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REVIEW

Potential therapeutic and pharmacological effects of Wogonin: an updated review

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Abstract

Flavonoids are members of polyphenolic compounds, which are naturally presented in fruits, vegetables, and some medicinal plants. Traditionally, the root of *Scutellaria baicalensis* is widely used as Chinese herbal medicine and contains several major bioactive compounds such as Wogonin, Scutellarein, Baicalein, and Baicalin. Experimental and clinical evidence has been proving that Wogonin exhibits diverse biological activities such as anti-cancer, anti-inflammation, and treatment of bacterial and viral infections. In this review, we summarize and emphasize the benefits of Wogonin as a therapeutic adjuvant for anti-viral infection, anti-inflammation, neuroprotection as well as anxiolytic and anticonvulsant. Moreover, the molecular mechanism(s) how Wogonin mediates the cellular signal pathways and immune responses are also discussed and highlighted valuable properties of Wogonin in multiple therapies.

Keywords *Scutellari baicalensis* · Wogonin · Anti-inflammation · Anti-viral · Neuroprotection

Introduction

Growing evidence prove the potential roles of herbal medicinal plants and their natural compounds as the herbal therapeutic approaches [1]. Serving as the supplemental therapeutics and adjuvants, herbal medicinal plants represent a great deal of anti-inflammation, neuroprotective activity, and against infectious diseases with fewer side effects and safe-dose compared to other therapies such as chemotherapies, radiotherapies, surgery, and hormonal therapies [1]. Among over 50 fundamental herbs used in Chinese traditional medicine, *Scutellari baicalensis* (*S. baicalensis*) Georgi is widely prescribed for patients with inflammatory diseases, allergies, arteriosclerosis, diarrhea, and hepatitis as an herbal remedy for centuries [1]. *S. baicalensis* is a member of the genus *Scutellaria* L. (Lamiaceae) which are perennial herbal medicinal plants with around 360 species commonly known as skullcaps and distribute widely in Europe, the United States, and East Asia [2, 3]. The root extracts of *S. baicalensis,* one of the most popular traditional Chinese medicines, contain around 126 small molecule compounds and 6 polysaccharides and has been widely used for thousands of years [2]. Among them, Wogonin, Scutellarein, Baicalin, and Baicalein are the major bioactive compounds, which possess antibacterial, anti-tumor, antioxidant, anti-inflammatory, and neuroprotective activities as previously described [2, 4] (Fig. 1). In this study, we aim to discuss and emphasize the advances in recent years on the bioactivities of Wogonin and its molecular mechanisms of action as well as the potential therapeutic for the future treatment of the inflammatory pathologies.

Wogonin (5, 7-dihydroxy-8-methoxyflavone) is an O-methylated flavone, a flavonoid compound, in *S. baicalensis* Georgi and represents itself as a good excipient, compared with the other *S. baicalensis*-derived compounds

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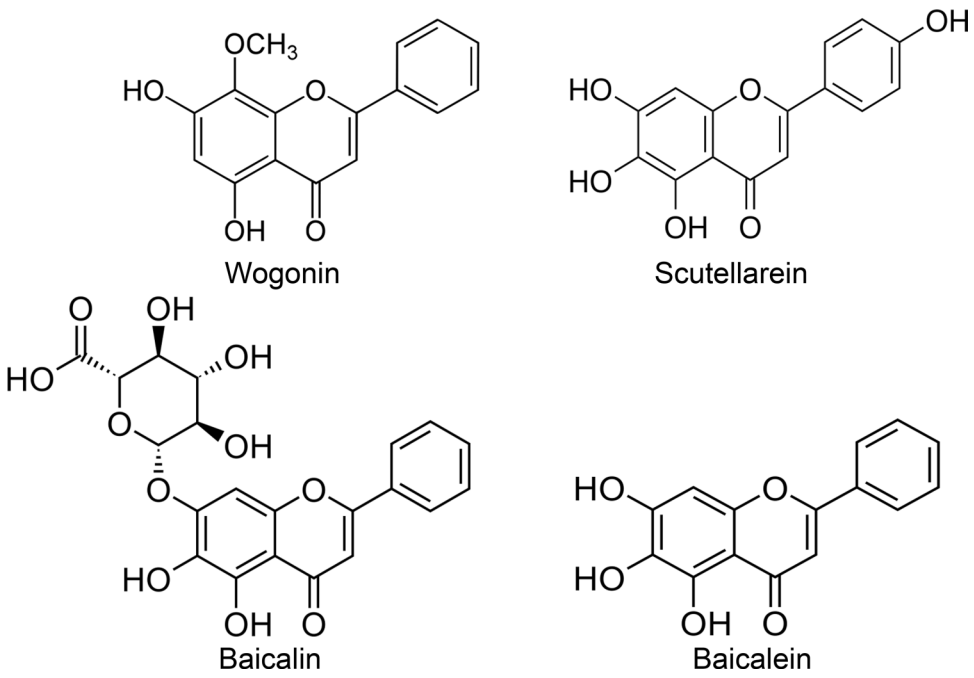

Fig. 1 The major bioactive compounds in root extracts of *S. baicalensis*. The root extracts of *S. baicalensis* contain several major bioactive compounds such as Wogonin, Scutellarein, Baicalin, and Baicalein. Wogonin (5, 7-dihyroxy-8-methoxyflavone) is an O-methylated flavone and its molecular formula is $C_{16}H_{12}O_5$, an active flavonoid-like compound in *S. baicalensis* Georgi and represents itself as a good excipient, compared with other *S. baicalensis*-derived compounds

[1, 5, 6]. The phenolic compounds including flavonoids and non-flavonoids polyphenols play an important role in human diseases especially in cancer and inflammatory diseases [7]. Our previous studies have reported that Wogonin targets multiple signaling pathways to prevent and inhibit the development of cancer both in vitro and in vivo [8, 9]. Also, Wogonin is believed to prevent hepatitis B virus (HBV) infection effectively [10], anti-inflammation [11–15]. Wogonin is also served as a type of tranquilizer (anxiolytic and anticonvulsant) without any adverse effects in animal disease models [16, 17], or have a neuroprotective activity [18, 19]. The molecular mechanisms and inhibitory effects of Wogonin are involved in multiple signaling pathways such as ER stress-mediated apoptosis and autophagy, mitogen-activated protein kinase (MAPK), reactive oxygen species (ROS), suppression of transcription factors (NF-κB and AP-1), intracellular Ca^{2+} signaling [1, 8]. Therefore, in the present study, we will focus on the virtue of Wogonin in vitro and in vivo related to human immunological pathologies and provide the synoptic outlook regarding this bioactive compound in *S. baicalensis*.

Wogonin inhibits the viral replication

S. Baicalensis has been wielding against viral infection in China and Japan for thousand years. The boiled extract of *S. Baicalensis* enables intercepting of the viral activity [1]. Ma et al. investigate the protective effects of bioactive compounds in *S. Baicalensis* against infection of respiratory syncytial virus (RSV), a major cause of lower respiratory tract infections in infants and children [20]. In a mouse RSV infection model, treatment of *S. baicalensis* extracts significantly inhibits the infiltration of $CD11b^+$ macrophages, $CD4^+$ and $CD8^+$ T cells to the lung as well as suppresses the lung inflammation through down-regulation of the inflammatory mediators such as IL-1β, IL-8, TNF-α, MCP1, and iNOS [21]. Extracts of Wogonin in $CHCl_3$, EtOAc, and n-BuOH, diminish the RSV replication activity and prevent effectively RSV infection with the highest selective index ($IC_{50} = 7.4$ μg/mL) as compared to other bioactive compounds of *S. Baicalensis* (Table 1).

Furthermore, Wogonin is believed to suppress the infective activity of vesicular stomatitis virus (VSV) in human peripheral blood leukocytes (PBLs) by modulating the production of antiviral cytokines including IFN-γ [23]. In another context, the evidence reports that Wogonin inhibits the E6 and E7 protein expressions of human papillomavirus (HPV)-16 during its infection in cervical cancer cells [24]. The E6 protein binds to p53 protein, a tumor suppressor, triggering the degradation of p53 whereas the E7 protein deregulates retinoblastoma (Rb) function in cell cycle progression, inducing the proliferation and transformation of non-malignant cells [25]. Treatment of Wogonin (160 μM) significantly inhibits E6/E7 levels in HPV-infected cancer cells [24]. Therefore, treatment of Wogonin may slowdown the malignity of HPV in cervical cancer. Varicella-zoster virus (VZV) is an α-herpesvirus and responsible for chickenpox and shingles [26]. Choi et al. demonstrate that Wogonin represses the replication of VZV in human fibroblast [27]. Further studies assert that Wogonin triggers IFN-α production via signal

Table 1 Antiviral activity of the active compounds in *S. baicalensis* against RSV [20–22]

Compounds	IC_{50} [a]	CC_{50} [b]	SI[c]	Molecular/Cellular targets	Study
Wogonin	7.4	119.2	16.1	PI3K/Akt, p53, NF-κB, MAPK	In vitro
Baicalin	20.8	250.0	12.0	IL-1β, IL-8, TNF-α, MCP1, iNOS, CD4 and CD8 T cells	In vitro In vivo
Baicalein	20.8	250.0	12.0	NF-κB, COX-2, Stat3, MAPK, IL-6, IL-8, TNF-α, IFN, MPO, NO, neutrophils, lymphocytes	In vitro In vivo
Oroxylin A	14.5	58.1	4.0	N/A	In vitro
Scutellarein	20.8	333.3	16.0	N/A	In vitro
Ganhuangenin	83.3	250.0	3.0	N/A	In vitro

[a]IC_{50} (μg/mL) is the concentration of the sample required to inhibit virus-induced cytopathic effect 50%

[b]CC_{50} (μg/mL) is the concentration of the 50% cytotoxic effect

[c]SI, is selective index, CC_{50}/IC_{50}

transducer and activator of transcription 1 (STAT1) and interferon regulatory factor 3 (IRF3) signaling pathway and further attenuates adenosine monophosphate-activated protein kinase (AMPK) activity, leading to the inhibition of the VZV viral replication.[28]. Similarly, Wogonin also inhibits HSV-1/2 (Herpes simplex virus) replication and blocks the HSV life cycle at the post-entry step in vitro [29]. During the HSV infection, Wogonin suppresses the inflammatory response via the reduction of NF-κB and MAPK (ERK and p38) signaling pathways. These evidences indicate that Wogonin could be a valuable option for anti-herpesvirus infection. However, further studies are needed to verify in humanized animal models to understand the anti-herpesvirus effects of Wogonin, an important step prior to the transition to clinical trials. In agreement, Wogonin also exhibits the inhibition of influenza A and B virus infection via down-regulation of the AMPK pathway and up-regulation of IFN-induced antiviral signaling [30].

Moreover, Wogonin is believed to suppress hepatitis B virus (HBV) infection in vitro and in vivo [10]. Specifically, treatment of Wogonin inhibits the HBV infection in HepG2 cell line at $IC_{50} = 4$ μg/mL through lowering the amounts of Hepatitis B surface antigen (HBsAg) and Hepatitis B e antigen (HBeAg) as compared to 10 μg/mL Lavimudine (commercial name as 3TC and a common drug for HBV infection). Interestingly, in vivo data shows that the plasma HBV DNA genome copies are reduced under treatment of 20 mg/kg Wogonin as compared to 3TC-treated group at 50 mg/kg, accompanied by the improvement of liver histology. Further study also shows that Wogonin treatment (28 mg/kg, intravenous route) decreases the plasma HBsAg level in mice infected with human HBV strain. Furthermore, S. *Baicalensis* extracts enable to inhibit the replication of hepatitis C virus (HCV) in vivo [1]. These evidences suggest that Wogonin and *S. Baicalensis* extracts could be the potential compounds and/or supplements to treat the HBV and HCV infection in the future.

Inhibitory effects of Wogonin in inflammatory pathology

Cyclooxygenases-1 (COX-1) and COX-2 are the anti-oxidant enzymes, catalyzing the converted reaction of the free arachidonic acid to the prostaglandin (PG) H_2, which plays important role in the inflammation and pain responses [31]. In 1976, COX-1 was first purified and dominantly expressed in most tissues whereas COX-2 recently has been identified as an inducible isoform known as the major isoform producing large amounts of PGH_2 [31]. The result from an in vitro study shows that Wogonin inhibits the expression of inducible COX-2 and the production of prostaglandin E_2 (PGE_2) in murine skin fibroblasts under the stimulation of phorbol 12-myristate 13-acetate (PMA), [32]. Consistently, other studies confirmed that treatment of Wogonin inhibits the expression of COX-2 and inducible nitric oxide synthase (iNOS) in LPS-treated mouse macrophages as well [12, 15]. In supporting this observation, Chen et al. demonstrate that Wogonin downregulates PMA-induced COX-2 expression via Protein kinase C (PKC) and Mitogen-activated protein kinase (MEK1/2) pathway, leading to the inactivation of Activator protein 1 (AP-1) and c-Jun protein [33]. In vivo study indicates that inhibitions of COX-2 and PGE_2 by Wogonin are the major molecular mechanisms against the ear intact skin or acute inflammation [11]. In the dermatitis mouse model, treatment of Wogonin reduces the ear thickness and skin inflammation through suppressing the expressions of inflammatory mediators such as TNF-α [11], IL1-β, intercellular adhesion molecule (ICAM)-1 [11, 34], and iNOS [12–14]. These mediators govern inflammation activities and are considered as the causes of acute or chronic inflammation [35]. Therefore, by targeting the COX-2 pathway and inflammatory mediators, Wogonin prevents effectively inflammation induced by macrophage or skin fibroblast in vitro and diminishes skin inflammation in the mouse disease model.

Moreover, treatment of Wogonin (10 and 30 mg/kg) decreases the serum levels of OVA-specific IgE in ovalbumin-induced allergic rhinitis murine models, as well as the production of the inflammatory mediator such as RANTES, eotaxin, IL-4, IL-5, IL-13 in the nasal fluid [36]. In addition, Wogonin induces apoptosis of eosinophils via a caspase-dependent mechanism [37]. Thus, the infiltration of inflammatory leukocytes including eosinophils also is reduced in the nasal mucosa [36]. Likewise, Shin et al. assert that Wogonin suppresses the production of the IgE and IL-5 in ovalbumin-induced allergic Th2 response.[38]. Ex vivo experiments show that Wogonin suppresses the production of IL-4 and IFN-γ in splenocytes from mice sensitized with ovalbumin.

In the dextran sulfate sodium (DSS)-induced colitis mouse model, Wogonin inhibits colitis by suppressing the production of immunoglobin (Ig) E while enhancing the IgA production [39]. Interestingly, Wogonin also increases the production of Th1 cytokines (IFN-γ and IL-2) but decreases the Th2 cytokines (IL-4, IL-5, and IL-10), suggesting that Wogonin might have either a direct impact on Th2 cytokine suppression or indirectly affect Th2 cells activities via regulation of Th1 cells [39]. Accordingly, Wogonin reduces the production of pro-inflammatory cytokines (IL-6 and IL-1β) and inhibits the phosphorylation of p38 and ERK as well as expression of NF-κB and Nrf2 in DSS-treated mice [40]. However, intraperitoneally injection of a high dose of Wogonin (100 mg/kg) exacerbates the murine colitis induced by DSS through suppressing the functions of effector T cells ($CD8^+$ and $CD4^+$) and promoting the regulatory T cells ($CD4^+CD25^+FoxP3^+$) [41]. These evidences suggest that Wogonin modulates the activities of Th1 and Th2 immune cells, resulting in the reduction of inflammation (Table 2).

Osteoarthritis (OA) is a chronic inflammatory disease associated with cartilage degradation, joint trauma, and aging, and negatively impacts on life quality. Interestingly, the topical administration of Wogonin attenuates the OA severity and reduces the pain in OA surgical mouse model [42]. Immunohistochemistry data also showed that Wogonin decreases significantly the expression of OA biomarkers such as transforming growth factor β1 (TGF-β1), matrix metalloprotease-13 (MMP-13), NF-κB, high temperature receptor A1 (HTRA1) [42]. In human osteoarthritis chondrocytes, Wogonin also inhibits the catabolic markers such as MMP-3, MMP-9, MMP-13, IL-6, COX-2, ADAM metallopeptidase with thrombospondin type 1 motif 4 (ADAMTS-4), and iNOS, which are crucial to OA pathogenesis [44]. Furthermore, Wogonin suppresses the production of ROS and depletes the cellular glutathione, thus regulates ROS/MAPKs/Nrf2/NF-κB signaling axis in OA chondrocytes [44]. In rabbit articular chondrocytes, Wogonin enhances the expression of type II collagen (COL2A1) but suppresses the expression of MMP-3, MMP-1, MMP-13, and ADAMTS-4 as well as proteolytic activity of MMP-3 in vitro in particular [43]. In Freund's adjuvant-induced rheumatoid arthritis, Wogonin reduces the arthritic severity score and paw thickness as well as improves the body weight. Wogonin substantially inhibits inflammatory cytokines (TNF-α and IL-1β) through suppression of p38 phosphorylation and induces the expressions of anti-oxidative stress markers (superoxide dismutase, catalase, GSH) [45]. These data suggest that Wogonin might be employed as a potential therapeutic agent for the inflammatory pathologies.

Wogonin has anxiolytic and anticonvulsant effects

In the mammal central nervous system (CNS), it is demonstrated that GABAergic neurons can produce γ-aminobutyric acid (GABA), which is considered as a main inhibitory neurotransmitter relating to anxiety or stress condition [46]. There are two types of GABA receptors including ionotropic receptor ($GABA_A$ receptor) and metabotropic receptor coupled with G protein ($GABA_B$ receptor) located at pre-and

Table 2 Cell types and inflammatory molecules targeted by Wogonin

Type of cells/diseases	Molecular targets	Study/dosing	References
Macrophages	↓: TNF-α, ICAM-1, IL-β1, COX-2, PGE2, iNOS	In vitro (5–40 μM)	[5, 12, 14, 15]
Th1 T cells	↑: IFN-γ, IL-2	In vivo (20 mg/kg)	[39]
Th2 T cells	↓: IL-4, IL-5, IL-10	In vivo (20 mg/kg)	[39]
Splenocytes	↓: IL-4, IL-5, IFN- γ, IgE	In vivo (1 mg/kg)	[38]
Epithelial cells	↓: IL-6, IL-8, COX-2	In vitro (1–10 μM)	[6, 33]
Lymphocytes DSS-induced Colitis	↓: IgE, $CD8^+$ and $CD4^+$ T cells ↑: IgA, $FoxP3^+$ Treg cells	In vivo (20–100 mg/kg)	[39]
Skin fibroblast cells Skin inflammation	↓: IL-β1, COX-2, PGE2	In vitro (10–100 μM) In vivo (1000 mg/ear)	[11, 32]
Chondrocytes Osteoarthritis	↓: MMP-1/3/13, ADAMTS-4 ↑: COL2A1	In vitro (10–100 μM) In vivo (100 μM)	[42, 43]

post-synaptic neurons [47]. Interaction of two molecules of GABA with their receptors induces the conformation changes regulating the chloride (Cl-) channel activities and allowing Cl- ion flux to enter into the cells, lead to an increase in the number of inhibitory inputs (IPSPs) at the post-synaptic neuron. As a consequence, the excitatory signals are attenuated result in reducing the anxiety and stress. Several common drugs of anxiolytic and anticonvulsant are GABA receptor agonists, which also bind to the active site of the GABA receptor and regulate the neural inhibitory inputs. For instance, benzodiazepine (BZD) is a kind of psychoactive drug and binds to an allosteric binding site known as benzodiazepine site (BZD-S) which modulates the activity of GABA the receptor (Fig. 2) [48]. Several studies have targeted BZD-S in an attempt to achieve an impeccable effect on anxiolytics. Still, some side effects have been recording [49–51].

Several studies have shown that natural flavonoids are known to repress the anxiety and anti-convulsion [52, 53]. Wogonin distinguishingly shows the potential in anxiolytics [17] with the highest affinity with BZD-S ($K_i = 0.92–2$ µM) comparing with other analogs from *S. baicalensis* such as Baicalein, Scutellarein, Baicalin [54]. Additionally, inhibitory concentration (IC_{50}) of Wogonin to [^{3}H] flunitrazepam and BDZ-S binding, is 1.26 µM whereas diazepam, a chemical compound in the Benzodiazepine family, was significantly lower 100 times with $IC_{50} = 0.012$ µM [17]. This suggests that Wogonin displays a moderate affinity to BDZ-S as compared to the synthetic chemical compound. Moreover, a study on *Xenopus laevis* oocytes model expressing the rat $GABA_A$ receptor indicates that the combination of Wogonin and GABA (2 µM) dose-dependently increases the electrophysiological current versus GAGA alone. However, the supplement of BDZ-S antagonist Ro15-1788 (1 µM) partly inhibits Wogonin stimulatory effect. To figure out the subunit that Wogonin targets, Hui et al. depleted the γ2 subunit of $GABA_A$ and the result showed that relative stimulation turned into a lower current in presence of Wogonin. This proof demonstrated that Wogonin targeting site on $GABA_A$ locates at the γ2 subunit and its anxiolytic property is strongly linked to BDZ-Site (Fig. 2). Moreover, Yoon et al. indicated that 5, 7-dihydroxyl groups in the Wogonin structure might be responsible for BZD binding site, which crucially determines the anxiolytic property of Wogonin [55] (Fig. 2).

Most drugs in the BDZ family for anxiolytics engender the unwanted side effects, including sedation and muscular relaxation [49–51]. However, the elevated plus-maze (EPM) assay indicated that Wogonin (3.75–30 mg/kg) increases the time of open arm as compared with vehicle control and the same pattern to anxiety disorder drugs-Diazepam. Furthermore, common methods for screening the potential anxiolytic effect of drugs constituting the hole-board test, horizontal wire test, or myorelaxation test based on locomotor activity and endurance time on rota-rod test have also reflected the efficiency of Wogonin on the sedative behavior

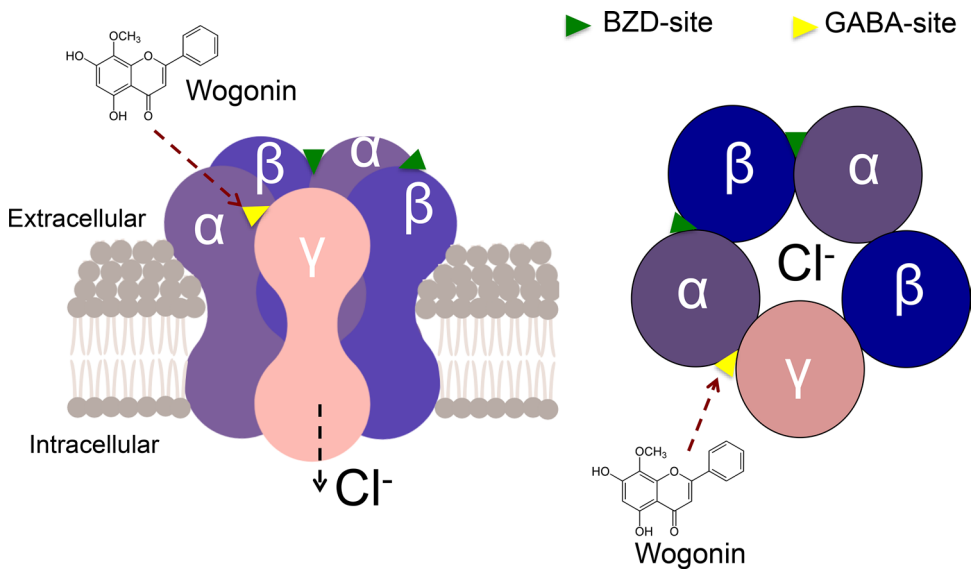

Fig. 2 The allosteric modulating of Wogonin in $GABA_A$ receptor. Ligation of two molecule of GABA with its receptors induces the conformation changes regulating the chloride (Cl-) channel activities and allowing Cl-ion flux enter into the cells lead to increase the number of inhibitory inputs (IPSPs) at the post-synaptic neuron. As a consequence, the excitatory signals are attenuated and reducing the anxiety and stress. Benzodiazepine (BZD) is a kind of psychoactive drugs and binds to allosteric binding site known as benzodiazepine site (BZD-S), which modulates the activity of GABA, the receptor. Wogonin target the site on $GABA_A$ locates at γ2 subunit and its anxiolytic property is strongly linked to BDZ-Site

and myorelaxation [17, 52]. Taken together, oral administration of Wogonin is a potential therapeutic supplement for anti-anxiety without sedative behavior and no sign of myorelaxation and partly helpful in anticonvulsant therapy instead of using conventional drugs-BDZ family. However, the effective and safety-dose of Wogonin in anti-anxiety and anticonvulsant are necessary to be further investigated.

Wogonin as an effective neuroprotector

Microglia are resident macrophages in CNS and play an important role in the maintenance of the CNS equilibrium by phagocytosis of cellular debris, death/damaged neurons, and infectious agents [56]. During the phagocytic activity, the microglia produce some inflammatory cytokines including TNF-α, IL-1β, or cytotoxic substances such as superoxide, hydrogen peroxide, nitric oxide (NO), which are potential to trigger inflammatory response cascades. Moreover, the microglia also secret some enzymes (such as lysozyme, peroxidases, elastase, and proteases) in the CNS microenvironment, resulting in impairment of the cellular membrane and promoting the demyelination of neuronal axons [57, 58]. Typically, the transient neuroinflammation is important for regulating the wound healing response, regeneration of neuron, or neuron remodeling during the CNS development. However, the chronic neuroinflammation represents the excessive activities of microglia leading to damage to the neurons results in several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis [59].

Studies indicate that Wogonin may serve as a neuroprotector [18, 19, 60] through the reduction of inflammatory mediators including TNF-α, IL-1β, and NO in LPS-stimulated murine microglial cells. In addition, further results show that Wogonin treatment attenuates the expression of the upstream genes such as iNOS and nucleus factor-kappa B (NF-κB) that is crucial for regulating the productions of inflammatory mediators in primary microglial cells [18, 19]. These data suggest that Wogonin targets specifically the iNOS gene via the NF-κB pathway and as a result, indirectly eradicate the amount of free radical NO in microglia (Fig. 3). Moreover, Wogonin not only scavenges free radicals in the neuron microenvironment but also suppresses the inflammation induced by microglia. Treatment of Wogonin (1–50 μM in vitro and 0.5–10 mg/kg in vivo) diminishes the ischemic death of hippocampal neurons and protects against experimental brain injury in vivo through reduction of cytokine production in activated microglia [19]. In addition, the low supply of oxygen or glucose triggers the neural apoptosis via

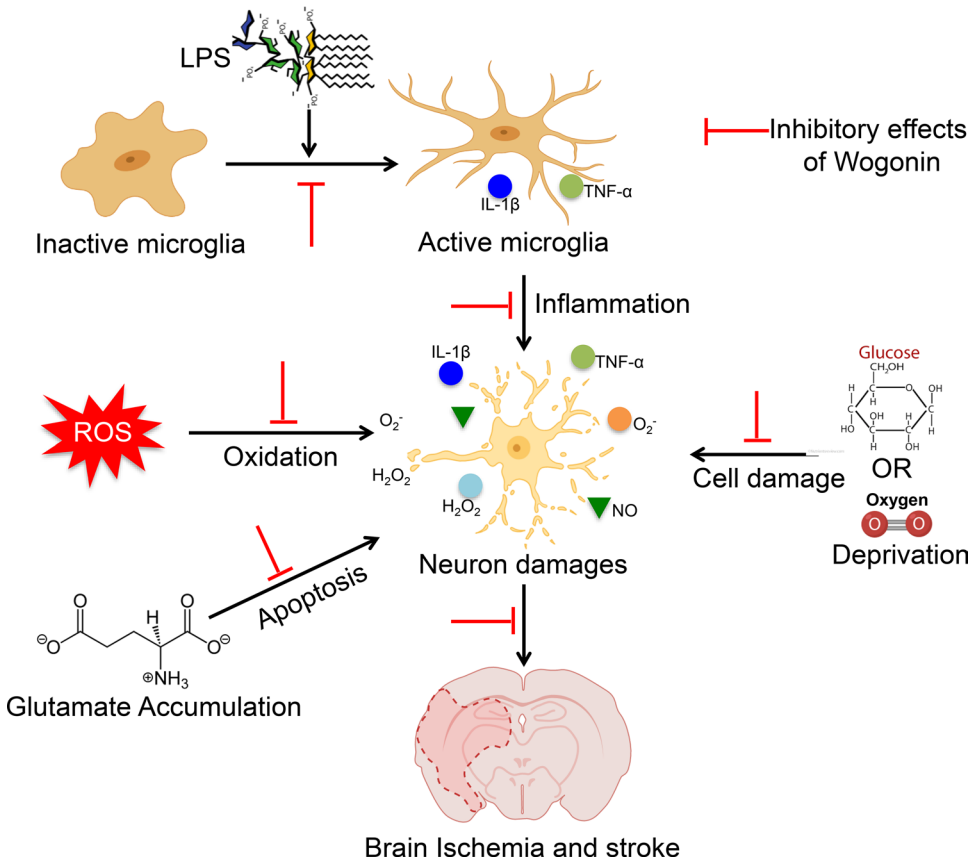

Fig. 3 Wogonin acts as an effective neuroprotector. Under the effects of LPS, microglia are activated and secreting the pro-inflammatory mediators such as IL-1β, TNF-α and NO which facilitate the inflammation events in neuron. Wogonin prevents the excessive inflammatory activities of microglia via regulation of production of inflammatory cytokines and mediators. Furthermore, Wogonin also reduces the harm effects from exogenous ROS sources to neurons, including H_2O_2, Xanthine or the deprivations of oxygen/glucose or lipid oxidation induced by NADPH. In addition, the apoptosis triggered by glutamate accumulation, is also minimized under Wogonin treatment. Therefore, Wogonin employment diminishes the neural damages and protects against the brain ischemia or stroke

loss of the permeability membrane and intracellular Ca^{2+} concentration [61]. Son et al. demonstrated that Wogonin treatment confers the neuroprotection under oxygen or glucose deprived conditions [62]. Especially, Wogonin prevents efficiently the neural cell death at the pyramidal cell layer of hippocampal slices, suggesting a potential therapeutic agent for the patients with ischemia.

Furthermore, Cho et al. evidenced that administration of Wogonin (20 mg/kg) intraperitoneally minimizes the permanent occlusion of the middle cerebral artery (pMCAO)-induced infarct areas in the cerebral cortex as well as in striatum [63]. The study also reported the improvement of rat behavior under Wogonin treatment. Likewise, Piao et al. also confirmed that Wogonin (50 mg/kg) reduces markedly infarct brain volume in a condition of 2-h middle cerebral artery occlusion and followed by 22 h in reperfusion [18]. These observations explain a possibility that Wogonin attenuates the production of inflammatory mediators in the activated microglia after hypoxic/ischemic injury, for instance, TNF-α, IL-6, and NO, therefore facilitates the expansion of infarct volume and neuroinflammation as well. In addition, Wogonin is believed to repress excitotoxic and oxidative neuronal damages [60]. Excitotoxicity is mainly caused by over-accumulation of L-Glutamate occurring in some disorders including ischemia, epilepsy, and Alzheimer [64]. Glutamate accumulation activates Ca^{2+} immobilization and a massive influx of cytoplasmic Ca^{2+} in astrocytes, leading to the production of secondary cascades involving reactive oxygen species (ROS) [65–67] and mitochondria-mediated apoptosis, resulting in the damage and death of neurons [66, 67]. Evidence showed that Wogonin (300 μg/mL) inhibits significantly glutamate or NMDA (*N*-Methyl-D-aspartate)-induced excitotoxicity [60]. The other studies also reported that Wogonin restricts the neural oxidation induced by H_2O_2, xanthine/xanthine oxidase, and DL-buthionine [S, R]-sulfoximine (a glutathione depleting agent) [60, 68–70]. Furthermore, Wogonin also suppresses lipid peroxidation induced by NADPH and consequently reduces superoxide radical in neuron areas [60, 69] (Fig. 3). These evidences consolidate the virtue of Wogonin in anti-neurodegenerative under the conditions of excitotoxicity, glucose and oxygen deprivation, and various types of oxidative stress-induced damages. Thus, it is obvious that Wogonin could be a potentially invaluable source as the novel neuroprotective drugs for brain ischemia and stroke patients.

Conclusion and perspectives

Wogonin is a medicinal plant-derived flavonoid that has a variety of pharmacological effects, acting as an inhibitor of inflammation mediators produced by macrophages, lymphocytes, microglia, and endothelial cells. Wogonin also serves as ROS scavenger, neuroprotector, anti-allergy, anxiolytics, and anticonvulsant. The molecular mechanisms and inhibitory effects of Wogonin are involved in multiple signaling pathways such as ER stress-mediated apoptosis and autophagy, mitogen-activated protein kinase (MAPK), reactive oxygen species (ROS), suppression of transcription factors (NF-κB and AP-1), intracellular Ca^{2+} signaling (Fig. 4). Specifically, Wogonin inhibits and prevents viral infection by blocking the interaction between the virus and the cells accompanied by suppressing the expression of viral proteins (such as E6 and E7 protein). Moreover, Wogonin triggers the IFN-induced antiviral signaling (STAT1/IRF3 pathway) as well as activates the anti-inflammatory responses via modulation of NF-κB/AP1/MAPK signaling pathways. In inflammatory diseases, Wogonin inhibits the inflammatory cytokines/chemokines (IL-6, IL-1β, IFN-γ, TNF-α, RANTES, eotaxin) production and oxidative stress mediators (COX-2, PGE_2, NO, iNOS) through regulation of ROS/MAPK/Nrf2/AP1/NF-κB signaling pathways. To attenuate the infiltration of inflammatory leukocytes, Wogonin suppresses the expression of ICAM-1, matrix metalloproteinases (MMP1, MMP2, MMP13), which are necessary for leukocyte migration and trafficking. The ratio of the effector T ($CD4^+$ and $CD8^+$) cells and Treg ($CD25^+FOXP3^+$) cells is crucial to maintain the immune homeostasis; thereby Wogonin also increases the Treg population and decreases the effector T cells results in a reduction of the inflammation. Interestingly, the effects of Wogonin on convulsion related behaviors such as myorelaxation, and anticonvulsant is mediated by the GABAergic neuron. The 5, 7-dihydroxyl groups of the Wogonin bind to BZD binding site of GABAA locates at γ2 subunit, thus increasing the Cl^- ion influx into the intracellular area and electro-physiological current. Finally, Wogonin also serves as a neuroprotector through the reduction of the inflammatory mediators (TNF-α, IL-1β, IL-6, NO, iNOS) and multiple signaling (MAPK/Nrf2/NF-κB, intracellular Ca^{2+}) in the microglial cells and brain. Importantly, Wogonin inhibits neurotransmitter glutamate or NMDA receptor; thus suppressing the neural cell death and preventing the ischemic death of hippocampal neurons.

It is obvious that the need for phytopharmaceuticals rapidly developed and proved its safety as well as benefits for thousand years. Confronting with drug resistance and side effects, it is necessary to discover new therapeutic agents to intensify treatment efficiency. During the last 20 years, studies on Wogonin therapeutic features have been increasing significantly in quality and quantitative. Meeting all such needs, Wogonin has been demonstrated as one of the alternative therapies, in an effort to minimize uses of chemicals or agents as well as lesser side effects. In addition, the Wogonin potentials in treatments are still not limited and could explode the industry of

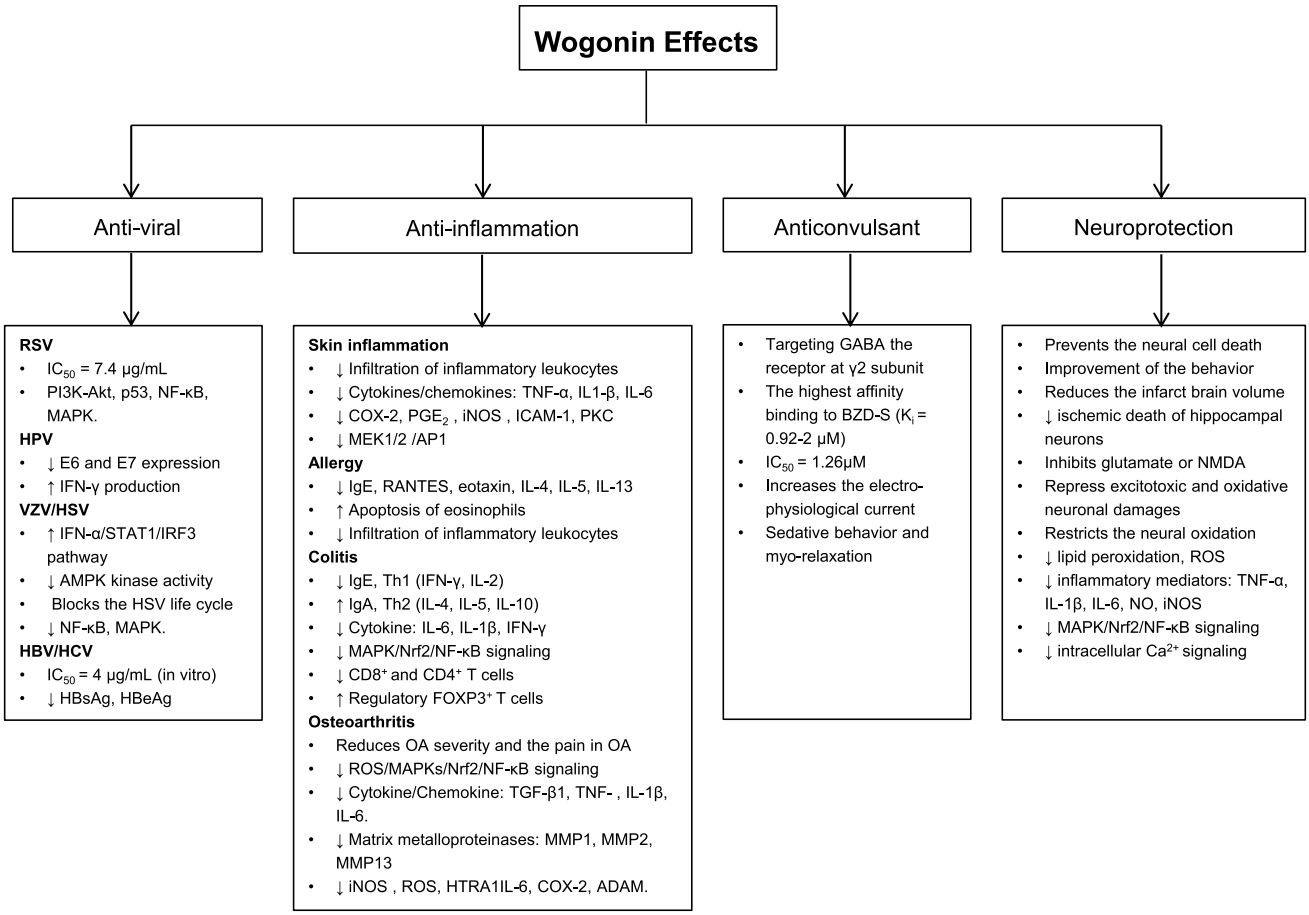

Fig. 4 A scheme for the protective effects of Wogonin. The scheme summarizes the novel therapeutic effects and detail molecular mechanisms as well as signaling pathways of Wogonin against the viral infection (RSV, HPV, VZV/HSV, and HBV/HCV), inflammatory diseases (skin inflammation, colitis, arthritis, and allergy), anti-convulsant/anxiolytic, and neurodegeneration. Up and down arrows indicate the stimulatory and inhibitory effects of Wogonin

herbal plant-derived extracts for treatment of inflammation, hypertension, cardiovascular diseases, and infectious diseases as well as anti-convulsant/anxiolytic/neuroprotective or anti-allergic. Importantly, it shows very little toxicity to normal epithelial cells as well as normal peripheral blood and myeloid cells. In 2014, the China Food and Drug Administration approved Wogonin for phase I clinical trial. However, it has not been used in Western medicine in the form of a pure chemical because the beneficial effects of Wogonin are still limited in certain conditions including in vitro and in vivo investigations. Previous pharmacokinetic studies also report that Wogonin has low oral bioavailability; hence it is extremely urgent to validate the results clinically and complete the pharmacokinetic data. Finally, the employment of Wogonin in clinical treatments remains elusive and needs further studies to ascertain the optimal treatment times and doses for each pathological disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human and animal subjects performed by any of the authors.

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