

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

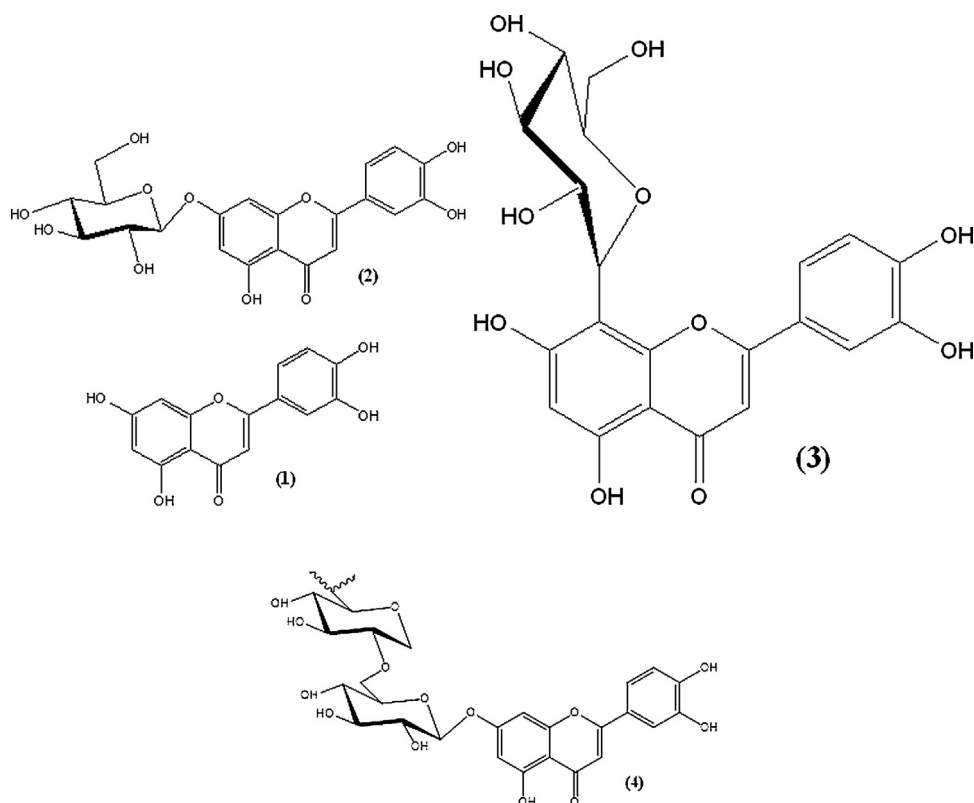


Fig. 1. Chemical structures of luteolin (1), luteolin-7-O-glucoside (2), luteolin-8-C-β-glucopyranoside (3), and luteolin-7-O-β-rutinoside (4).

with traditional usages of *S. persiana* as a treatment of sexually transmitted diseases (STD's). Luteolin has also been extracted from the flower of *Chrysanthemum morifolium* Ramat. (the accepted name of *Chrysanthemum sinense* Sabine ex Sweet) (Gu et al., 2013). In this case, luteolin extracts have been reported to show significant xanthine oxidase activity (IC₅₀, 1.3 mM), with stronger activity than the one of the clinically used drug allopurinol (IC₅₀, 2.5 mM).

3. Isolation from natural sources

Luteolin and its derivatives have been isolated from a wide variety of natural sources, which possess several pharmacological activities.

3.1. Luteolin glycosides

In the most recent study, luteolin (1) and luteolin-7-O-glucoside (2) were first isolated in glucoside form, from the ethanolic extract of *Dendranthema morifolium* Ramat Tzvel (Fig. 1) (Lin et al., 2015). The chemical structure of these analytes was then identified by spectroscopic data, using NMR and mass spectrometry. A pharmacokinetic study showed that, in rats, the oral bioavailability of luteolin and luteolin-7-O-glucoside is approximately 26 ± 6% and 10 ± 2% respectively. The authors also found that following oral consumption, luteolin-7-O-glucoside is firstly hydrolyzed to luteolin and then absorbed through the gastrointestinal tract.

A recent study described a simple method for the isolation of luteolin-7-O-β-D-glucoside (called cynaroside) (2) from *Anthriscus sylvestris* (L.) Hoffm, a short-lived perennial plant (Žemlička et al., 2014). In the experiment, (2) was isolated by using HPLC, thermal, and NMR analysis techniques. Spectroelectrochemical studies also showed that the hydrogen-donating ability of (2) is the main antioxidant behavior of this compound. Luteolin 8-C-β-

glucopyranoside (3) is another luteolin-glucoside derivative, which was isolated from the root of *Salvadora persica*, using column chromatographic techniques (Fig. 1) (Almahy and Fouda, 2013). The structure of the compound was established using several spectroscopic techniques, such as UV, IR, 1D, and 2D-NMR analysis. It is noteworthy to highlight that this compound has never been previously isolated from this plant.

Pedilanthus tithymaloides (PT) is an important Indian medicinal plant, traditionally used to reduce inflammation and pain. Research was carried out to evaluate the anti-inflammatory, antinociceptive, and anti-pyretic activity of the chloroform (CF) and methanol (ME) extracts of PT leaves and its isolated constituents, in animal models (Ghosh et al., 2013). The results revealed significant anti-inflammatory activity of CF and ME in carrageenan-induced paw edema (acute) and in vascular permeability and cotton pellet granuloma (chronic) models. Phytochemical analysis of PT showed that luteolin is one of its main compounds. Administration of purified luteolin (1, 10 mg/kg, p.o.) significantly attenuated acetic-acid-induced pain responses and suppressed inflammation induced by carrageenan and cotton pellets, in mice. These data suggest that (1) acts as an anti-inflammatory agent. Another study carried out a chemical investigation of the phenolic content of the ethanolic extract from aerial parts of *Scabiosa atropurpurea* Linn. (Dipsacaceae) (Elhawary et al., 2011). This led to the isolation of luteolin 7-O-glucoside (2), luteolin (1) and luteolin-7-O-β-rutinoside (4), among others (Fig. 1). The total ethanolic extract showed antioxidant, antihyperglycemic and hepatoprotective activities. The activity was assessed, on albino adult male rats, through decreasing glucose levels, increasing blood glutathione and decreasing alanine transaminase (ALT), aspartate amino transferase (AST) and alkaline phosphatase (ALP) levels. These studies have provided additional knowledge on the type of solvents required to extract luteolin and related derivatives.

3.2. Luteolin pyranosides

Further compounds were isolated in two different studies. The first evaluated the structural elucidation of flavone-*o*-glycoside, luteolin-8- β -D-glucopyranoside, isolated from the flowers of *Jatropha curcas* Linn (Shaikh et al., 2008). This plant is traditionally used for its medicinal value; while the seeds are purgative, the juice of the plant is useful for the treatment of scabies, eczema and ring worm, and its twigs are useful for curing swollen gums. The second study was a phytochemical analysis of *P. auriculata*, resulting in the isolation of a series of hydroxyl compounds and of a mixture of two flavonoids (luteolin and 5-methoxyluteolin) (De Paiva et al., 2013).

3.3. Luteolin rutinoside and esculetin

Another study was concerned with the isolation of luteolin 7-*O*-rutinoside (**4**) and esculetin (a coumarin), with potential antioxidant activity, from the aerial parts of *Artemisia montana* (Kim et al., 2000b). Previous research had indicated strong radical-scavenging action of methanol extracts of *A. montana* on 1,1-diphenyl-2-picrylhydrazyl (DPPH), even at 10.1 $\mu\text{g}/\text{mL}$. Therefore, in the more recent study, DPPH radical was used to assess the inhibitory activity of *A. montana* extracts against free radical generation in hepatocytes. It was demonstrated that the antioxidant activity of these luteolin analogues were comparable to that of L-ascorbic acid.

Finally, the activity-guided fractionation of *Senna siamea* leaves resulted in the isolation of luteolin (Ingkaninan et al., 2000). This flavone demonstrated antagonistic behavior against adenosine A_1 receptor, with a K_i value in the low micromolar range. Taken together, these reports show the variety of natural sources, in which luteolin and its derivatives are present in considerable amounts and with several pharmacological activities. The key for discovering new health applications will be to isolate and to assess new luteolin derivatives.

4. Synthesis of luteolin derivatives

In discussing the synthesis of luteolin and its bioactive derivatives, it is necessary to mention the variety of methodologies applied by researchers, especially from Asian countries, where the study of the biochemistry of natural products is very advanced. Contributions about the importance of luteolin and the experimental procedures for obtaining several derivatives will be discussed below. Earlier studies, from the 1980s, were limited to the synthetic field; therefore, this review will only describe important advances from the year 2000 to the present.

4.1. Semi-synthetic methods

A semi-synthetic method for preparation of luteolin, luteoloside and luteolin rutinoside has been revealed by another study. The process consists of dehydrogenation and demethylation of hesperidin, hesperidin glucoside, hesperidin in the presence of halogenated aluminum, iodine, and pyridine, to generate the product. The process is highly efficient, since it is performed under mild conditions, easy to control and environmentally friendly, with high demethylation yields. Methods as efficient as the one above have been reported for the synthesis of luteolin through the acylation of 1,3,5-trimethoxybenzene and condensation with 3,4-dimethoxybenzaldehyde, or the reaction of 3,4-dimethoxycinnamic acid with 1,3,5-trimethoxybenzene (Zhang et al., 2014).

Due to their potent anti-oxidant activity covering a wide spectrum, emerging evidence suggests that luteolin and its derivatives

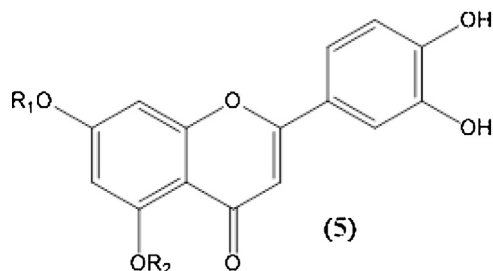


Fig. 2. Chemical structure of new luteolin derivative with alkyl chain in R_1 and R_2 .

may be important for the treatment and management of cardiovascular diseases. In this respect, a recent patent was concerned with the development of several luteolin derivatives for the prevention and treatment of cardiovascular diseases, containing an alkyl chain in R_1 and R_2 , as shown in Fig. 2 ($R_1 = \text{H}$, COR_3 ; $R_3 = \text{C}_1\text{--C}_6$ alkyl, hydroxy-substituted aryl; $R_2 = \text{C}_1\text{--C}_6$ alkyl, $\text{C}_2\text{--C}_6$ alkenyl, $\text{C}_3\text{--C}_6$ alkynyl, 1–3 hydroxy substituted aryl, benzenesulfonyl, toluenesulfonyl, 1–3 hydroxy substituted benzene sulfonyl, aminosulfonyl, substituted aminosulfonyl, heterocycloalkyl, heteroaryl, 1–3 hydroxy substituted heteroaryl) (Yongju et al., 2014).

4.2. Synthetic methods

Synthetic methods for the synthesis of luteolin have also been developed using specific catalysts for obtaining luteolin derivative (**6**), which is summarized in Fig. 3. Briefly, the well-known PEPPSI-IPr catalyst is reported to promote the carbonylative Suzuki–Miyaura cross-couplings reaction and to provide a diversity of biaryl ketones in excellent yield. The PEPPSI-IPr catalyst is also reported to promote carbonylative Negishi cross-coupling reaction, using alkynyl-zinc reagents to provide the corresponding alkynyl aryl ketones. The use of this protocol for the synthesis of the luteolin derivative (**6**) has been previously reported (O’Keefe et al., 2011). Another synthetic method to obtain chloro-luteolin derivatives is referred as the Vilsmeier–Haack–Arnold reaction, from the intermediate compound 3',4',7-trichloro-5-hydroxyflavone, which was obtained from luteolin (Fig. 4). The chloro derivative (**7**) may be used to improve the pharmacological activities of luteolin (Li et al., 2010).

4.3. Metal complexes of luteolin

Finally, two metal complexes of luteolin have also been synthesized (Jing-fen, 2006). These complexes were prepared by reacting luteolin with $\text{Cu}(\text{Ac})$, $\text{Zn}(\text{Ac})_2$ in ethanol solution. These compounds were characterized by elemental analysis, IR and UV spectra. The electrochemical properties of their modified carbon-paste electrodes were tested in pH 5 B-R buffer solution. A recent study has synthesized a luteolin-chrome complex and ascertained its molecular structure as well as its ability to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) derived free radicals (Jie et al., 2014). The synthesis procedure was carried out at pH 9.76 and 80 °C. The resulting structure was identified by IR, UV, TG-GTA, and elemental analysis techniques; the ability of the resulting complex to scavenge DPPH free radicals was then determined through HPLC and spectrophotometry. The experiments showed the superiority of luteolin–chrome complex compared to luteolin alone in scavenging DPPH.

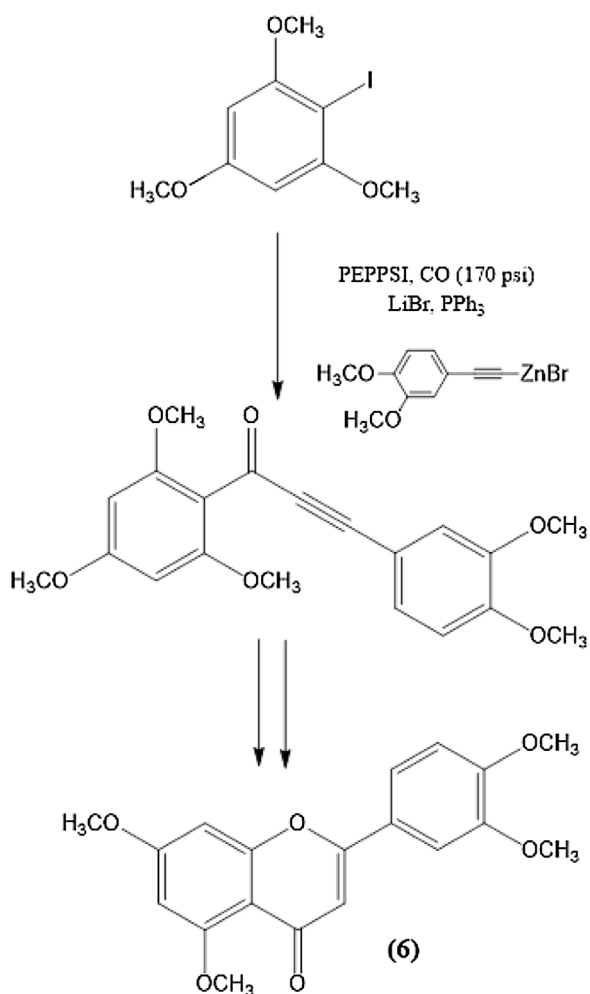


Fig. 3. Experimental procedure for synthesis of luteolin derivative 6.

5. Bioavailability, oral absorption and safety profile of luteolin

5.1. Bioavailability and oral absorption

It was previously thought that the oral bioavailability of flavonoids is very low. However, one study recently investigated the bioavailability of luteolin in peanut hull extracts (PHE) (Zhou et al., 2008). More specifically, the study showed that the effective permeability (Peff) and absorption rate constant (k_a) of pure luteolin (5.0 $\mu\text{g}/\text{mL}$) were not significantly different in the duodenum and jejunum, but significantly greater in the colon and ileum. The Peff and k_a of PHE were significantly greater than that of pure luteolin. Following oral administration of a single dose of pure luteolin (14.3 mg/kg) or PHE (containing 14.3 mg/kg of luteolin) in rats, The pharmacokinetics study showed that following oral administration, the peak concentration of luteolin in plasma

reached $1.97 \pm 0.15 \mu\text{g}/\text{mL}$ for luteolin, and $8.34 \pm 0.98 \mu\text{g}/\text{mL}$ for PHE. Luteolin appears to be passively absorbed in the intestine of rats (Zhou et al., 2008).

An analogue of luteolin, 5,7,3',4'-tetramethoxyflavone (TMF) is a methoxyflavones isolated from *Kaempferia parviflora*. After oral administration of 50 mg/kg TMF, the C_{max} was determined as $0.79 \pm 0.30 \mu\text{g}/\text{mL}$ (Jansat et al., 2002; Wei et al., 2014). The bioavailability of TMF was calculated as 14.3% following oral administration. An excretion study, reported that after 48 h, 0.81% of the oral administered TMF was excreted mostly in its pure form faecally whilst only 0.05% from urinary excretion; it suggested that TMF mainly excreted as the metabolites form (Jansat et al., 2002). This suggests that luteolin and its analogues may be clinically useful.

5.2. Toxicity

The safety profile of luteolin remains unclear (Harwood et al., 2007). Recent reports suggest that luteolin and its analogues may be deleterious to mammalian cells due to their effects on the endocrine system (Nordeen et al., 2013). This likely attributed to the oestrogenic activity of luteolin and its affinity to antagonize progesterone receptor activation (Nordeen et al., 2013). On the contrary, other studies have reported the inhibitory effect of luteolin against oestrogen production (Scippo et al., 2004), and progesterone displays little or no affinity to the progesterone receptor (Guo et al., 2009). Moreover, the anti-tumorigenic effect of luteolin have been extensively documented (Aksamitiene et al., 2012; Bai et al., 2012; Baskar et al., 2011; Cai et al., 2011; Iratni et al., 2010; Jeon and Suh, 2013; Johnson and de Mejia, 2013; Kim and Kim, 2012; Kim et al., 2012; Lee et al., 2012, 2011; Lim et al., 2012; Lin et al., 2011; Pandurangan et al., 2013; Rao et al., 2012; Ruan et al., 2012; Sakai et al., 2012; Starkey et al., 2010; Wang et al., 2014, 2012; Xie et al., 2012; Yan et al., 2012; Zhang et al., 2009; Zhao et al., 2011; Zhou et al., 2009). Moreover, the concentration of luteolin present in available dietary supplements are unlikely to reach the concentration capable of inducing toxicity since the oral absorption of luteolin 15% (Nordeen et al., 2013). Considering that the body as a whole is a singular compartment, the blood concentrations reached after consuming these dietary supplements would be 10 to 100 times smaller than the micromolar range capable of inducing toxicity in T47D cell lines as previously reported (Lopez-Lazaro, 2009).

6. Mechanism of action of luteolin in the central nervous system

Luteolin exerts a variety of pharmacological activities and antioxidant properties associated with its capacity to scavenge oxygen and nitrogen species. Luteolin has been shown to inhibit cytokine expression, nuclear factor kappa B (NFkB) signaling, and TLR4 signalling at micromolar concentrations in immune cells, including mast cells (Kim and Jobin, 2005; Lee et al., 2009; Weng et al., 2015). As well, luteolin has been shown to attenuate microglial activation and mediate BDNF-like behavior both *in-vitro* and *in-vivo* (Lin et al., 2010; Patil et al., 2014; Patil and Sathaye, 2015). Luteolin also reduced the mRNA expression of numerous genes upregulated in

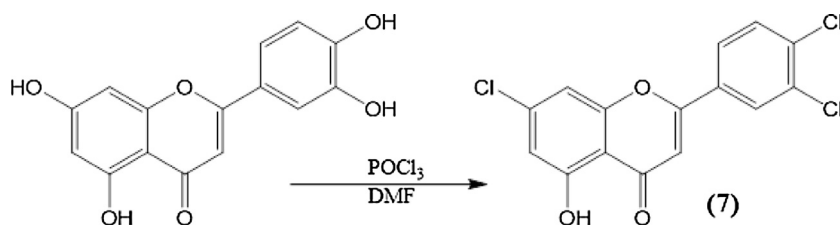


Fig. 4. Synthetic procedure for chloro-luteolin derivative (7).

response to exogenous 6-OHDA, including BIM (a pro-apoptotic BH3-only member of the Bcl-2 family, required for initiation of apoptosis induced by endoplasmic reticulum (ER) stress), the p53 target genes, GADD45 α and PUMA, TRB3 (a pro-apoptotic gene that is upregulated in response to a variety of stresses, including ER stress, nutrient deprivation, and hypoxia), and its unfolded protein response, leading to decreases in phosphor-eIF2 α , ATF4, GRP78 and CHOP (which are upregulated in response to ER stress). Luteolin can also inhibit the Keap1-Nrf2-ARE pathway, leading to a decrease in the expression of heme oxygenase-1 (HO-1) and glutamate cysteine ligase (GCL) (Lin et al., 2010). Recently, a luteolin analogue, 7,8-dihydroxyflavone, has demonstrated potent high-affinity selective tyrosine kinase receptor B (TrkB) agonism leading to receptor dimerization and autophosphorylation, and activation of down-stream signaling (Jang et al., 2010). Additionally, luteolin showed only partial affinity to the benzodiazepine binding site of GABA_A receptors, suggesting that the anxiolytic effects of luteolin are mediated by a yet unidentified mechanism (Coleta et al., 2008).

7. Neuroprotective effects of luteolin

7.1. Epilepsy

The plant extract obtained from *Eclipta alba*, which contains small quantities of luteolin, has been traditionally used in Ayurvedic medicine for the treatment of epilepsy. *E. alba* has demonstrated anticonvulsant properties in a maximal electroshock rat model (Shaikh and Sathaye, 2011). Acute luteolin administration has also been shown to attenuate oxidative stress in neuroblastoma cells (Zhou et al., 2011). Anxiolytic-like effects of luteolin have been reported following oral and intraperitoneal administration in mice, suggesting that it can cross the blood brain barrier (Coleta et al., 2008). Inflammation, in the form of microglial activation, generation of the cytokine interleukin 1 β (IL-1 β), and stimulation of toll-like receptor 4 (TLR4) have been reported in epilepsy patients (Maroso et al., 2010). Lipopolysaccharide (LPS)-mediated activation of TLR4 receptors can produce epileptiform discharges that can be attenuated by IL-1 receptor antagonists (Rodgers et al., 2009).

The effects of acute and chronic intraperitoneal luteolin injections was evaluated by Shaikh et al. (2013) in four mouse seizure models, (a) the 6 Hz model, (b) maximal electroshock test (MEST), (c) pentylenetetrazole (PTZ), and (d) second hit PTZ test in the chronic stage of the pilocarpine model (Shaikh et al., 2013). The study showed that luteolin did not exert any significant anti- or pro-convulsant effects after a single dose in the 6 Hz, MEST and PTZ tests, and following repeated daily dosing in the 6 Hz model. Moreover, while TLR4 mRNA levels were upregulated 3 days after pilocarpine-induced status epilepticus, they remained unaltered in the chronic stage of the model. No effect was observed in the second hit PTZ test following repeated luteolin injections (Shaikh et al., 2013). This suggests that seizure threshold may be independent of TLR4 signalling.

7.2. Autism spectrum disorders

Autism spectrum disorder (ASD) is a detrimental life-long neurological disease, characterized by significant impairments in social communication and language and repetitive behavior (McPartland and Volkmar, 2012). The limited understanding of the etiology of ASD has prevented the development of effective treatment strategies to attenuate the core symptoms of ASD. Current treatments target only specific behavioral symptoms of ASD (Broadstock et al., 2007). Many recent studies have shown that neuroinflammation may play a considerable role in the pathogenesis of ASD (El-Ansary

and Al-Ayadhi, 2012, 2014; McDougale and Carlezon, 2013). In particular, mast cells, which play a critical role in inflammation, are activated in autism, and prevalence of ASD is ten times higher in children with mastocytosis (Theoharides, 2012; Theoharides et al., 2012, 2013; Theoharides and Doyle, 2008). Microglial activation, mast cell-mediated allergic inflammation, and impaired brain-derived neurotrophic factor (BDNF) signaling which are a prominent feature in ASD, can be attenuated by luteolin (Kritas et al., 2013).

Apart from its potent antioxidant and anti-inflammatory properties, luteolin has been shown to inhibit the release of inflammatory mediators from human mast cells (Kempuraj et al., 2005). It can also reduce maternal interleukin 6-induced autism-like behavioral deficits associated with social interactions in mice (Kempuraj et al., 2005). It is likely that improved formulations may be useful in the treatment of ASD.

Likewise, an open labeled study involving fifty children (4–10 years old; 42 boys and 8 girls) with ASD reported that there was a significant improvement in adaptive functioning (as measured using the Vineland Adaptive Behavioral Scales domains) following dietary supplementation with a combination of luteolin (100 mg/capsule) and another flavonoid, quercetin (70 mg/capsule) for 26 weeks (Taliou et al., 2013). Similarly, a significant reduction in Aberrant Behavior Checklist subscale scores was also reported after stratification for age, sex, and history of allergies. These results are promising, since a combination of flavonoids, luteolin and quercetin attenuated ASD symptoms, with no major adverse effects.

7.3. Alzheimer's disease

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder and is classified as the major subtype of dementia (Fratiglioni et al., 2000). This progressive disorder is characterized by neuropsychiatric symptoms and pathologically by intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau fragments, extracellular amyloid-beta (A β) plaques containing insoluble, and the loss of cortical neurons and synapses (Terry et al., 1991). A β fragments between 39 and 43 amino acids, form the core constituent of these plaques (Masters et al., 1985). Although the exact mechanism mediating A β -induced neuronal cell death remains unclear, oxidative stress and generation of free radicals appear to be the likely cause of cytotoxicity. A β can also induce cell death via excitotoxicity and neuroinflammation (Small et al., 2001).

Numerous studies have shown that compounds with free-radical scavenger activities can attenuate A β -induced neuronal death (Di Domenico et al., 2015). Choi et al. (2014) showed that luteolin could ameliorate the neurotoxicity of A β fragment 25–35 (A β _{25–35}) in murine cortical neurons due to its potent antioxidant activity (Choi et al., 2014). In comparison with ten flavonoids, this study demonstrated the following sequence from the highest to the lowest activity: epigallocatechin gallate > myricetin > quercetin = luteolin = catechin \geq rutin \geq epicatechin \geq baicalein > kaempferol = trolox. The inhibitory effects of luteolin were maintained after 48 h (Choi et al., 2014). This study suggests that luteolin may be developed as a neuroprotective agent against AD.

Another recent study showed that the combination therapy with palmitoylethanolamide (PEA) and luteolin, given as a co-ultramicrosized compound Co-ultraPEALut, could attenuate neuroinflammation in an experimental AD model. Treatment with Co-ultraPEALut improved cell viability, significantly reduced inducible nitric oxide synthase and glial fibrillary acidic protein expression, restored neuronal nitric oxide synthase and brain-derived neurotrophic factor and reduced the apoptosis in differentiated SH-SY5Y neuroblastoma cell line following 24 h

treatment with A β _{1–42}. These cells exhibit similar structural morphology and functional axonal vesicles to mature neurons and therefore represent a suitable model to investigate the pathogenesis of AD. It is likely that co-ultraPEALut may represent a viable treatment option for AD.

7.4. Parkinson's disease

Parkinson's disease (PD) is another progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the *substantia nigra pars compacta*. The presence of Lewy bodies, which consist in abnormal fibrillary aggregates of α -synuclein protein within neurons, represents another pathological hallmark of PD. A large body of evidence suggests that oxidative stress and neuroinflammation play a pivotal role in disease progression and contribute to nigrostriatal degeneration (Taylor et al., 2013). Our understanding of the pathogenesis of PD stems from data obtained from experimental animal and cell models using the neurotoxins, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP⁺) (Bove et al., 2005).

6-OHDA shares similar structural features to dopamine and noradrenaline, and it induces cell death through the generation of free radicals and cytotoxic quinines (Saito et al., 2007). A recent study showed that treatment with luteolin (20 μ M) can attenuate 6-OHDA-mediated oxidative stress production, cytotoxicity, and caspase-3 activation in PC12 cells (Hu et al., 2014). Luteolin can also attenuate 6-OHDA-mediated increases in the Keap1-Nrf2-ARE pathway, leading to a decrease in the expression of heme oxygenase-1 (HO-1) and glutamate cysteine ligase (GCL) (Hu et al., 2014).

Another recent study showed that luteolin (10 and 20 mg/kg) and apigenin (5, 10, and 20 mg/kg) could improve locomotor and muscular changes in mice exposed to MPTP, a precursor to MPP⁺ in mice (Patil et al., 2014). The study also showed a significant decrease in TH-positive cells. These changes occurred in parallel to a decrease in the neurotrophic factors, glial fibrillary acidic protein (GFAP), and brain-derived neurotrophic factor (BDNF) (Patil et al., 2014). BDNF levels were significantly improved in luteolin and apigenin treatment group compared to MPTP treatment mice alone. Taken together, these studies suggest that luteolin can protect dopaminergic neurons by mitigating oxidative stress, neuroinflammation, glial activation, and inducing neurotrophic potential *in vitro*.

7.5. Diabetes-associated cognitive decline

Diabetes is a chronic metabolic disorder associated with chronic hyperglycemia. Diabetes is also associated with complications of the peripheral nervous system, retinopathy, nephropathy, and cardiomyopathy (Huynh et al., 2015; McVicar et al., 2015). Recent evidence suggests that diabetes can also induce cognitive dysfunction, and decline in memory and mental speed (Allen et al., 2015; Mousavi et al., 2015; Zhang et al., 2015). Although the pathogenesis of learning and memory impairments in diabetes remain unclear, several factors, such as oxidative stress and neuroinflammation have been shown to play a prominent role (Mastrocola et al., 2005; Somfai et al., 2006). Additionally, an increase in acetylcholinesterase (AChE) activity can lead to disruption in cholinergic transmission, leading to the cognitive decline observed in diabetes mellitus (Kuhad and Chopra, 2008). Hyperglycemia can lead to increased production of advanced glycation end products (AGEs), which can induce neuronal cell death via oxidative stress (Yan et al., 2003).

Emerging evidence suggests that flavonoids may potentially improve cognitive decline due to their potent antioxidant, and anti-inflammatory properties. Several studies have shown that luteolin can improve spatial learning and memory in A β _{25–35}

induced amnesic mice *via* modulation of microvascular function and neuronal activity by maintaining the blood brain barrier (Liu et al., 2009). Recently, Liu et al. (2013) showed that treatment with luteolin (50 and 100 mg/kg) can attenuate cognitive decline in streptozotocin-induced diabetes by reducing neuronal damage, lipid peroxidation and AChE activity. Therefore, oral supplementation with luteolin may represent a preventative strategy to reduce diabetes-associated cognitive decline.

7.6. Traumatic brain injury

Traumatic brain injury (TBI) is a major public health concern, leading to high morbidity (Brooks et al., 2013). While the outcome is largely dependent on the severity of primary insult, TBI is aggravated by secondary insult caused by pathological processes, including oxidative stress, excitotoxicity, inflammation, and increased vascular permeability (Werner and Engelhard, 2007). Over the last decade, there has been a concerted effort to develop drugs that alleviate the secondary insult, and thereby improving the outcome of TBI. However, most approaches to the treatment of TBI target a single injury mechanism and have failed in clinical trials (Sun et al., 2015).

More recently, Xu et al. (2014) showed that treatment with luteolin (30 and 50 mg/kg) can attenuate secondary brain injury induced by TBI, including neurological deficits, brain water content, and neuronal apoptosis. Furthermore, the levels of malondialdehyde (MDA) and the activity of glutathione peroxidase (GPx) were restored in the group with luteolin treatment. Luteolin enhanced the translocation of nuclear erythroid 3-related factor 2 (Nrf2) to the nucleus both in *in vivo* and *in vitro* conditions. These results were achieved by Western blot, immunohistochemistry, and electrophoretic mobility shift assay (EMSA) (Xu et al., 2014). Nrf2 is a known transcription factor, which represents the cell main defence mechanism against stress. However, luteolin was not neuroprotective after TBI in Nrf2^{-/-} mice (Xu et al., 2014). This suggests that the neuroprotective effects of luteolin in TBI are mediated through the activation of the Nrf2-ARE pathway.

7,8-Dihydroxyflavone rescued wild-type, but not TrkB deficient neurons from apoptosis in another study. Treatment with 7,8-dihydroxyflavone (5 mg/kg) also suppressed kainic acid (KA) levels following intraperitoneal injection with KA (20 mg/kg). Administration with 7,8-dihydroxyflavone also reduced infarct volume in the transient middle cerebral artery occlusion (MCAO) model of stroke (Jang et al., 2010).

Co-ultraPEALut formulation has also been shown to attenuate locomotor impairments, neuroinflammation and autophagy through activation of NF- κ B (Cordaro et al., 2014). In addition, the treatment with Co-ultraPEALut, at the dose of 1 mg/kg, reduced apoptosis, the release of cytokine and oxidative stress, the activation of chymase, tryptase and nitrotyrosine, and inhibited autophagy (Cordaro et al., 2014). This suggests that a combination of both PEA and luteolin can counteract the neurodegeneration and neuroinflammation induced by TBI.

7.7. Multiple sclerosis

Multiple sclerosis (MS) is a debilitating incurable autoimmune disorder involving demyelination of the protective myelin sheaths insulating the nerves of the central nervous system (Bando et al., 2015). While the most effective treatment is interferon-beta (IFN- β), it only provides asymptomatic relief in relapsing-remitting MS (RRMS) patients, and its mechanism of action remains unclear (Bertolotto et al., 2015). As well, Moreover, IFN- β treatment can only be administered parenterally with several undesirable adverse effects. Luteolin and other naturally occurring compounds have been implicated for the treatment of MS due to their potent, anti-

oxidant and anti-inflammatory effects, and inhibition of activated peripheral blood leukocytes isolated from MS patients (Sternberg et al., 2009; Theoharides, 2009). Luteolin effectively inhibited myelin basic protein-induced human mast cell activation at 10 and 100 μm , whereas it exhibited a dose-dependent inhibition (1–100 μm) of mast cell-dependent stimulation of Jurkat T cells and mast cell-induced IL-2 release, which are associated in the pathogenesis of MS (Kempuraj et al., 2008). As well, luteolin can inhibit experimental allergic encephalomyelitis (EAE), which is currently used as a murine model to study MS (Verbeek et al., 2005). Luteolin may also demonstrated protective immunomodulatory effects in peripheral blood mononuclear cells isolated from human MS patients when treated alone (Sternberg et al., 2009). Luteolin treatment also displayed additive effects in modulating cell proliferation, and the production of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and the ratio of the cell migration mediator MMP-9 and its inhibitor TIMP-1 (Sternberg et al., 2009). This suggests that luteolin may be a useful adjuvant to IFN- β for the treatment of MS.

8. Conclusion and recommendations

Recent epidemiological studies have shown that the elderly is the fastest growing population in the developed world. Accurate estimates of the prevalence of neurodegenerative diseases are important for optimal healthcare planning. The growing burden on public health of neurological deficits is not helped by the failure of synthetic agents to slow down or to prevent the progression of these diseases and related morbidities. This suggests that naturally occurring protective agents may provide therapeutic benefits. Among them, flavonoids, which exhibit little side effects, are considered as the most important and well-known natural neuroprotective agents and are widely found in different plant species. Luteolin is one of the most important bioactive flavonoids, which possesses potent neuroprotective effects. In this review, convincing evidence has been presented for the potent antioxidant activity of luteolin in several *in vitro* and *in vivo* assay systems. Luteolin also suppresses inflammation in the brain tissues and regulates different cell signaling pathways. Moreover, since oxidative stress and neuroinflammation have a crucial role in the initiation and progression of neurodegenerative diseases and neuronal cell death, antioxidants and anti-inflammatory agents, such as luteolin, can be used as novel therapeutic agents for the treatment of neurodegenerative diseases. However, there are negligible clinical trials evaluating the therapeutic effects of luteolin in a large cohort. Therefore, our understanding of the clinical efficacy of luteolin remains limited. We recommend that future studies should be performed to: (1) increase the bioavailability and absorption of luteolin by different delivery systems; (2) determine the most effective doses of luteolin in humans for future clinical studies; and (3) revisit the clinical impact of luteolin in patients with neurological diseases.

Conflict of interest

There is no conflict of interest.

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