| Hepatoprotective activity | [40], [41], [42] |

## Antioxidant activity

Quercetin is capable of scavenging reactive oxygen species and its antioxidant potential is attributed to this free radical scavenging activity [5]. During *in vitro* studies antioxidant behavior makes quercetin capable of inhibiting cataract formation caused by oxidative stress in rat eye lens cultured in a hydrogen peroxide environment [6]. Recently, *in vivo* study, it has been reported that oxidative damage caused by an industrial compound $CCl_4$ can be effectively reduced using methanolic extract of *Heterotheca inuloides* containing quercetin [7]. Moreover, quercetin has also been reported to show *in vivo* inhibitory effect against *tert*-butylhydroperoxide induced lipid peroxidation in human sperm cells [8]. In another study, quercetin at a dose of 25-50 mg/kg reported to show antioxidant behavior against the oxidative stress caused by streptozotocin-induced diabetes mellitus in rats [9]. Moreover, quercetin has also been reported as an efficient antioxidant and stabilizer in polyethylene with a dosage of 250 ppm an increase was described in the long term residual stability of the polymer [10]. Furthermore, quercetin-cadmium complexes has also been reported to have higher stability constant (*Kf*) value, therefore, quercetin is proposed to be used as chelating agent in the chelation therapy treatment for the removal of toxic metal ions [11].

**Neurological effects**

Quercetin is neuroprotective as well as neurotoxic. Therefore, it has been reported to behave as a neuroprotector in rat brain when used in combination to fish oil [12]. Quercetin has been reported to show beneficial effects against neurodegenerative diseases (example, Alzheimer's disease) where it shows inhibitory effect against acetylcholinesterase [13]. Moreover, quercetin has been reported to reduce the oxidative stress induced by 6-hydroxydopamine in neurons from the brain striatum of rats [14]. A study on healthy P19 neurons reported that quercetin treatment did not affect neuron survival but a depletion in intracellular glutathione contents has been observed which can affect working of nervous system [15]. However, prolonged use of antioxidant supplements is safe for human health is still a big question. .

**Antiviral activity**

Viral diseases are a growing threat for human health. Quercetin has also been found affective against a variety of viruses. In a study, quercetin has been reported potent against budding in MT-2 cells caused by human T-lymphotropic virus 1 [16]. Moreover, a low antiviral activity of quercetin with $IC_{50}$ = 212.1 µg/mL was reported against anti-Japanese encephalitis virus (JEV) which is responsible for mosquito-borne disease known as Japanese encephalitis [17]. However, quercetin has been reported for profound antiviral effect against dengue virus type-2 [18]. Quercetin enriched lecithin formulations, are reported to show antiviral activity *in vitro* using African green monkey's Vero cells [19]. Furthermore, quercetin has been reported to suppress the hepatitis C virus by inhibiting nonstructural protein 3 protease activity [20]. Quercetin-3-O-β-D-glucuronide, during *in vivo* studies has been reported to be effective against influenza-A virus [21] and quercetin 7-rhamnoside was found effective against porcine epidemic diarrhea virus [22].

**Anticancer activity**

Cancer has been found in sixty different parts of the human body and currently requires new therapeutics for its treatment. Quercetin has been reported as a potent anticancer agent during *in vitro* studies in various cancer cell lines and *in vivo* studies in rodents especially mice [2]. Quercetin has radical scavenging potential, therefore, it is capable of preventing cancer induced by oxidative stress [23]. The chemoprotective action of quercetin through apoptosis and metastasis against tumor cell lines makes it a strong candidate as a potential anticancer agent [24]. Moreover, quercetin in combination with intratumoral doxorubicin injection has been reported to result in enhancing immune responses against growth in breast tumors [25]. However, during *in vitro* study using human MCF-7 cells (Michigan Cancer Foundation-7), quercetin has been reported to inhibit angiogenesis in tamoxifen-resistant cancer in breast cells [26].

**Cardiovascular protection**

Quercetin has been reported to play a role in reducing cardiovascular diseases and this property is attributed to its anti-inflammatory nature [27]. During an *in vitro* study on isolated rat arteries, quercetin in its a-glycan form has been demonstrated to be a vasodilator [28]. Epidemiological data show a positive correlation between a diet rich in quercetin and reduction in cardiovascular problems [4]. However, quercetin has also been reported for a reduction in cardiovascular endangering factors including fibrinogen and human C-reactive protein in human transgenic mice [29]. Moreover, *in vivo* study in mice reported that due to its anti-inflammatory effect quercetin is also capable of preventing calcium chloride induced abdominal aortic aneurism [30].

**Antimicrobial activity**

Quercetin being antimicrobial agent plays its role in meat of fattening lambs which have been supplemented by quercetin diet, a decrease in microbial growth has been reported upon freezing [31]. Additionally, chitosan functioned by quercetin in the presence of Lucas has a remarkable antimicrobial activity against bacterial species such as *Escherichia coli, Salmonellae enterica* and *Listeria monocytogenes* [32]. Moreover, quercetin also act as bacteriostatic due to its capacity to inhibit D-Ala-D-Ala ligation in bacterial cells, by inhibiting D-alanine: D-alanine ligase enzyme and preventing the bacterial growth [33]. Currently, bacteria are getting resistant against the available antibacterial drugs therefore; more advanced and effective drugs are required to counter these resistant bacteria. Quercetin being bacteriostatic is a good molecule for antibacterial drug research.

**Antiinflammatory activity**

Quercetin is known for anti-inflammatory effects, during *in vivo* study, it has been reported that orally administered quercetin mixed with

polysorbate 80 inhibited paw edema in rats [34]. Quercetin and its glycoside derivatives, due to their lower absorption through the skin surface were reported ineffective against topical inflammation, however, a pentamethylether derivative of quercetin has excellent absorption properties through skin route in rat and is reported as anti-inflammatory agent [35]. Furthermore, quercetin applied on a cultured hepatocyte cell line has been reported to show an inhibitory effect against inflammatory causing agents like reactive C-protein and nitric oxide synthase [36]. However, *in vivo* study in mice has been reported to show a reduction in expression of inflammatory genes by using quercetin enriched diet [37]. An improvement in insulin sensitivity has been reported by intraperitoneal administration of quercetin in mice, subsequently a reduction in inflammation was reported which is attributed to the insulin resistance [38]. However, during *in vivo* and *ex vivo* studies performed in healthy human volunteers administered with quercetin reported no effect on inflammatory agents present in human blood [39]. Beneficial effects of quercetin and its derivatives against inflammation, *in vivo* models suggest that it is a potent anti-inflammatory agent.

**Hepatoprotective activity**

*In vivo* study in non-alcoholic steatohepatitis gerbils, it has been reported that gerbils which had been orally administered with quercetin showed a decreased deposition of fats in liver cells, thereby protecting liver cells from fibrosis [40]. Moreover, *in vivo* study in mice relating to the hepatoprotective mechanism of quercetin reported that it is the hemeoxygenase 1 that triggers the function of quercetin against induced hepatotoxicity; hepatoprotectivity was then observed by the decrease in plasma concentration of alanine aminotransferase [41]. Oxidative damage induced by ethanol in rat hepatocytes has been reported to be curable with the quercetin administration [42]. Hepatoprotectivity of quercetin suggests that its administration may be helpful to prevent liver damage, thus quercetin may be a suitable natural product as hepatoprotective agent.

Along with above mentioned pharmacological activities, quercetin has also been reported for its protective effect on the reproductive system of embryonic chicken and induced toxicity by quinine sulfate in rats [43,44]. Literature also reveals anti-obesity use of quercetin [45].

## CONCLUSION

Quercetin and its derivatives have been studied for their pharmacological properties in the recent years. We have discussed some of the pharmacological properties, including, antiviral, antioxidant, anticancer, antimicrobial, anti-inflammatory, neurological effects, cardiovascular, and hepatoprotective. However, research published on anti-inflammatory aspect of quercetin and its derivatives is not enough for its application in humans. Quercetin and its derivatives are versatile molecules and should be investigated more extensively for their wider applications in human health, including their therapeutic activities.

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