Micro Nano Bio Aspects

https://www.mnba-journal.com

Online ISSN: 2980-8081

# Therapeutic applications of apigenin and its derivatives: micro and nano aspects

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**ARTICLE INFO**

**Mini-review paper**

Article history:
Received: 05 Mar 2023
Revised: 31 Mar 2023
Accepted: 32 Mar 2023
ePublished: 33 Mar 2023

**Keywords:**
Apigenin, Anticancer activity, Antihyperlipidemic activity, Lower bioavailability, Micro aspects, Nano aspects, Neuroprotective activity

**DOI:** https://doi.org/10.22034/mnba.2023.388488.1025

**ABSTRACT**

Antibacterial, antifungal, antiviral, antiparasitic, antioxidant, antiangiogenic, antitumor, antidiabetic, antihyperlipidemic, and antineurodegenerative properties have been indicated for various types of flavonoids and their derivatives. Apigenin as a flavonoid metabolite, a flavone, from the genus Apium related to the flavone class can be found in many plant species including *Petroselinum crispum*, *Apium graveolens*, and *Matricaria recutita*. Lower bioavailability and specificity are two main barriers to obtaining effective formulations. Application of micro and nanoformulations based on organic and inorganic materials can improve the bioavailability and specificity of apigenin and its derivatives such as apigenin 7-O-beta-d-glucoside, apigenin 7-glucoside-4'-trans-caffeate, and apigenin 7-glucoside-4'-p-coumarate. However, there are various limitations to getting suitable formulations in physiological conditions. In this regard, this review has addressed these issues according to recent studies.



## Introduction

Polyphenols or polyphenolic compounds are the main secondary metabolites found in various parts of the plant species, particularly in the roots, leaves, and fruits [1]. Apigenin ($C_{15}H_{10}O_5$), is a flavonoid metabolite from the genus Apium in the Umbelliferae or Apiaceae family. This metabolite is a yellow crystalline solid and bioactive product related to the flavone class (4′,5,7-trihydroxyflavone) found in many fruits and vegetables including *Petroselinum crispum*, *Apium graveolens*, *Combretum erythrophyllum*, *Gentiana veitchiorum*, *Matricaria recutita*, and *Portulaca oleracea* (Figure 1) [2, 3]. Antiinflammatory, neuroprotective, antioxidant, antigenotoxic, anticancer, antiallergic, and antimicrobial activities have been reported for this bioactive compound [4, 5]. Additionally, this metabolite has been used in the treatment of myocardial injury, atherosclerosis, stroke, and diabetic cardiomyopathy, hypertension [3]. Celery seeds, spinach, parsley, marjoram, oregano, sage, and chamomile have 78.65, 62, 45.94, 4.4, 3.5, 2.4, and 3-5 mg/100mL of apigenin, respectively [6]. The major hindrance to medicinal applications of apigenin is low hydrophilic property or poor bioavailability (30%) in physiological conditions [5, 7].

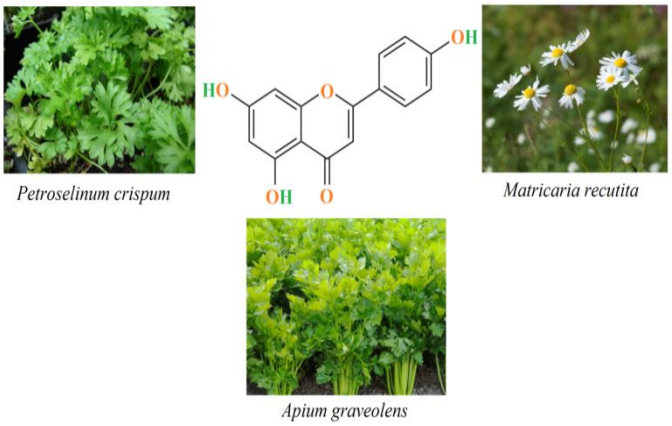


**Fig. 1.** The main plant species with the chemical structure of apigenin [6].

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**Anticancer activity**

Apigenin is an edible plant-derived flavonoid that has been reported as an anticancer agent in several experimental and biological studies. It exhibits cell growth arrest and apoptosis in different types of tumors such as breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach, by modulating several signaling pathways. Apigenin induces apoptosis by the activation of extrinsic caspase-dependent pathway by upregulating the mRNA expressions of caspase-3, caspase-8, and TNF-α. It induces an intrinsic apoptosis pathway as evidenced by the induction of cytochrome c, Bax, and caspase-3, while caspase-8, TNF-α, and B-cell lymphoma 2 levels remained unchanged in human prostate cancer PC-3 cells. Apigenin treatment leads to significant downregulation of matrix metallopeptidases-2, −9, Snail, and Slug, suppressing invasion. The expressions of NF-κB p105/p50, PI3K, Akt, and the phosphorylation of p-Akt decreases after treatment with apigenin. However, apigenin-mediated treatment significantly reduces pluripotency marker Oct3/4 protein expression which might be associated with the downregulation of PI3K/Akt/NF-κB signaling [8]. Apigenin effectively inhibited proliferation in various breast cancer cell lines, consistent with apigenin's dose- and time-dependent inhibition of MDA-MB-453 human breast cancer cell proliferation. In contrast, the antiproliferative effects of 5-fluorouracil were observed only at higher concentrations than apigenin ($IC_{50}$ = 35.15 μM) [9].

Apigenin can potentially modulate anticancer therapy by changing different signaling pathways of cancer cells. By reducing the phosphorylation of Akt (protein kinase B), metastatic cancer cells are inhibited by down-regulating and up-regulating matrix metallopeptidase-9 (MMP-9) and transgelin expression, respectively under apigenin effect (Figure 2) [4]. Anticancer mechanisms for various types of cancers may be different. For example, in the case of cervical cancer, down-regulation of PI3K/AKT signaling (mTOR, AKT, and PI3K) and FAK signaling (integrin β1, paxillin, and FAK) were observed for anticancer mechanisms of apigenin (Figure 3) [10].

Proliferation of cancer cells can be hindered via apigenin through modulating the cell cycle, cell apoptosis, and autophagy. In addition, cancer cell motility is reduced by this flavone followed by inhibition of migration and invasion of cancer cells. In recent studies, apigenin stimulated an immune response via modulating multiple signaling pathways and protein kinases including the phosphoinositide 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK)/ERK, the Janus kinase (JAK)/STAT, wingless/integrated (Wnt)/β-catenin, and nuclear factor kappa B (NF-κB) [11].

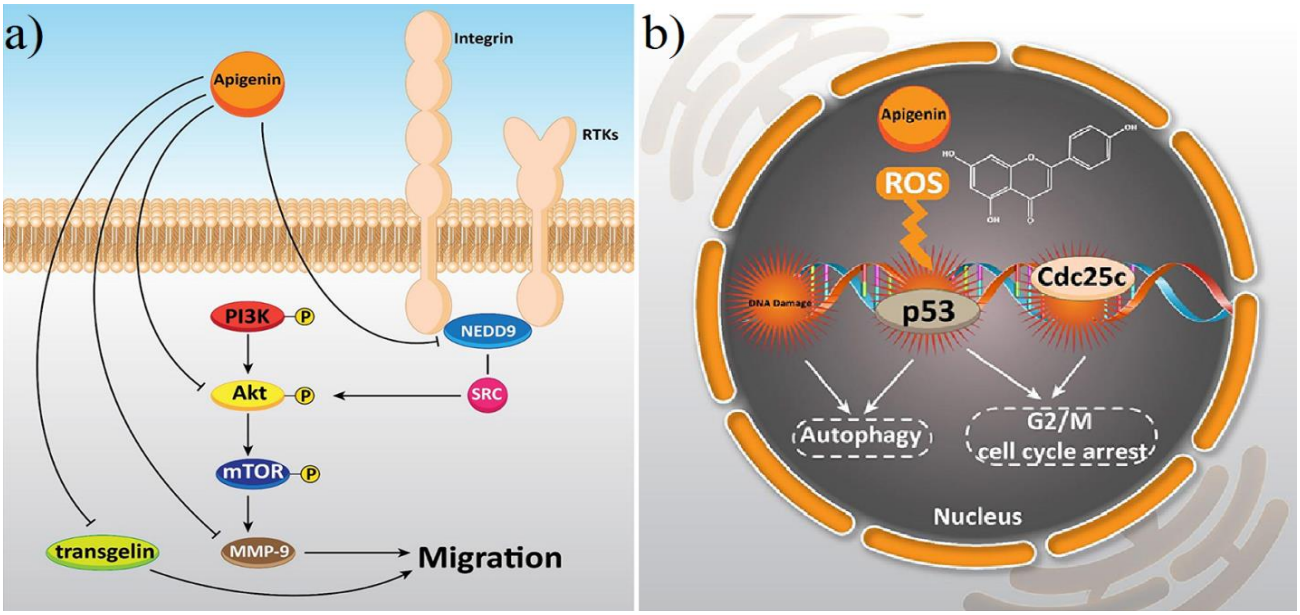


**Fig. 2.** Anticancer activity of apigenin as inhibition mechanism of metastasis (a) and promotion of autophagy in cancer cells (b) through ROS production, cell cycle arrest, and DNA damage (reprinted with modification from [4]).

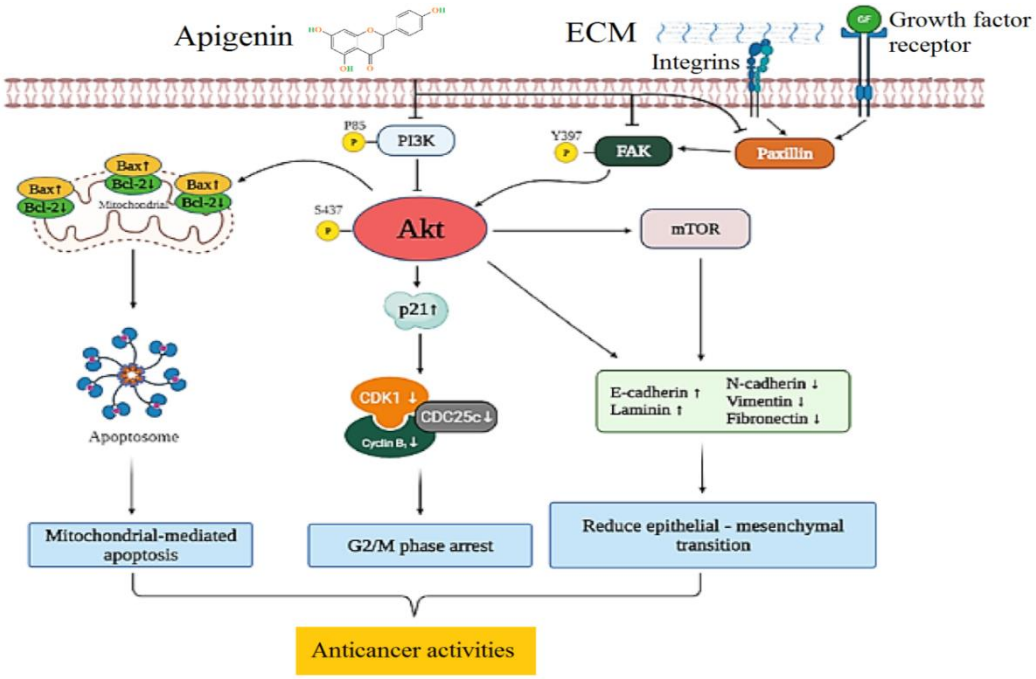


**Fig. 3.** The anticancer mechanisms of apigenin metabolite toward cervical cancer cells (adopted and modified from [10]).

**Antimicrobial activity**

Apigenin has a high partition coefficient as well as able to penetrate the cell membrane of bacteria through the disorientation and disordering of lipids membrane which makes it a suitable drug candidate for anti-bacterial activities [12, 13]. It inhibited the function of D-alanine:D-alanine ligase (Ddl) and competed with ATP [14]. Furthermore, inhibition of DNA replication, synthesis of protein, and metabolism of energy [15]. Several researches indicated the anti-bacterial activities of apigenin against different drug resistance strains of *H. pylori* infection. Furthermore, it could be used both systemically and locally. Therefore, its anti-bacterial activity makes apigenin a significant applicant for the eradication of *H. pylori* infection. Thus, it decreases the progression of *H. pylori* induced gastric cancer [12, 14].

Studies show that the antibacterial activity of nanoformulation of apigenin was more effective than the pure apigenin and had a better sustained-release [13]. The antibacterial activity of microsponge formulation apigenin against *H. pylori* was longer and had better action in comparison to the pure apigenin. Additionally, this formulation improved the drug delivery efficacy [13]. Suhyun et al, reveal that apigenin isolated from *A. yomena* degraded calcium homeostasis in *E. coli* through the accumulation of NO. As well, its treatment causes the production of $O_2^-$. Therefore, apigenin has an influential inhibitory effect against pathogenic bacteria. Moreover, apigenin has antifungal activity via generation pores in the cell membrane and leads to fungal apoptosis. Apigenin induced apoptosis and inhibited the growth of fungal pathogens by disrupting calcium homeostasis [15].

Improved bioavailability of herbal metabolites such as apigenin in physiological conditions can be possible by novel formulations in nanoscale [16]. Lipidic nanoformulations such as micelles, liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carrier (NLC), cubosomes, niosomes, phytosomes, and bilosomes are the most common types [17-20]. Bilosomes are bile salts-based vesicles composed of lipid and nonionic surfactants such as sodium deoxy cholate (bile salt detergent) for encapsulation of hydrophilic and hydrophobic drugs [21, 22]. Chitosan-coated apigenin bilosomes were prepared by sodium deoxy cholate, cholesterol, phosphatidyl choline, chitosan, and apigenin as the main ingredients (Figure 4). Improved mucoadhesion properties, permeation, and antibacterial activity have been indicated for chitosan-coated apigenin bilosomes. There were significant antibacterial effects because of the permeation ability of this formulation into the cell wall of bacteria and fungi. *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans* exhibited 24, 28, 28, 28, and 20

mm values of inhibition zone diameters (IZDs) [23]. Apigenin can form multifunctional bio-based benzoxazine monomers by reacting with formaldehyde and furfurylamine/stearylamine. Ring-opening polymerization with thermal treatment can lead to the formation of apigenin-based polybenzoxazine bio-films with antimicrobial activity. Antibiofilm activity of the multifunctional benzoxazines monomers composed of apigenin and stearylamine (AP-s) and apigenin and furfurylamine (AP-f) was evaluated against the methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Candida albicans*. Poly(AP-f) reduced biofilm formation by *S. aureus* at values of > 80% and > 60% at 100 µg/mL and 50 µg/mL, respectively. In addition, a reduction (< 10%) of biofilm formation of *C. albicans* on Poly(AP-s) was observed at the concentrations of 100 µg/mL [24]. In a comparative molecular docking study, the binding energies of apigenin 7-O-beta-d-glucoside, apigenin 7-glucoside-4'-trans-caffeate, apigenin 7-glucoside-4'-p-coumarate, apigenin, and boceprevir toward the main protease of SARS-CoV-2 ($M^{pro}$) were −8.0, −8.7, −8.8, −7.2, and −6.6, kcal/mol, respectively [25].

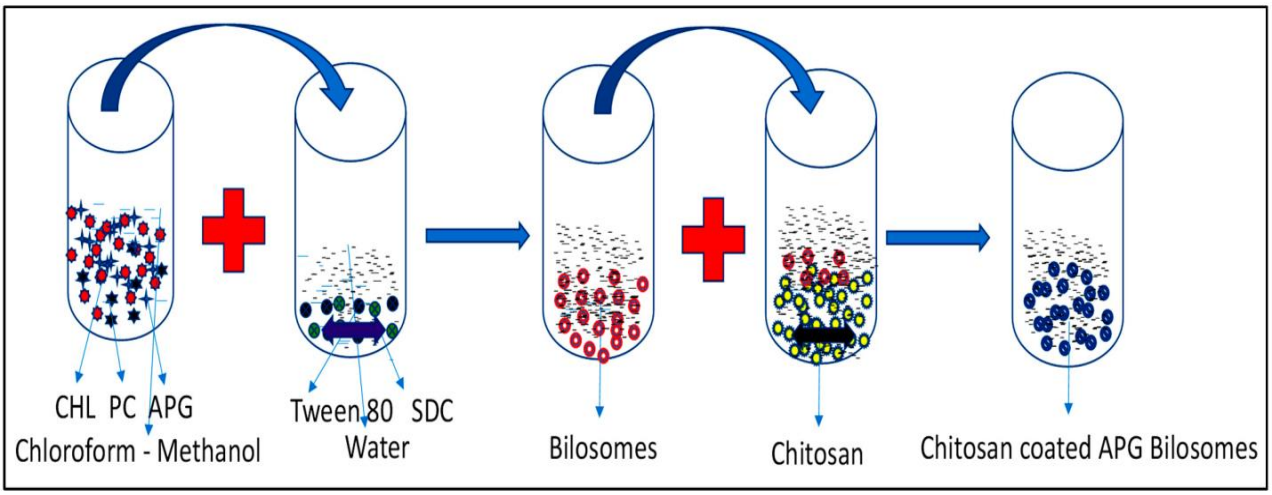


**Fig. 4.** Chitosan-coated apigenin bilosomes formulation (extracted from [23]).

**Antidiabetic and antihyperlipidemic activities**

The conventional therapies for diabetes include injection and oral hypoglycemia drugs. These drugs have side effects and cytotoxicity[5]. Severe health problems including kidney disease, heart disease, and vision loss are resulted from high levels of blood sugar in the bloodstream in diabetes. Glucolipid metabolism can be affected by apigenin or apigenin derivatives as an antidiabetic drug compound [5]. According to molecular docking, α-Amylase and α-Glucosidase enzymes were inhibited by apigenin by affinity values of -9.3 and -8 Kcal/mol [26]. These two enzymes can augment glucose levels in diabetic patients by hydrolysis of the carbohydrates [27]. In a similar study, inhibition of α-glucosidase and α-amylase was indicated for apigenin derivative isolated from the methanolic leaf extracts of an evergreen shrub of *Tetrastigma angustifolia* [28]. As a derivative of apigenin, luteolin-(6→8")-apigenin isolated from methanol extract of *Schinus polygama* showed antidiabetic activity by inhibition of α-amylase enzyme by $IC_{50}$ of 64.70 µg/mL and anti-inflammatory activity with $IC_{50}$ of 47.60 µg/mL via membrane stabilization impact on erythrocytes [29]. Moreover, apigenin (10 mg/kg) and methanolic extract of Ocimum basilicum seed (40 mg/kg) exhibited antidiabetic and antihyperlipidemic activity by a significant reduction of blood glucose level and serum lipid factors, respectively [30].

**Anti-ischemic properties**

Ischemic stroke is one of the common leading causes of death worldwide [31]. Various factors including glutamate excitotoxicity, oxidative stress, apoptosis, ion balance disorder, inflammation, and energy metabolism disorder are involved in the pathogenesis of ischemic stroke [32]. Lack of energy and oxygen supply during ischemia leads to decreased activity of the Na-K ATPase [33]. Apigenin significantly inhibited changes induced by oxygen and glucose

deprivation/reperfusion (OGD/R) as reduced mitochondrial membrane potential, cell viability, mRNA levels of detoxifying enzymes, and NF-E2–related factor 2 (Nrf2) protein expression [34]. In addition, apigenin alleviates ROS generation and apoptosis in CoCl2-induced oxidative injury in PC12 cells *in vitro* model of cerebral ischemia/reperfusion injury [35].

**Antiepileptic properties**

Epilepsy is a chronic neurological condition characterized by recurrent, unprovoked seizures [36]. One of the underlying mechanisms of epilepsy is the imbalance between the glutamatergic (stimulating) and GABAergic (inhibitory) neuronal systems leading to excitotoxicity, seizures, and cell death [37]. It is indicated that apigenin can enhance GABA-induced currents through GABAA receptors (α1β2γ2S) [38] and inhibits glutamate release in the rat hippocampus [39]. Furthermore, apigenin showed anti-seizure activity by decreasing hippocampal neuronal loss and cytochrome c release in the kainic acid-induced rat model of epilepsy [40]. Apigenin also alleviated KA-induced excitotoxicity by quenching ROS and reduction of GSH in hippocampal neurons [41].

**Neuroimmunomodulatory and Neuroprotective activity**

Deposition of tau and amyloid proteins in the different parts of the brain leads to Alzheimer's disease (AD) as the common dementia. Expression of glycoprotein 130 (gp130), CD11b/c monoclonal antibody (OX42; microglial activation marker), and interleukin-6 (IL-6) was decreased upon apigenin treatment. In addition, apigenin elevated the expression of brain-derived neurotrophic factor (BDNF) [42]. Alzheimer's disease is the most common neurodegenerative disease characterized by the accumulation of extracellular amyloid β (Aβ) in the cerebrum which results in cognitive impairment and memory loss [43]. Apigenin improved the spatial working memory deficits by inhibiting caspase 9 and cytochrome c release in Aβ 25-35 induced rat model of AD [44]. Treatment of AD neurons with apigenin inhibited the activation of cytokines and NO production and reduced neuronal hyper-excitability and apoptosis in the human-induced pluripotent stem cell model of AD [45]. Apigenin restored learning and memory deficits by preventing Aβ burden and reducing insoluble Aβ levels in APP/PS1 double transgenic mouse model of AD [46]. Apigenin protected neurons against Aβ-mediated toxicity induced by copper through the mechanisms that regulate redox imbalance, preserve mitochondrial function, inhibit MAPK pathways, and depress neuronal apoptosis [47]. In addition, apigenin elevated the expression of brain-derived neurotrophic factor (BDNF) [42].

Neurodegenerative diseases are associated with neuroinflammation which can lead to glial activation and the production of proinflammatory cytokines. In different inflammatory model using co-cultures of neurons and glial cells, apigenin was able to decrease proinflammatory markers after inflammatory stimuli [48]. Parkinson's disease is another progressive neurodegenerative disorder associated with neuroinflammation[49]. Apigenin treatment inhibited the release of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), IL-6, and pro-inflammatory enzyme iNOS-1 and ameliorate the motor impairments in a rat model of Parkinson's disease induced by rotenone [50]. Furthermore, apigenin administration reversed the changes in expressions and concentrations of TNF- α, interleukin-1 beta (IL-1β), IL-6, IL-10, and transforming growth factor-β1 (TGF-β1) in brain tissue of Parkinson's mouse model [51].

**Conclusions**

Low solubility and bioavailability are two main limitations of the formulation of apigenin for therapeutic aspects. Micro and nanoformulations including micelles, liposomes, SLN, NLC, cubosomes, niosomes, phytosomes, and bilosomes may optimize the bioavailability of apigenin inside the body. As the main antidiabetic mechanism, apigenin can block α-Amylase and α-Glucosidase enzymes. A significant reduction of blood glucose level and serum lipid parameters has been found for apigenin at 10 mg/kg dose. Apigenin can form antimicrobial multifunctional benzoxazine by reacting with formaldehyde and furfurylamine/stearylamine. In the case of Parkinson's mouse model, apigenin administration reversed the changes in expressions and concentrations of TNF-α, IL-1β, IL-6, IL-10, and TGF-β in brain tissue. Notwithstanding recent advances in micro and nanoformulations of apigenin, there is a growing need

for finding more effective and safer formulations with suitable bioavailability.

**Study Highlights**

- Low solubility and bioavailability are two main limitations of the formulation of apigenin for therapeutic aspects.
- Micro and nanoformulations including micelles, liposomes, SLN, NLC, cubosomes, niosomes, phytosomes, and bilosomes may optimize the bioavailability of apigenin inside the body.
- Apigenin can form antimicrobial multifunctional benzoxazine by reacting with formaldehyde and furfurylamine/stearylamine.
- In the case of Parkinson's mouse model, apigenin administration reversed the changes in expressions and concentrations of TNF-α, IL-1β, IL-6, IL-10, and TGF-β in brain tissue.

**Abbreviations**

**BDNF:** Brain-derived neurotrophic factor
**gp130:** glycoprotein 130
**IL-1β:** Interleukin-1 beta
**IL-6:** Interleukin-6
**JAK:** The Janus kinase
**MAPK:** Mitogen-activated protein kinase
**MMP-9:** Matrix metallopeptidase-9
**$M^{pro}$:** The main protease of SARS-CoV-2
**NF-κB:** Nuclear factor kappa B
**NLC:** Nanostructured lipid carrier
**Nrf2:** NF-E2–related factor 2
**OGD/R:** Oxygen and glucose deprivation/reperfusion
**OX42:** CD11b/c monoclonal antibody
**PI3K:** Phosphoinositide 3-kinase
**SLN:** Solid lipid nanoparticles
**TGF-β1:** Transforming growth factor-β1
**TNF-α:** Tumor necrosis factor-α
**Wnt:** Wingless/integrated

**Funding**

This work was not supported by any institutes.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Ethical approval**

This article does not contain any studies with animals or human participants performed by any of the authors.

**Author Contributions**

All authors: conceptualization, preparing the first draft, and editing.

**Acknowledgments**

Declared none.

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**HOW TO CITE THIS ARTICLE:**
Javid H, Ahmadi S, Mohamadian E. Therapeutic applications of apigenin and its derivatives: micro and nano aspects. Micro Nano Bio Aspects. 2023; 2(1): 30-38.
doi: https://doi.org/10.22034/mnba.2023.388488.1025