How to cite this article: Kumar V, Kundu S. Studies on apigenin and its biological and pharmacological activity in brain disorders. Advanced Pharmaceutical Bulletin, doi: 10.34172/apb.2022.068

Studies on apigenin and its biological and pharmacological activity in brain disorders

Vishal Kumar, Satyabrata Kundu*

Department of Pharmacology, ISF College of Pharmacy Moga, Punjab 142001 India.

Kundu : https://orcid.org/0000-0002-4850-5345

Corresponding Author: Satyabrata Kundu, Email- satyabratak96@gmail.com

Abstract

The bioactive compounds from the various plants have shown functional effects that describe they could exhibit a remarkable role in mitigating a wide range of brain-related disorders. One of the largest groups of natural polyphenols are flavonoids, such as apigenin. This paper is based on the updated biological and pharmacological role of apigenin in brain disorders, focusing on its therapeutic effects and, mainly in *in-vivo* and *in vitro* research. The main key outcomes from researches, including animal models, clinical trials are described. The beneficial effects of apigenin are summarized in disorders like Alzheimer's disease, depression, Parkinson's disease, multiple sclerosis, and autism.

Keywords: Apigenin; Polyphenols; Flavonoids; Brain disorders

Dear editor,

Apigenin (4′,5,7-trihydroxyflavone) is a dietary flavonoid that is abundantly present in many fruits, medicinal herbs, vegetables and formally belongs to the flavon sub-class.[1] The best sources of apigenin are parsley, chamomile, celery, artichokes, and oregano.[2] Apigenin is a compound with low toxicity and multiple beneficial bioactivities. Apigenin has several beneficial effects as an antioxidant, anti-inflammatory, blood pressure reduction, and chemo-preventive.[3] Apigenin has an effect in the downregulation of IL-1β and TNF-α, also, it shows anti-inflammatory properties by attenuating the expression of COX-2 and iNOS [1]. At the cellular level, apigenin acts as an inhibitor of several protein-tyrosine and serine-kinases.[3] Apigenin has many pharmacological roles as antiphlogistic, antispasmodic, and antibacterial agent, anti-asthmatic, anti-parkinsonism agent.[4]

Table 1: Recent studies on apigenin and its biological and pharmacological activities.

S.No.	Key outcomes	References
1.	Apigenin shows a protective effect in the preclinical model of down syndrome, via reduction of oxidative stress and activation of proliferative and pro-neurogenic genes (KI7, Nestin, Sox2, and	[5]

	PAX6). Apigenin may be a potential therapeutic candidate for the management of the down syndrome.	
2.	Apigenin reversed decreased cell viability, the activity of sodium pump, increased LDH release, and apoptotic rate in OGD/R injury in rat hippocampal neurons. The finding suggested that it can be a novel therapeutic candidate to improve sodium pump activity.	6
3.	The combination of apigenin and trolox, apigenin shows a strong inhibitory effect in H_2O_2 induced ROS production in RAW264.7 cells as well as free radical-induced oxidative damage in erythrocytes than trolox. However, apigenin also exerts a strong inhibitory effect on LPS induced NF-kB/NLRP3/caspase-1 signaling in RAW246.7 cells than trolox. Results suggested that apigenin might be a potent drug candidate for the management of oxidative stress and inflammatory diseases.	7
4.	Solid dispersion of apigenin (AP-SD) prospers the nuclear translocation of Nrf2 and increases the expression of Nrf2 as well as target genes HO-1 and NQO-1. It also enhanced the activity of SOD, GSH-Px, and decreased the level of ROS and MDA in a mouse model of age-related molecular degeneration (AMD). The finding suggested that AP-SD could be an effective compound for the treatment of AMD.	8
5.	Apigenin and luteolin resist the activation of astrocytes and inhibit the protein and mRNA expression in lipopolysaccharide-induced astrocyte cultured neurons. Apigenin also inhibits the IL-31 and IL-33 via suppression of ERK, NF-kB, and STATE. Similarly, luteolin inhibits IL-31 via suppression of JNK, p38, ERK, NF-kB, and STAT3 in astrocytes. The finding suggested that both apigenin and luteolin have the potential to treat diseases involving astrocyte activation.	9
6.	Apigenin increased Nrf2 nuclear translocation, GSK-3β phosphorylation, and reduced apoptosis, decrease LDH release, and promote cell viability in both OGD/R cell cultures and a rat model of ischemic-reperfusion. The study suggested that apigenin could be a strong neuroprotective drug candidate.	10
7.	Apigenin significantly delayed peripheral nerve degeneration via inhibiting of degradation of myelin and peripheral axons, and also inhibit the proliferation of Schwann cells. Thus, apigenin can be a novel therapeutic choice for treating peripheral neurodegenerative diseases.	11
8.	Apigenin rescues memory deficits and decreases cell viability in hilus, however, it also decreases the release of cytochrome c in the kainic acid-induced rat model of temporal lobe epilepsy. The study suggested that, clinically apigenin could reverse memory impairment via anticonvulsant and neuroprotective activity.	12
9.	Apigenin significantly fettles spatial working memory and decreased degenerative neurons in hilus via complete blockade of caspase 9 and cytochrome c release in Aβ 25-35 induced rat model of Alzheimer	13

	disease. The finding suggested that apigenin can rescue the spatial working memory and neuronal degeneration via reversal of mitochondrial dysfunction.	
10.	Apigenin decreases oxidative stress, levels of IL-6, TNF-α, mitochondrial-mediated neuron apoptosis and also downregulates TLR4/NF-kB signaling pathways in the acrylonitrile rat model of neuroinflammation. Results suggested that it could be a potent neuroprotective agent.	14
11.	Apigenin rescues the behavioral impairments, cognitive deficits and increases the level of BDNF, cAMP, and CREB without altering seizure severity in pentylenetetrazole kindling associated behavioral and cognitive impairments in the mouse model. However, it also increases the serotonin level in the brain. The finding suggested that apigenin may be a potent therapeutic candidate to treat memory impairment and related diseases.	15
12.	Apigenin shows a protective effect via detracting autophagy and apoptosis in the brain against ischemia/reperfusion injury. In-vivo results show apigenin significantly decreases neurobehavioral score and increases cell proliferation by the up-regulation of VEGFR22/CD3 and affecting caveolin-1, VEGF, eNOS expression in brain tissue of MCAO/R rats.	16
13.	Apigenin promotes the upregulation of NF-kB gene expression and inhibits the release of pro-inflammatory cytokines IL-l, TNF-α, and also prevents the reduction of BDNF and GDNF levels in rotenone-induced rat model of Parkinson's disease. Thus, the results suggested that apigenin could serve as an effective agent for the management of Parkinson's disease.	17
14.	Apigenin rescues the antioxidant machinery via the reduction of ROS levels, prevention of activation of stress kinase (IKKβ), JNK, and activation of (NF-kB) in high fat-high fructose diet induce rat model of hippocampal derangements. Results suggested that it has better antioxidant potential.	18
15.	Apigenin recovers cognitive function via restoration of histone acetylation, BDNF signaling, and suppression of pro-inflammatory cytokines and NFkB signaling pathway in an aged rat model of isoflurane-induced cognitive dysfunction. Thus, the study suggested that apigenin can be a potential drug candidate for the treatment of post-operational cognitive dysfunction.	19
16.	Apigenin improves cognitive impairments in the rat model of post-stroke cognitive deficits, through decreased HDAC content, up-regulation H3 and H4 acetylation in the hippocampus and increased the level of BDNF in dose-dependent manner.	20
17.	Apigenin exhibits protective effect via reduction of myeloperoxidase (MPO), reactive oxygen species (ROS), malondialdehyde (MDA), and increase the level of oxidized glutathione (GSSG), glutathione (GSH),	21

	hydrogen peroxide, and superoxide dismutase (SOD) in a rat model of subarachnoid hemorrhage (SAH). Thus, the study suggested that apigenin may be considered as a potential drug for the management of SAH.	
18.	Apigenin exerts a neuroprotective effect against cerebral ischemic/reperfusion injury by promoting cell viability, cell proliferation and by reducing apoptotic cell death. The study revealed the neuroprotective effect of apigenin which is possibly induced by the STATE3 phosphorylation-mediated Mn-SOD up-regulation.	[22]
19.	Apigenin significantly increased retention of immune cells in the periphery and decreased expression of α4 integrin and CLEC12A on splenic dendritic cells in the autoimmune encephalomyelitis mice model. The study suggested that it could be a better treatment for the management of multiple sclerosis as compared to available treatment.	[23]
20.	The study revealed that apigenin rescues the neurons from neuroinflammation, neuronal excitability, and apoptosis in the human induced pluripotent stem cell model of Alzheimer's disease via the down-regulation of cytokines and nitric oxide release. These findings highlighted that apigenin could be a better therapeutic strategy for the management of Alzheimer's disease.	[24]
21.	Apigenin mitigates neuroinflammation and astrocytes integrity by the downregulation of IL-6, IL-1β expression, and upregulation of IL-10 in lipopolysaccharide induce *in vitro* model of neuroinflammation associated with Alzheimer disease. Thus, the finding suggested that apigenin could be a potential agent for the treatment of neurodegenerative diseases.	[25]
22.	Apigenin shows a protective effect by the up-regulation of PPARγ expression, oxidative stress, inhibition of microglia, and NLRP3 activation, which subsequently down-regulate the production of IL-1β and IL-18 in a chronic unpredictable mild stress rat model of depression. Results suggested that it may be beneficial for the management of depression.	[26]
23.	Apigenin reverses the decreased level of Bcl-2 and Bid, loss of mitochondrial transmembrane potential, increase levels of Bax and p53, the release of Cytochrome c, activation of caspases (3, 8, and 9), and cleavage of PARP-1 in proteasome inhibitor induce neuronal apoptosis in both PC12 and SH-SY5Y cell lines.	[27]
24.	Apigenin significantly decreases early brain injury such as BBB disruption, brain edema, and cell apoptosis via the repression of NF-kB, TLR4, and their pro-inflammatory cytokines in the cortex in a rat model of subarachnoid hemorrhage. The finding suggested that apigenin could be protective against early brain injury.	[28]
25.	Apigenin elevates body weight, improves cognitive dysfunction, reduces blood glucose, MDA content, and increases SOD level in the cerebral cortex and hippocampus in the streptozotocin-induced rat	[28]

	model of diabetes-associated cognitive dysfunction. Finding suggested that apigenin could be an effective therapeutic agent for diabetes-associated cognitive decline in rats via the suppression of apoptotic, nitric oxide, and oxidative stress pathways.	
26.	Apigenin rescues from the oxygen and glucose deprivation/reperfusion (OGD/R) induced neuron injury by the suppression of cell apoptosis, lactate dehydrogenase, and intracellular ROS level in PC12 cells. These results suggested that apigenin could be a therapeutic candidate against neuronal death.	[29]
27.	Apigenin and luteolin both in combination rescue the dopaminergic neurons through reducing microglial activation, neuroinflammation, oxidative stress as well as enhancement of BDNF in MPTP induced mice model of Parkinson disease (PD). The study suggested that both the molecules could be potential therapeutics in Parkinson's disease.	[30]
28.	Apigenin restores Alzheimer's disease (AD) associated learning and memory impairment via the suppression of the amyloidogenic process, alleviating the Aβ burden, restoring ERK/CREB/BDNF pathway, and through prevention of oxidative stress in APP/PS1 double transgenic mouse model of AD. The finding suggested that apigenin could be an alternative agent for the prevention of AD-associated symptoms.	[31]
29.	Apigenin exerts neuroprotective effect via maintaining redox balance by increasing cellular superoxide dismutase, glutathione level, and reduced ROS generation; obstructing p38 MAPK, MAPKAP kinase-2, heat shock protein 27 and c-jun N-terminal signaling pathways and reduced neuronal apoptosis in a copper-mediated β-amyloid neurotoxicity cell model of Alzheimer disease (AD). The finding suggested that it could be a potential therapeutic for AD.	[32]
30.	Apigenin exhibits a protective effect via the up-regulation of SOD, GSH-Px activity, decrease serum level of IL-1β and TNF-α, and shows antioxidative, anti-inflammatory, and anti-apoptotic properties in modified weight-drop method induced rat model of spinal cord injury.	[33]
31.	Apigenin elicits neuroprotective effect through suppression of excitotoxicity in dose-dependent manner, ROS generation, reduction of glutathione (GSH) in hippocampal neurons in kainic acid induce an *in-vitro* and *in-vivo* model of excitotoxicity.	[34]
32.	Apigenin shows a neuro-protective effect in the *Drosophila* model of Parkinson's disease through increasing glutathione (GSH), dopamine content, life span and reducing the level of glutathione-S-transferase (GST) activity, monoamine oxidase (MAO), lipid peroxidation, and caspase 3/9 in a dose-dependent manner. The study highlighted the neuroprotective potential of apigenin in PD.	[35]

Declaration:

Conflict of interest: The authors declare that there is no conflict of interest.

Acknowledgment: The authors express their gratitude to Chairman, Mr. Praveen Garg and Director, Dr. G. D. Gupta, ISF College of Pharmacy Moga, Punjab, India for their excellent vision and support.

References:

1. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, *et al.* The therapeutic potential of apigenin. *Int. J. Mol. Sci.* **2019**; 20: 1305. doi: 10.3390/ijms20061305
2. Kumar A, Butt N, Levenson A. Natural epigenetic-modifying molecules in medical therapy. *Medical Epigenetics*: Elsevier; **2016**. p. 747-98. doi: 10.1016/B978-0-12-803239-8.00039-9
3. Shankar E, Goel A, Gupta K, Gupta S. Plant flavone apigenin: An emerging anticancer agent. *Curr pharmacol Rep* **2017**; 3: 423-46. doi: 10.1007/s40495-017-0113-2
4. Shukla S, Gupta S. Apigenin: a promising molecule for cancer prevention. *Pharm Res* **2010**; 27: 962-78. doi: 10.1007/s11095-010-0089-7
5. Guedj F, Siegel AE, Pennings JL, Alsebaa F, Massingham LJ, Tantravahi U, *et al.* Apigenin as a Candidate Prenatal Treatment for Trisomy 21: Effects in Human Amniocytes and the Ts1Cje Mouse Model. *Am J Hum Genet* **2020**; 107: 911-31. doi: 10.1016/j.ajhg.2020.10.001
6. Ding Y-M, Lin J-T, Fang L-M, Lou Z-Q, Liang G-n, Zhang X-y, *et al.* The neuroprotective effect of apigenin against OGD/R injury in rat hippocampal neurons. *Pak J Pharm Sci* **2020**; 33. doi: 10.0.143.113/PJPS.2020.33.4.REG.1527-1533.1
7. Wang W, Yue RF, Jin Z, He LM, Shen R, Du D, *et al.* Efficiency comparison of apigenin- 7- O- glucoside and trolox in antioxidative stress and anti- inflammatory properties. *J Pharm Pharmacol* **2020**; 72: 1645-56. doi: 10.1111/jphp.13347
8. Zhang Y, Yang Y, Yu H, Li M, Hang L, Xu X. Apigenin Protects Mouse Retina against Oxidative Damage by Regulating the Nrf2 Pathway and Autophagy. *Oxid Med and Cell Longev* **2020**; 2020. doi: 10.1155/2020/9420704
9. Che DN, Cho BO, Kim J-s, Shin JY, Kang HJ, Jang SI. Luteolin and apigenin attenuate LPS-induced astrocyte activation and cytokine production by targeting MAPK, STAT3, and NF-κB signaling pathways. *Inflammation* **2020**; 43: 1716-28. doi:10.1007/s10753-020-01245-6
10. Wang J, Wang S, Sun S, Lu Y, Gao K, Guo C, *et al.* Apigenin-7-O-β-D-(-6”-p-coumaroyl)-glucopyranoside treatment elicits a neuroprotective effect through GSK-3β phosphorylation-mediated Nrf2 activation. *Aging (Albany NY)* **2020**; 12: 23872. doi: 10.18632/aging.104050
11. Kim M, Jung J, Jeong NY, Chung H-J. The natural plant flavonoid apigenin is a strong antioxidant that effectively delays peripheral neurodegenerative processes. *Anat Sci Int* **2019**; 94: 285-94. doi: 10.1007/s12565-019-00486-2
12. Hashemi P, Babaei JF, Vazifekhah S, Nikbakht F. Evaluation of the neuroprotective, anticonvulsant, and cognition-improvement effects of apigenin in temporal lobe epilepsy: Involvement of the mitochondrial apoptotic pathway. *Iran J Basic Med Sci* **2019**; 22: 752. doi: 10.22038/ijbms.2019.33892.8064
13. Nikbakht F, Khadem Y, Haghani S, Hoseininia H, Sadat AM, Heshemi P, *et al.* Protective Role of Apigenin Against Aβ 25–35 Toxicity Via Inhibition of Mitochondrial Cytochrome c Release. *Basic Clin Neurosci* **2019**; 10: 557. doi:10.32598/bcn.9.10.385

14. Zhao F, Dang Y, Zhang R, Jing G, Liang W, Li Z. Apigenin attenuates acrylonitrile-induced neuro-inflammation in rats: involved of inactivation of the TLR4/NF-κB signaling pathway. *Int Immunopharmacol* **2019**; 75: 105697. doi: 10.1016/j.intimp.2019.105697
15. Sharma P, Sharma S, Singh D. Apigenin reverses behavioural impairments and cognitive decline in kindled mice via CREB-BDNF upregulation in the hippocampus. *Nutr Neurosci* **2020**; 23: 118-27. doi: 10.1080/1028415x.2018.1478653
16. Pang Q, Zhao Y, Chen X, Zhao K, Zhai Q, Tu F. Apigenin protects the brain against ischemia/reperfusion injury via caveolin-1/VEGF in vitro and in vivo. *Oxid Med Cell Longev* **2018**; 2018. doi: 10.1155/2018/7017204
17. Anusha C, Sumathi T, Joseph LD. Protective role of apigenin on rotenone induced rat model of Parkinson's disease: Suppression of neuroinflammation and oxidative stress mediated apoptosis. *Chem Biol Interact* **2017**; 269: 67-79. doi: 10.1016/j.cbi.2017.03.016
18. Kalivarathan J, Chandrasekaran SP, Kalaivanan K, Ramachandran V, Venkatraman AC. Apigenin attenuates hippocampal oxidative events, inflammation and pathological alterations in rats fed high fat, fructose diet. *Biomed Pharmacother* **2017**; 89: 323-31. doi: 10.1016/j.biopha.2017.01.162
19. Chen L, Xie W, Xie W, Zhuang W, Jiang C, Liu N. Apigenin attenuates isoflurane-induced cognitive dysfunction via epigenetic regulation and neuroinflammation in aged rats. *Arch Gerontol Geriatr* **2017**; 73: 29-36. doi: 10.1016/j.archger.2017.07.004
20. Tu F, Pang Q, Huang T, Zhao Y, Liu M, Chen X. Apigenin ameliorates post-stroke cognitive deficits in rats through histone acetylation-mediated neurochemical alterations. *Med Sci Monit* **2017**; 23: 4004. doi: 10.12659/msm.902770
21. Han Y, Zhang T, Su J, Zhao Y, Li X. Apigenin attenuates oxidative stress and neuronal apoptosis in early brain injury following subarachnoid hemorrhage. *J Clin Neurosci* **2017**; 40: 157-62. doi: 10.1016/j.jocn.2017.03.003
22. Cai M, Ma Y, Zhang W, Wang S, Wang Y, Tian L, *et al.* Apigenin-7-O-β-D-(-6''-p-coumaroyl)-Glucopyranoside treatment elicits neuroprotective effect against experimental ischemic stroke. *Int J of Biol Sci* **2016**; 12: 42. doi: 10.7150/ijbs.12275
23. Ginwala R, McTish E, Raman C, Singh N, Nagarkatti M, Nagarkatti P, *et al.* Apigenin, a natural flavonoid, attenuates EAE severity through the modulation of dendritic cell and other immune cell functions. *J Neuroimmune Pharmacol* **2016**; 11: 36-47. doi: 10.1007/s11481-015-9617-x
24. Balez R, Steiner N, Engel M, Muñoz SS, Lum JS, Wu Y, *et al.* Neuroprotective effects of apigenin against inflammation, neuronal excitability and apoptosis in an induced pluripotent stem cell model of Alzheimer's disease. *Sci Rep* **2016**; 6: 1-16. doi: 10.1038/srep31450
25. Li R, Wang X, Qin T, Qu R, Ma S. Apigenin ameliorates chronic mild stress-induced depressive behavior by inhibiting interleukin-1β production and NLRP3 inflammasome activation in the rat brain. *Behav Brain Res* **2016**; 296: 318-25. doi: 10.1016/j.bbr.2015.09.031
26. Kim A, Nam YJ, Lee MS, Shin YK, Sohn DS, Lee CS. Apigenin reduces proteasome inhibition-induced neuronal apoptosis by suppressing the cell death process. *Neurochem Res* **2016**; 41: 2969-80. doi: 10.1007/s11064-016-2017-7
27. Zhang T, Su J, Guo B, Wang K, Li X, Liang G. Apigenin protects blood–brain barrier and ameliorates early brain injury by inhibiting TLR4-mediated inflammatory pathway in subarachnoid hemorrhage rats. *Int Immunopharmacol* **2015**; 28: 79-87. doi: 10.1016/j.intimp.2015.05.024

28. Mao X-Y, Yu J, Liu Z-Q, Zhou H-H. Apigenin attenuates diabetes-associated cognitive decline in rats via suppressing oxidative stress and nitric oxide synthase pathway. *Int J Clin Exp Med* **2015**; 8: 15506.
29. Guo H, Kong S, Chen W, Dai Z, Lin T, Su J, *et al.* Apigenin mediated protection of OGD-evoked neuron-like injury in differentiated PC12 cells. *Neurochem Res* **2014**; 39: 2197-210. doi: 10.1007/s11064-014-1421-0
30. 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. doi: 10.1016/j.neuropharm.2014.07.012
31. Zhao L, Wang J-L, Liu R, Li X-X, Li J-F, Zhang L. Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. *Molecules* **2013**; 18: 9949-65. doi: 10.3390/molecules18089949
32. Zhao L, Wang J-l, Wang Y-r, Fa X-z. Apigenin attenuates copper-mediated β-amyloid neurotoxicity through antioxidation, mitochondrion protection and MAPK signal inactivation in an AD cell model. *Brain Res* **2013**; 1492: 33-45. doi: 10.1016/j.brainres.2012.11.019
33. Zhang F, Li F, Chen G. Neuroprotective effect of apigenin in rats after contusive spinal cord injury. *Neurol Sci* **2014**; 35: 583-8. doi: 10.1007/s10072-013-1566-7
34. Han J-Y, Ahn S-Y, Kim C-S, Yoo S-K, Kim S-K, Kim H-C, *et al.* Protection of apigenin against kainate-induced excitotoxicity by anti-oxidative effects. *Biol and Pharm Bull* **2012**; 35: 1440-6. doi: 10.1248/bpb.b110686
35. Long J, Gao H, Sun L, Liu J, Zhao-Wilson X. Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and extends lifespan in a Drosophila Parkinson's disease model. *Rejuvenation Res* **2009**; 12: 321-31. doi: 10.1089/rej.2009.0877