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Review

Luteolin as an anti-inflammatory and neuroprotective agent: A brief review

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ABSTRACT

According to the World Health Organization, two billion people will be aged 60 years or older by 2050. Aging is a major risk factor for a number of neurodegenerative disorders. These age-related disorders currently represent one of the most important and challenging health problems worldwide. Therefore, much attention has been directed towards the design and development of neuroprotective agents derived from natural sources. These phytochemicals have demonstrated high efficacy and low adverse effects in multiple *in vitro* and *in vivo* studies. Among these phytochemicals, dietary flavonoids are an important and common chemical class of bioactive products, found in several fruits and vegetables. Luteolin is an important flavone, which is found in several plant products, including broccoli, pepper, thyme, and celery. Numerous studies have shown that luteolin possesses beneficial neuroprotective effects both *in vitro* and *in vivo*. Despite this, an overview of the neuroprotective effects of luteolin has not yet been accomplished. Therefore, the aim of this paper is to provide a review of the available literature regarding the neuroprotective effects of luteolin and its molecular mechanisms of action. Herein, we also review the available literature regarding the chemistry of luteolin, its herbal sources, and bioavailability as a pharmacological agent for the treatment and management of age-related neurodegenerative disorders.

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1. Introduction

According to World Health Organization reports, the number of elderly people (>60 years old) will significantly increase over the next 40 years (Fries, 2002; Wancata et al., 2003). Worldwide, the increase in the number of elderly people is associated with the rapidly growing incidence of morbidity and mortality due to age-related diseases (Carranza et al., 2013; de Lau and Breteler, 2006; Hendrie, 1998; Sosa-Ortiz et al., 2012; Nabavi et al., 2012a, 2013a,b). In the last two decades, scientific research has focused on the discovery and design of novel neuroprotective agents with high efficacy and low adverse effects (Guttmacher et al., 2003; Matteo and Esposito, 2003; Youdim and Buccafusco, 2005). Although the pathophysiology of Alzheimer's disease and Parkinson's disease remains unclear, it is well known that neuronal dysfunction is associated with neuroinflammation, glutamatergic excitotoxicity, and redox active metals, which play an important role in the initiation and progression of these neurocognitive and locomotor disorders (Ahmed et al., 2015; Guttmacher et al., 2003; Matteo and Esposito, 2003; Renaud et al., 2015; Youdim and Buccafusco, 2005). In addition, abundant scientific evidence shows that oxidative stress plays a crucial role in the neurodegeneration that underlies these diseases. Therefore, much attention has been focused on the beneficial role of natural neuroprotective substances with potent antioxidant and anti-inflammatory effects (Ahmed et al., 2015; Orhan et al., 2015; Renaud et al., 2015).

Phytochemicals are plant-derived bioactive chemical constituents, which are responsible for the pharmacological effects of medicinal plant extracts (Nabavi et al., 2014a, 2012b, 2015a). 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, such as antioxidant, anti-inflammatory, anticancer, neuroprotective, and cardioprotective effects. (Daglia et al., 2014; Donato et al., 2014; Nabavi et al., 2014b, 2012c, 2015b; Middleton et al., 2000; Xue et al., 2014). To date, there are more than 8000 flavonoids which are classified into different sub-groups, such as chalcones, flavones, flavonols, flavanones, flavanols, anthocyanins, and isoflavones (Corcoran et al., 2012; Orhan et al., 2015).

Luteolin (3′,4′,5,7-tetrahydroxy flavone, Fig. 1) is an important flavone, which is naturally found in several plant species (Kim et al., 2000a; Peters et al., 1986). 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 (Fig. 1) (Bravo, 1998; Lin et al., 2008). 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 (Lin et al., 2008). Luteolin, which is naturally found as a glycosylated form, is present in different fruits and vegetables, including broccoli, pepper, thyme, and celery (Lopez-Lazaro, 2009; Shimoi et al., 1998). A growing body of literature shows that luteolin possesses antioxidant, anticancer, anti-inflammatory, and neuroprotective effects (Chen et al., 2008; Cheng et al., 2010; Dirscherl et al., 2010; Kang et al., 2004; Lin et al., 2008; Pandurangan and Esa, 2014; Qiao et al., 2012; Theoharides et al., 2015; Zhang et al., 2013); however, a coherent review of the scientific literature regarding its neuroprotective effects is still lacking. Therefore, the aim of the the present paper is to review existing literature, evaluating the neuroprotective effects of luteolin. In addition, in the following sections the natural sources, chemistry, and bioavailability of luteolin will be discussed, providing a more comprehensive assessment of the beneficial effects of this important compound.

2. Sources of luteolin

Luteolin is one of the most common flavonoids present in edible plants. For example, it has been found in carrots (*Daucus carota* L.), peppers (*Capsicum annuum* L.), celery (*Apium graveolens* L.), olive oil (*Olea europaea* L.), peppermint (*Mentha piperita* L.), thyme (*Thymus vulgaris* L.), rosemary (*Rosmarinus officinalis* L.), oregano (*Origanum vulgare* L.), lettuce (*Lactuca sativa* L.), perilla leaves (*Perilla frutescens* (L.) Britton), pomegranate (*Punica granatum* L.), artichoke (*Cynara scolymus* L.), chocolate (*Theobroma cacao* L.), rooibos tea (*Aspalathus linearis* (Burm.f.) R.Dahlgren), buckwheat sprouts (*Fagopyrum esculentum* Moench), turnip (*Brassica napus* L.), capers (*Capparis spinosa* L.) and cucumber (*Cucumis sativus* L.). Luteolin has also been identified in lemon, beets, brussels sprouts, cabbage, cauliflower, chives, fennel, harwort, horseradish, kohlrabi, parsley, spinach and green tea (Lopez-Lazaro, 2009; Shimoi et al., 1998).

Luteolin is also present in plants used in traditional medicine such as *Terminalia chebula* Retz. (Combretaceae). It is found quite often in leaves, rinds, barks, clover blossom, and ragweed pollen (Lopez-Lazaro, 2009; Shimoi et al., 1998). In Tibet, *T. chebula* is called the "King of medicines" due to its efficacy in healing, with a wide spectrum of biological, anti-ulcerogenic, neuroprotective antioxidant, and antibacterial activities (Upadhyay et al., 2014). Luteolin is a flavone aglycone that is present in *Veronica*, the largest genus of the *Plantaginaceae* (formerly *Scrophulariaceae*), which consists of about 500 species. *Veronica* species have attracted attention because of their traditional uses and biological activities (Barreira et al., 2014). Luteolin has also been isolated from the aromatic flowering plant *Salvia tomentosa* Mill. (Lamiaceae), widespread in the Mediterranean and Aegean regions of Turkey. It has been traditionally used for reducing abdominal pains and healing wounds (Ulubelen et al., 1979). Phytochemical isolation from the seeds of *Senna petersiana* (Bolle) Lock resulted into the isolation of luteolin, which has been found to have antibacterial activity against three gram-positive bacteria, at the concentration of 1 mg/ml (Tshikalange et al., 2005). This finding is in agreement