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Original article

Bioactive effects of quercetin in the central nervous system: Focusing on the mechanisms of actions

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ABSTRACT

Quercetin, a ubiquitous flavonoid that is widely distributed in plants is classified as a cognitive enhancer in traditional and oriental medicine. The protective effects of quercetin for the treatment of neurodegenerative disorders and cerebrovascular diseases have been demonstrated in both *in vitro* and *in vivo* studies. The free radical scavenging activity of quercetin has been well-documented, wherein quercetin has been observed to exhibit protective effects against oxidative stress mediated neuronal damage by modulating the expression of NRF-2 dependent antioxidant responsive elements, and attenuation of neuroinflammation by suppressing NF-κB signal transducer and activator of transcription-1 (STAT-1). Several *in vitro* and *in vivo* studies have also shown that quercetin destabilizes and enhances the clearance of abnormal protein such as beta- amyloid peptide and hyperphosphorlyated tau, the key pathological hallmarks of Alzheimer's disease. Quercetin enhances neurogenesis and neuronal longevity by modulating a broad number of kinase signaling cascades such as phophoinositide 3- kinase (P13-kinase), AKT/PKB tyrosine kinase and Protein kinase C (PKC). Quercetin has also been well reported for its ability to reverse cognitive impairment and memory enhancement during aging. The current review focuses on summarizing the recent findings on the neuroprotective effect of quercetin, its mechanism of action and its possible roles in the prevention of neurological disorders.

Contents

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1. Introduction

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is an unique bi-flavonoid that was first isolated by the physiologist Albert Szent-Györgyi de Nagyrápolt, a Nobel Prize winner for Physiology/Medicine in the year 1936 [1]. The name “quercetin” is derived from the latin name “quercetum” meaning “oak forest, quercus oak”. Vernacular names of quercetin are quercetine, sophretin, memetin [2]. Quercetin is a major component of flavonol subclass and represents 60–75% of total flavonoid intake. It is primarily conjugated with a carbohydrate moiety and forms the backbone of other flavonoids such as rutin, hesperidin, naringenin and tangeritin [3]. Medicinal herbs widely used in traditional ayurvedic, unani, Chinese medicine and Native American remedies contains rich source of quercetin. Multiple pharmacological applications of quercetin, including antioxidant, neuroprotective, anti-viral, anti-cancer, cardiovascular, anti-microbial, anti-inflammatory, hepatoprotective and anti-obesity activities, have made this phytochemical a promising food component for the prevention of lifestyle related disorders [4].

2. Sources of quercetin

Quercetin is commonly distributed in vegetables, fruits, nuts and grains in association with sugars, phenolic acids and alcohols (Table 1). It is widely distributed in the plant kingdom, specifically in rinds and barks and it is responsible for the bright color of fruits and vegetables. High concentration of quercetin is found in vegetables such as onions (*Allium cepa* L.), asparagus (*Asparagus officinalis* L.), and red leaf lettuce (*Lactuca sativa* L.), while lower concentration has been reported in broccoli, green peppers, peas, and tomatoes. Among the fruits, apples together with cherries and berries are the richest source of quercetin. The concentration of quercetin in beverages such as beer, white wine, coffee and chocolate milk was observed to be below 1 mg/l. However, the highest concentration of quercetin was observed in red wine and tea infusions i.e. 4 to 16 and 10 to 25 mg/l respectively [5]. The concentration of quercetin in food is affected by various factors such as temperature, storage and growth conditions. High temperature and storage of food materials lowers the quercetin content [6], which varies according to the nature of foods. For eg: onions retain the stability of quercetin conjugates up to temperature of 100 °C, but on storage 25–33% of their quercetin content is lost [7]. However, in the case of strawberries, the level of quercetin increases approximately by 32% on storage at −20 °C for nine months. Plants grown exposed to ultraviolet rays contain high level of quercetin content when compared to greenhouse plants, and this is related to the defense mechanism against UV light [6].

3. Chemistry and bioavailability of quercetin

Quercetin is 2-(3,4-dihydroxyphenyl)-trihydroxy-4Hchromen-4-one with molecular weight 302.24, melting point 316 °C, molecular formula $C_{15}H_{10}O_7$. Quercetin consists of five hydroxyl groups whose presence determines the compound’s biological activity and the possible number of derivatives. Quercetin is generally synthesized either according to the Kostanecki’s method or Robinson method. The Kostanecki method involves claisen condensation of 1 2,4-dimethoxy-6-hydroxyacetophenone with 3,4-dimethoxybenzaldehyde under alkaline condition, followed by acidic condensation and reaction with isoamyl nitrite [8]. On the contrary, the Robinson method involves the condensation of ω-methoxyphloroacetophenone with veratric anhydride in the presence of the potassium salt of 3,4- dimethoxybenzoic acid (veratric acid), which leads to formation of flavonols [9].

Naturally, quercetin is distributed as derivatives either in glycosidic form i.e. mainly bound to glucose and rutinose, or bound to ethers, very rarely occurring as sulfate and prenyl substituent [1,10]. Quercetin *O*-glycosides are quercetin derivatives with at least one O-glycosidic bond primarily glycosylated at the hydroxyl group of C-3 carbon with glucose, galactose, rhamnose or xylose [11]. Quercetin derivatives and their plant derived sources are listed in Table 2 [12]. Another glycosylation site is the hydroxyl group at C-7 carbon e.g: quercetin 7-*O*-glucoside which is found in beans [13]. Ether derivatives of quercetin are formed between the OH group of quercetin and alcohol molecule, mostly methanol. Quercetin ether derivatives associated with sugar moiety group such as 7-methoxy-3-glucoside and quercetin 3′-methoxy-3-galactoside occurs widely in nature [14]. Quercetin is highly lipophilic in nature due to the presence of five hydroxyl groups. However, the solubility of quercetin derivatives depends on the type of substituent molecules present in the OH group. *O*-methyl, *C*-methyl and prenyl derivatives of quercetin are lipophilic in nature, which are widely found on the surface of leaves, flowers and fruits of *Labiatae* or *Compositae* family [10]. Glycosylation of quercetin increases the hydrophilicity and these glycosylated derivatives are cytosol-soluble, easily transported to all the parts of plants and mostly stored in vacuoles [10,15].

The unique chemical structure of quercetin (Fig. 1) is responsible for its potent antioxidant property. Structural groups responsible for the stability and antioxidant activity of quercetin are (a) orthodihydroxy or catechol group, (b) 3- and 5-OH groups in conjugation with 4-oxo group [16]. Quercetin donates a proton to the free radical such as DPPH and transforms itself to quinone intermediate, which are stabilized by the electrons donated by these functional groups [17]. Quercetin derivatives such as C_3 and C_4—OH glycoside derivatives shows decreased H- donating ability. Reducing potential of C_3—OH derivatives of quercetin is higher when compared to its aglycone form [18].