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Letter to the editor:

RECENT UPDATES ON NEUROPHARMACOLOGICAL EFFECTS OF LUTEOLIN

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Dear Editor,

Luteolin (3,4,5,7-tetrahydroxyflavone) is a naturally found flavone, which is obtained from numerous plant species (Kim and Kim, 2012). 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. Structure-activity studies (SAS) have revealed 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 accountable for its numerous pharmacological activities (Lin et al., 2008). Luteolin is naturally found as a glycosylated form, is existing in several types of fruits and vegetables, such as pepper, thyme, broccoli, and celery (Lopez-Lazaro, 2009). Various research studies have confirmed that luteolin possesses antioxidant, anticancer, anti-inflammatory, and neuroprotective effects; though, a coherent review of the scientific literature related to its neuroprotective effects is still lacking.

In this letter, conclusive evidences have been presented for the potent antioxidant activity of luteolin reported in various *in vitro* and *in vivo* studies (Table 1). Luteolin also reduces inflammation in brain tissues and in regulating different cell signaling pathways (Dirscherl et al., 2010). Oxidative stress and neuro-inflammation are possible drivers of neurodegeneration. Thus, a chemical moiety like luteolin with potential antioxidant and anti-inflammatory activity could be used as a therapeutic agent for neurodegenerative diseases.

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Table 1: Recent updates on neuropharmacological effects of luteolin

Key Findings	References
Luteolin induces apoptosis of numerous types of cancerous cells. It induces apoptosis by activating ER stress and mitochondrial dysfunction in glioblastoma cell lines and *in vivo*, which delivers the anti-cancer agent to treat glioblastoma.	(Wang et al., 2017)
Luteolin assists as a potential interference for neurodegenerative diseases related to oxidative stress. Luteolin demonstrated to decrease H_2O_2- or xanthine/xanthine oxidase-induced oxidative damage and generation of intracellular reactive oxygen species (ROS).	(Kim et al., 2017)
Luteolin serves as a potential therapeutic agent for protection of blood-brain barrier (BBB) by preventing inflammation following fAβ1-40-induced injury.	(Zhang et al., 2017)
Luteolin showed an inhibitory effect on the course of kindling and related oxidative stress and henceforth might be a potential molecule in the epilepsy treatment.	(Tambe et al., 2017)
Luteolin has negative modulatory effects on both recombinant and endogenous GABAARs and prevents phasic rather than tonic inhibition in the hippocampus.	(Shen et al., 2016)
Luteolin suggestively upgraded the spatial learning and memory weakening induced by treatment of streptozotocin. Streptozotocin expressively decreased the CA1 pyramidal layer thickness and luteolin treatment entirely stopped the inhibitory effect of streptozotocin.	(Wang et al., 2016)
Pretreatment with luteolin repressed seizure initiation, length, and severity following injection of pentylenetetrazole, reversed cognitive impairment, decreased neuronal and oxidative stress impairment, and increased phosphoactivation of PKA and CREB as well as BDNF expression.	(Zhen et al., 2016)
By addition of luteolin as a dietary supplement, it inhibited the activity of brain microglia during aging and activation by LPS in adults. Hence, luteolin inhibits neuroinflammation and improves cognition in the healthy aged animal.	(Burton et al., 2016)
Luteolin protects Alzheimer's disease rats against Aβ-induced cognitive impairment via regulating the cholinergic system as well as preventing oxidative injuries. Consequences suggesting that luteolin have potential as a therapy for Alzheimer's disease.	(Yu et al., 2015)
Luteolin has an ability to reduce expression of the IL-1 receptor, and treatment with IL-1 receptor antagonist inhibited IL-1β/luteolin-induced expression of COX-2, which activates anti-survival and anti-inflammatory mechanisms that contribute to the chemopreventive activity of this diet-derived molecule.	(Lamy et al., 2015)
The chronic dose of luteolin expressively down-regulated the BACE1 and NF-κB expression as well as accompanied by weakening the Aβ deposition. This suggests a potential therapeutic use of luteolin for cerebral hypo perfusion linked cognitive dysfunction in Alzheimer's disease.	(Fu et al., 2014)
Luteolin and quercetin can be direct inhibitors of monoamine oxidase-A in nerve cells by targeting mitochondria.	(Bandaruk et al., 2014)
Luteolin protects mice brain from traumatic brain injury by preventing inflammatory response, as well as luteolin-induced autophagy may perform an essential role in its neuroprotection.	(Xu et al., 2014a)
Luteolin and apigenin protect the dopaminergic neurons possibly by decreasing oxidative damage, neuroinflammation along with activation of microglia as well as improved neurotrophic potential.	(Patil et al., 2014)
Luteolin has a positive effect on neuroinflammatory events in neurodegenerative diseases by MAPK, NF-κB, and Akt pathways suppression in activated microglial cells.	(Zhu et al., 2014)
Luteolin prevents methamphetamine-induced hyperactivity and behavioural sensitization in mice through the ERK1/2/ΔFosB pathway.	(Yan et al., 2014)
Luteolin suggestively induces growth inhibition of SH-SY5Y tumor cells by inducing apoptosis accompanied by G0/G1 cell cycle growth arrest and connected loss in mitochondrial membrane potential. As such, luteolin can be established as a potent anticancer molecule against brain tumor disorders.	(Wang et al., 2015)

Key Findings	References
Luteolin suggestively ameliorated secondary brain injuries induced by traumatic brain injury, such as neurological deficits, brain water content, and neuronal apoptosis.	(Xu et al., 2014b)
Orally administered luteolin protects mice brain from sodium nitroprusside-induced oxidative damage through scavenging and chelating effects.	(Nazari et al., 2013)
Treatment with luteolin recovers the scopolamine-induced reduction in cell proliferation and neuroblast differentiation in the dentate gyrus. The amelioration of scopolamine-induced amnesia by luteolin is associated with the increase in brain-derived neurotrophic factor, acetylcholine, as well as a reduction in lipid peroxidation.	(Yoo et al., 2013)
Long-term oral administration of luteolin enhanced neuronal injury and cognitive performance through decreasing oxidative stress and ChE activity in diabetic rats, which shows that luteolin, might be a potential therapeutic agent for the treatment and/or prevention of diabetic encephalopathy.	(Liu et al., 2013)
Luteolin protects the brain from ischemic damage, and this outcome might be *via* reduction of oxidative stress and apoptosis, as well as upregulation of the claudin-5 expressions.	(Qiao et al., 2012a)
Luteolin protects the brain from the damage caused by permanent middle cerebral artery occlusion (pMCAO), and this outcome might be through downregulation of NF-κB, p38MAPK, TLR4, TLR5, as well as upregulation of expression of ERK.	(Qiao et al., 2012b)

Conflict of interest

The authors declare no conflict of interest.

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