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Editorial

Luteolin: A Natural Therapeutic Molecule for Nutritional and Inflammatory Disorders

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Received: March 25, 2017; **Published:** June 24, 2017

Phytochemicals are plant-derived bioactive chemical constituents, which are responsible for the pharmacological effects of medicinal plant extracts. Among them, polyphenolic compounds, in particular flavonoids, are one of the most effective chemical classes which possess a wide range of health-promoting activities and pharmacological effects.

Luteolin (3,4,5,7-tetrahydroxy flavone) is an important flavone, which is naturally found in several plant species. Chemically, it has a C6-C3-C6 structure that contains two benzene rings and one oxygen-containing ring with a C2-C3 carbon double bond [1]. Structure-activity studies have shown that the presence of hydroxyl moieties at carbons 5, 7, 3 and 4 positions of the luteolin structure and the presence of the 2 - 3 double bond are responsible for its multiple pharmacological effects [2]. Luteolin, which is naturally found as a glycosylated form, is present in different fruits and vegetables, including broccoli, pepper, thyme, and celery [3]. Luteolin possesses antioxidant, anticancer, anti-inflammatory, and neuroprotective effects. Therefore, the aim of the present paper is to review existing literature regarding anti-inflammatory effects of luteolin.

Inflammation is a physiological process in response to tissue damage resulting from microbial pathogen infection, chemical irritation, and/or wounding. After tissue injury, a multifactorial network of chemical signals initiates and maintains a host response designed to heal the damaged tissue. The activation and migration of leukocytes (neutrophils, monocytes and eosinophils) from the venous system to the site of damage and the release of growth factors, cytokines and reactive oxygen and nitrogen species are known to play a crucial role in the inflammatory response. Inflammatory processes are required for immune surveillance, optimal repair, and regeneration after injury. When acute inflammation is not resolved, however, chronic inflammation occurs, which has a detrimental effect in several diseases including atherosclerosis, cancer, asthma and some neurological disorders, such as Alzheimer's disease and Parkinson's disease [4].

Luteolin, and its glycosides have been reported to exert anti-inflammatory effects *in vitro* and *in vivo*. Several mechanisms seem to be involved in the anti-inflammatory activity of this flavonoid.

- Luteolin inhibits NF-kappa B activity at concentrations in the low micromolar range that increases the expression of pro-inflammatory cytokines, chemokines and enzymes (e.g. TNF, IL-1, IL-6, IL8, COX-2, iNOS).
- The enzymes cyclooxygenases (COX), lipoxygenases (LOX) and inducible nitric oxide synthase (iNOS) are known to play important roles in inflammation by participating in the synthesis of eicosanoids (e.g. prostaglandins, leukotrienes) and in the production of reactive species. Some reports have shown that luteolin can inhibit COX-2, LOX and iNOS. The inhibitory effects of luteolin on these pro-inflammatory enzymes may contribute to its anti-inflammatory activity.
- Luteolin have abilities to inhibit enzymes for the synthesis of thromboxane B2 and leukotriene B4 as well as hydrogen peroxide scavenging activity. Luteolin exhibited a high inhibitory activity against both thromboxane and leukotriene synthesis.
- These reported work suggest that the activities of luteolin and its related glycosides against arachidonic acid synthesis and hydrogen peroxide scavenging are dependent on their molecular structures. The presence of ortho-dihydroxy groups at the B ring and OH substitution pattern at C-5 position of the A ring could significantly contribute to the anti-inflammatory and antioxidant activities of flavonoids [4,5].

The bioavailability of luteolin needs to be sufficiently high and its metabolism sufficiently low; otherwise, many activities of luteolin observed *in vitro* will not be relevant *in vivo*. Since luteolin is a common dietary constituent and since the oral route is the preferred route of administration for most drugs, it is important to know the bioavailability and metabolism of this flavonoid after oral ingestion [4].

Various reports indicate that luteolin can be absorbed after oral administration. Although most luteolin found in plasma is in the form of glucuronide and sulfateconjugates, low concentrations of free luteolin can be achieved in plasma after oral ingestion of this flavonoid. The plasma concentrations of luteolin depend on the form in which luteolin is ingested. The maximum concentrations of luteolin are achieved after 1 - 2h, and luteolin remains in the plasma for several hours. This suggests that the bioavailability of luteolin is sufficiently high and its metabolism sufficiently low to allow this flavonoid to exert some of its biological activities in an *in vivo* setting [4].

Luteolin and its glycosides are widely distributed in the plant kingdom and have been found in many edible plants. Numerous preclinical studies have shown that luteolin possesses a wide range of biological activities and several possible mechanisms of action have been elucidated. Although the oral bioavailability of luteolin and its glycosides is not too high, animal experiments have shown that luteolin exerts its biological properties *in vivo*. Accumulating evidence suggests that luteolin could be developed as a potential anti-inflammatory agent as well as cancer chemopreventive agent and be useful in cancer therapy to sensitize tumor cells to the cytotoxic effects of some chemotherapeutic drugs. It is suggested that long-term animal toxicity studies should be conducted before people are able to take high doses of luteolin safely over a long period of time.

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Volume 9 Issue 5 June 2017