

## Letter to the editor:

### RECENT UPDATES ON NEUROPHARMACOLOGICAL EFFECTS OF LUTEOLIN

Gaurav Gupta<sup>1</sup>, Juhi Tiwari<sup>1</sup>, Rajiv Dahiya<sup>2</sup>, Rakesh Kumar Sharma<sup>3</sup>, Anurag Mishra<sup>3</sup>, Kamal Dua<sup>4,5</sup>

<sup>1</sup> School of Pharmaceutical Sciences, Jaipur National University, Jagatpura 302017, Jaipur, India

<sup>2</sup> Laboratory of Peptide Research and Development, School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad & Tobago, West Indies

<sup>3</sup> School of Pharmacy, Suresh Gyan Vihar University, Jagatpura 302017, Jaipur, India

<sup>4</sup> Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW 2007, Australia

<sup>5</sup> School of Pharmaceutical Sciences, Shoolini University, Solan, Himachal Pradesh, 173229, India

\* corresponding author: Dr. Gaurav Gupta, School of Pharmaceutical Sciences, Jaipur National University, Jagatpura 302017, Jaipur, India, E-mail: [gauravpharma25@gmail.com](mailto:gauravpharma25@gmail.com), Contact number: +91 7014790412

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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 neuro-protective effects; though, a coherent review of the scientific literature related to its neuro-protective 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.

**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 <i>in vivo</i> , 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 <sub>2</sub> O <sub>2</sub> - 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 fA $\beta$ 1-40-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 A $\beta$ -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-1 $\beta$ /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- $\kappa$ B expression as well as accompanied by weakening the A $\beta$ 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- $\kappa$ B, 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/ $\Delta$ FosB 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- $\kappa$ B, 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.

### REFERENCES

Bandaruk Y, Mukai R, Terao J. Cellular uptake of quercetin and luteolin and their effects on monoamine oxidase-a in human neuroblastoma sh-sy5y cells. *Toxicol Rep.* 2014;1:639-49.

Burton MD, Rytych JL, Amin R, Johnson RW. Dietary luteolin reduces proinflammatory microglia in the brain of senescent mice. *Rejuvenation Res.* 2016;19:286-92.

Dirscherl K, Karlstetter M, Ebert S, Kraus D, Hlawatsch J, Walczak Y, et al. Luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype. *J Neuroinflammation.* 2010;7:3. [Erratum in *J Neuroinflammation.* 2012;9:118].

Fu X, Zhang J, Guo L, Xu Y, Sun L, Wang S, et al. Protective role of luteolin against cognitive dysfunction induced by chronic cerebral hypoperfusion in rats. *Pharmacol Biochem Behav.* 2014;126:122-30.

Kim AK, Kim EY. Luteolin enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis of Sk-Br3 human breast cancer. *Pharm Biol.* 2012;50:594.

Kim S, Chin YW, Cho J. Protection of cultured cortical neurons by luteolin against oxidative damage through inhibition of apoptosis and induction of heme oxygenase-1. *Biol Pharm Bull.* 2017;40:256-65.

Lamy S, Moldovan PL, Ben Saad A, Annabi B. Biphasic effects of luteolin on interleukin-1beta-induced cyclooxygenase-2 expression in glioblastoma cells. *Biochim Biophys Acta.* 2015;1853:126-35.

Lin Y, Shi R, Wang X, Shen HM. Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr Cancer Drug Targ.* 2008;8:634-46.

Liu Y, Tian X, Gou L, Sun L, Ling X, Yin X. Luteolin attenuates diabetes-associated cognitive decline in rats. *Brain Res Bull.* 2013;94:23-9.

Lopez-Lazaro M. Distribution and biological activities of the flavonoid luteolin. *Mini Rev Med Chem.* 2009;9(1):31-59.

Nazari QA, Kume T, Takada-Takatori Y, Izumi Y, Akaike A. Protective effect of luteolin on an oxidative-stress model induced by microinjection of sodium nitroprusside in mice. *J Pharmacol Sci.* 2013;122:109-17.

Patil SP, Jain PD, Sancheti JS, Ghumatkar PJ, Tambe R, Sathaye S. Neuroprotective and neurotrophic effects of apigenin and luteolin in mptp induced parkinsonism in mice. *Neuropharmacology.* 2014;86:192-202.

- Qiao H, Dong L, Zhang X, Zhu C, Zhang X, Wang L, et al. Protective effect of luteolin in experimental ischemic stroke: upregulated SOD1, CAT, Bcl-2 and claudin-5, down-regulated MDA and Bax expression. *Neurochem Res.* 2012a;37:2014-24.
- Qiao H, Zhang X, Zhu C, Dong L, Wang L, Zhang X, et al. Luteolin downregulates TLR4, TLR5, NF- $\kappa$ B and p-p38MAPK expression, upregulates the p-ERK expression, and protects rat brains against focal ischemia. *Brain Res.* 2012b;1448:71-81.
- Shen ML, Wang CH, Chen RY, Zhou N, Kao ST, Wu DC. Luteolin inhibits gabaa receptors in hek cells and brain slices. *Sci Rep.* 2016;6:27695.
- Tambe R, Patil A, Jain P, Sancheti J, Somani G, Sathaye S. Assessment of luteolin isolated from *eclipta alba* leaves in animal models of epilepsy. *Pharm Biol.* 2017;55:264-8.
- Wang F, Gao F, Pan S, Zhao S, Xue Y. Luteolin induces apoptosis, g0/g1 cell cycle growth arrest and mitochondrial membrane potential loss in neuroblastoma brain tumor cells. *Drug Res.* 2015;65(2):91-5.
- Wang H, Wang H, Cheng H, Che Z. Ameliorating effect of luteolin on memory impairment in an alzheimer's disease model. *Mol Med Rep.* 2016;13:4215-20.
- Wang Q, Wang H, Jia Y, Pan H, Ding H. Luteolin induces apoptosis by ros/er stress and mitochondrial dysfunction in gliomablastoma. *Cancer Chemother Pharmacol.* 2017;79:1031-41.
- Xu J, Wang H, Ding K, Zhang L, Wang C, Li T, et al. Luteolin provides neuroprotection in models of traumatic brain injury via the Nrf2-ARE pathway. *Free Radic Biol Med.* 2014a;71:186-95.
- Xu J, Wang H, Lu X, Ding K, Zhang L, He J, et al. Posttraumatic administration of luteolin protects mice from traumatic brain injury: Implication of autophagy and inflammation. *Brain Res.* 2014b;1582:237-46.
- Yan T, Li L, Sun B, Liu F, Yang P, Chen T, et al. Luteolin inhibits behavioral sensitization by blocking methamphetamine-induced MAPK pathway activation in the caudate putamen in mice. *PloS One.* 2014; 9(6):e98981.
- Yoo DY, Choi JH, Kim W, Nam SM, Jung HY, Kim JH, et al. Effects of luteolin on spatial memory, cell proliferation, and neuroblast differentiation in the hippocampal dentate gyrus in a scopolamine-induced amnesia model. *Neurol Res.* 2013;35:813-20.
- Yu TX, Zhang P, Guan Y, Wang M, Zhen MQ. Protective effects of luteolin against cognitive impairment induced by infusion of abeta peptide in rats. *Int J Clin Exp Pathol.* 2015;8:6740-7.
- Zhang JX, Xing JG, Wang LL, Jiang HL, Guo SL, Liu R. Luteolin inhibits fibrillary beta-amyloid1-40-induced inflammation in a human blood-brain barrier model by suppressing the p38 MAPK-mediated NF- $\kappa$ B signaling pathways. *Molecules (Basel, Switzerland).* 2017;22(3).
- Zhen JL, Chang YN, Qu ZZ, Fu T, Liu JQ, Wang WP. Luteolin rescues pentylene tetrazole-induced cognitive impairment in epileptic rats by reducing oxidative stress and activating PKA/CREB/BDNF signaling. *Epilepsy Behav.* 2016;57(Pt A):177-84.
- Zhu L, Bi W, Lu D, Zhang C, Shu X, Lu D. Luteolin inhibits SH-SY5Y cell apoptosis through suppression of the nuclear transcription factor- $\kappa$ B, mitogen-activated protein kinase and protein kinase B pathways in lipopolysaccharide-stimulated cocultured BV2 cells. *Exp Ther Med.* 2014;7:1065-70.