

Wogonin a Promising Component of *Scutellaria baicalensis*: A Review on its Chemistry, Pharmacokinetics, and Biological Activities

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ABSTRACT

Scutellaria baicalensis Georgi (Huang-Qin or Chinese skullcap) is a native medicinal plant in China that is commonly used for the treatment of seizures, viral infections, and cancer. The numerous pharmacodynamics of this plant is referred to as its rich content of flavones (baicalin and wogonoside) and their corresponding aglycones (baicalein and wogonin). Wogonin is one of the most extensively investigated active components of *Scutellaria baicalensis*. A multitude of preclinical studies indicated that wogonin possesses many pharmacological activities including anti-inflammatory, antioxidant, cytotoxic, neuroprotective, antidiabetic and antiviral effects. However, studies regarding the toxicity profile of wogonin are lacking. This review focuses on the recently published data regarding the chemistry and the pharmacokinetic profile of wogonin. Moreover, it highlights some of wogonin's well documented biological activities such as cytotoxic, neuroprotective, antidiabetic and antiviral activities. The information in this review encourages further investigations to elucidate the wogonin's full toxicological profile for verification of the safety of wogonin and the determination of the maximal tolerable dose (MTD) to be able to extrapolate wogonin's benefits to the clinical setting.

Keywords: wogonin; neuroprotective; antidiabetic; anti-inflammatory; antioxidant; pharmacokinetics

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1. INTRODUCTION

Natural products have long been an important player in the process of drug discovery. Flavonoids comprise an important category of bioactive compounds of natural origin. *Scutellaria baicalensis* Georgi is a native Chinese medicinal plant. Its significant medicinal value increases progressively and over 5000 tons

have been required in the traditional medicine market [1]. Wogonin is a promising component of *Scutellaria baicalensis*. Several studies elucidated that wogonin has a multitude of beneficial biological properties. It has anti-inflammatory, antitumor, neuroprotective, anxiolytic and antiviral [2-4]. Numerous experiments conducted *in vitro* and *in vivo* have

demonstrated wogonin's excellent anti-cancer properties [5]. This promising compound has a well-documented antioxidant and anti-inflammatory properties, which are probably the major underlying mechanisms responsible for most of its biological activities. The present review discusses wogonin chemistry, pharmacokinetics, and some of its well documented biological activities through summarizing studies published within the time range 2010-2019. Numerous preclinical studies support the beneficial biological activity of wogonin. However, there is a paucity of studies regarding wogonin toxicity profile and safety data. The information covered in this review encourages further investigations of wogonin to assess the maximal tolerable dose (MTD) of wogonin to be able to extrapolate its benefits to the clinical setting after the verification of its safety.

1.1. Wogonin Chemistry

Wogonin was first isolated from the Chinese flowering plant *Scutellaria baicalensis* that belongs to the *Lamiaceae* family [6]. Wogonin can be prepared either by extraction or by chemical synthesis, either by cyclization of 1,3-diaryl-diketone or by Wessely-Moser rearrangement [7]. Wogonin's chemical name is 5,7-dihydroxy-8-methoxy flavone. Its molecular weight is 284.267 g/mol [8]. The chemical structure of wogonin is depicted in Fig. 1.

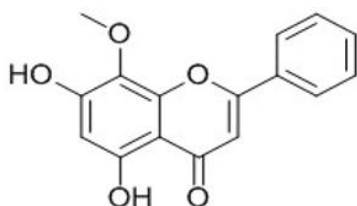


Fig.1. The chemical structure of wogonin

Wogonin is a crystalline solid soluble in organic solvents including ethanol, dimethyl

sulfoxide (DMSO), and dimethylformamide (DMF) and has limited solubility in aqueous buffers [6].

1.2. Pharmacokinetics

The pharmacokinetic studies of wogonin are important to help the investigation of its pharmacological activities *in vivo*. The LD₅₀ of wogonin administered to rats by the intravenous route was 286.15 mg/kg. The elimination half-life of wogonin (40 mg/kg) after intravenous administration was 14 min. C_{max} value of wogonin (100 mg/kg) was 300 ng/mL after 28 min. of intragastric infusion [9]. Wogonin was rapidly distributed to all rat tissues with markedly higher distribution to liver and kidney tissues [9].

Only 21% of wogonin was excreted unchanged in rat feces, urine, and bile [10]. Wogonin exhibits a high plasma protein binding (>90%) according to studies in rat plasma [10]. At high doses of wogonin, nonlinear pharmacokinetic behavior was observed with a disproportionate increase in plasma levels [11]. This behavior was due to partial saturation of clearance pathways in addition to other enzymes responsible for wogonin metabolism [12]. The oral bioavailability of wogonin is low (1.10%) [9] which could be attributed to its low solubility and the extensive exposure to gastrointestinal first-pass effect [13]. Wogonin can cross the Blood-Testis Barrier (BTB) effectively [14]. Based on the pharmacokinetic data discussed above, wogonin cannot be administered orally due to its low bioavailability. This fact encourages the development of wogonin nano-formulations to improve its oral bioavailability.

1.3. Cytotoxic Activity

A multitude of studies reported a broad-spectrum anticancer activity for wogonin through a diversity of mechanisms as summarized in Fig. 2. Wogonin enhanced TNF-related apoptosis-inducing ligand (TRAIL) induced apoptosis in

malignant cells *in vitro* through antiapoptotic proteins downregulation. These proteins include the long form of cellular FLICE-like inhibitory protein (cFLIP L), X-linked inhibitor of apoptosis protein (XIAP) and cellular inhibitor of apoptosis protein 1 and 2 (cIAP-1 and cIAP-2) [15]. Wogonin robustly induced intracellular reactive oxygen species (ROS) accumulation in cancer cells [16]. Wogonin was reported to be a promising agent in the treatment of human colorectal cancer [17]. Wogonin interfered with the transcriptional activity of the T-cell factor/lymphoid enhancer-binding factor (TCF/LeF) through inhibition of β -catenin mediated transcription and suppressed the kinase activity of Cyclin-Dependent Kinase 8 (CDK8) [17]. Treatment with wogonin also suppressed

cell proliferation and induced G0/G1 cell cycle arrest [18] and inhibited cancer cell invasion [19]. Wogonin treatment significantly induced mitochondrial damage and apoptosis *via* the modulation of B-cell lymphoma 2 (Bcl-2) and Bcl-2 Associated X (Bax) protein expression. It was reported to decrease Bcl-2 expression and increase Bax protein, leading to mitochondrial dysfunction, caspase activation and PARP cleavage in HT29 cells [20]. Previous *in vitro* studies showed that wogonin inhibited tumor angiogenesis by downregulating the expression of the hypoxia-inducible factor-1 α protein (HIF-1 α) and monocarboxylate transporter-4 (MCT-4) [21, 22]. Moreover, wogonin increased the sensitivity of ovarian cancer cells through modulating PI3K/AKT signaling pathway [23].

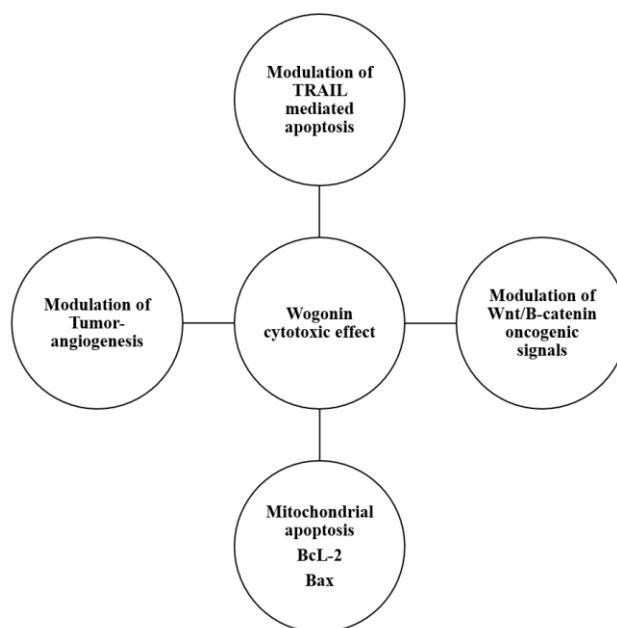


Fig. 2. A diagram summarizing the chief aspects of wogonin's cytotoxic effects

1.4. Neuroprotective Activity

Flavonoids can modulate the neuronal functions and protect against age-related neurodegeneration [24]. Neuroprotection against cerebral ischemia is thought to be mainly *via*

glutamate receptor modulation and suppression of both inflammatory reactions and oxidative stress [25]. Anti-inflammatory and antioxidant activities of wogonin are responsible for its neuroprotective activity [26].

The neuroprotective effect of wogonin was tested in two brain injury models; transient global ischemia by four-vessel occlusion and systemic injections of kainite to elicit excitotoxic injury. Wogonin inhibited the inflammatory activation of microglia leading to the reduction of hippocampal neurons death [27]. Wogonin inhibited inflammatory activation of cultured brain microglia and suppressed lipopolysaccharide (LPS) -induced tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and nitric oxide (NO) production [27]. It was reported that wogonin exhibited significant inhibition of Nicotinamide adenine dinucleotide phosphate (NADPH)-induced lipid peroxidation in rat brain cortex mitochondria [28]. Wogonin exhibited marked inhibition of lipid peroxidation in rat brain tissues [29]. *In vitro* study reported that wogonin downregulated the genetic expression of Notch-1 indicating that wogonin has a promising therapeutic effect for the treatment of retinal degenerative diseases [30].

It is noteworthy that flavonoids can also act as modulators for the γ -aminobutyric acid (GABA-A) receptor [31]. Wogonin maximally upregulated the expressions of the presynaptic protein, synapsin I and postsynaptic protein PSD95 and promoted the differentiation of Neural Progenitor Cells (NPCs) into mature neurons *in vivo* [32]. Furthermore, wogonin enhanced the differentiation rate of hippocampal precursor cells induced by platelet-derived growth factor (PDGF) [32]. In global ischemia models, wogonin decreased the inflammatory mediators; inducible nitric oxide synthase (iNOS) and TNF α , in the hippocampus tissues [33]. Additionally, wogonin elicited vasodilatory effects *via* the interference with extracellular Ca²⁺ influx and Ca²⁺ release from the endoplasmic reticulum [34]. Wogonin counteracted fluid precision injury *in vivo* [2] and showed a neuroprotective effect against Alzheimer's

disease by downregulating the amyloidogenic pathway via decreasing Bax expression [35]. In a focal ischemia model, wogonin repressed cerebral ischemic injury and the infarct volume through activated microglial cells inhibition [36, 37]. Neuronal cell damage induced by deprivation of oxygen and glucose in rat hippocampal culture was counteracted by wogonin [25]. The cell viability of rat dorsal root ganglion (DRG) neurons was significantly enhanced by wogonin. On the other hand, the number of apoptotic propidium iodide positive DRG neurons was decreased [21]. Furthermore, wogonin decreased the activation glucose-regulated protein 78 (GRP78), GRP94, C/EBP-homologous protein, active caspase12 and 3, phosphorylation of pancreatic ER stress kinase, and eukaryotic initiation factor 2 alpha (eIF2a) [38].

Wogonin pretreatment was reported to the downregulated expression of the CHOP protein level in tunicamycin-induced DRG neurons [38]. Wogonin also counteracted tunicamycin-induced depletion of glutathione (GSH) with subsequent reduction in lactate dehydrogenase (LDH) leakage [38]. The mechanisms of wogonin's neuroprotective effects are summarized in Fig. 3.

1.5. Antidiabetic Activity

Diabetes pathogenesis is strongly correlated with inflammation and increased oxidative stress [39-41]. As discussed above, wogonin possesses both antioxidant and anti-inflammatory properties [42]. *In vivo* study was conducted in mice followed by *in vitro* mechanistic investigations using 3T3-L1 cells [43]. Wogonin treated group showed decreased weight gain and improved glucose tolerance. The levels of cholesterol and insulin were significantly decreased. Wogonin enhanced the expression of Peroxisome proliferator-activated receptors α (PPAR α) and PPAR γ in white adipose tissue which in turn mediated several genes involved in

glucose and lipid metabolism and adiponectin expression level in white adipose tissue [43]. Wogonin ameliorated insulin sensitivity by downregulating insulin levels and decreasing blood glucose [38]. Wogonin improved

dyslipidemia by lowering cholesterol levels in macrophages and apolipoprotein E [44]. The aforementioned activities of wogonin were *via* 5' adenosine monophosphate-activated protein kinase (AMPK) activation [45].

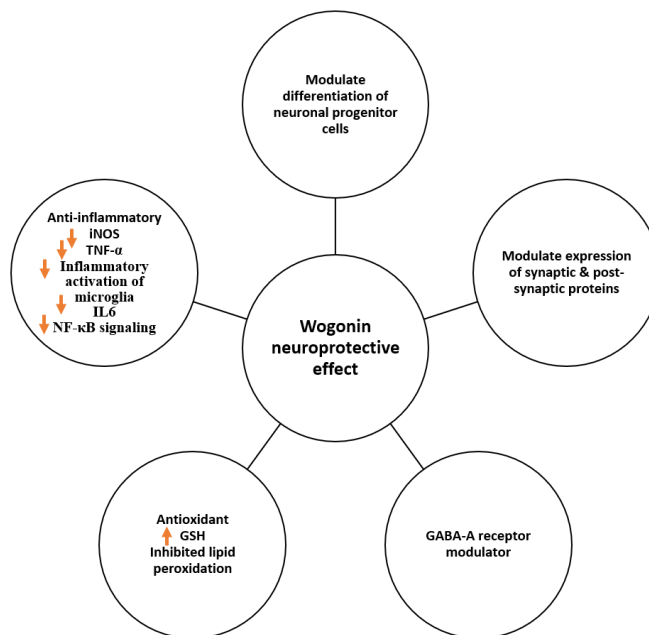


Fig. 3. The schematic diagram for the mechanisms of wogonin's neuroprotective effects

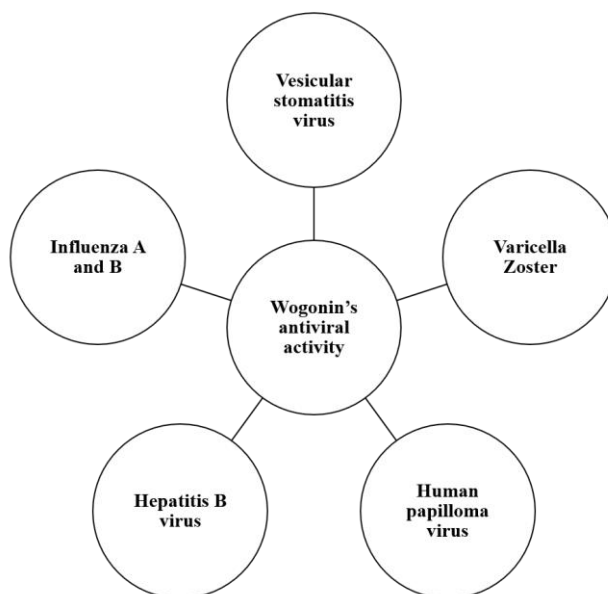


Fig. 4. Wogonin exhibits a broad-spectrum antiviral activity

Wogonin counteracted the increase in serum osteopontin levels and downregulated osteopontin expression in adipose tissue from type 1 diabetic mice induced by streptozotocin [46]. Moreover, wogonin upregulated PPAR α expression [46]. Furthermore, the levels of both c-Fos and phosphorylated c-Jun levels were reduced by wogonin treatment in adipose tissue and *in vitro* in 3T3-L1 adipocytes [47]. Molecular docking study showed that wogonin had a promising antidiabetic activity *via* Glucose transporter type 4 (GLUT4) [48] as wogonin increased its signaling thus modulating the AKT/GLUT4 pathway [49]. Besides, wogonin significantly suppressed p38 MAPK phosphorylation [46]. PPAR α has been reported to negatively regulate osteopontin expression by negative intervention with c-Fos/c-Jun [50]. Based on the aforementioned studies we can conclude that wogonin has valuable actions on blood glucose level, insulin sensitivity, and lipid metabolism. Wogonin is a beneficial treatment for the management of several metabolic disorders including diabetes.

1.6. Antiviral Activity

Studies have shown that wogonin suppresses the replication of multiple viruses, such as vesicular stomatitis virus [51] and varicella-zoster virus [52] and human papillomavirus [53]. Wogonin had potent suppressive activity against HBV antigens secretion. Also, it proportionally downregulated the expression of HBV DNA. *In vivo* and *in vitro* studies showed that wogonin had a powerful anti-HBV activity [54]. The wogonin treatment effectively suppressed both influenza A and B virus replication in Madin-Darby Canine Kidney cells and human lung epithelial cells [3]. The potent anti-influenza activity of wogonin was mediated by the regulation of AMPK activation [3, 52]. The spectrum of wogonin's antiviral activities is summarized in **Fig. 4**.

Conclusion

Wogonin is a promising flavonoid derived from *Scutellaria baicalensis*. This review addresses the up-to-date studies about wogonin chemistry, pharmacokinetics, biological activities. As discussed above wogonin's anti-inflammatory and antioxidant activities are the main underlying mechanisms for its biological activities. However, until now there is a paucity of information regarding wogonin's genotoxic potential and safety profile on both the short term and the long term. Considering the translational potential of wogonin in fostering effective alternative therapeutic strategies, the elucidation of its safety profile warrants further investigations.

Declarations

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Ethics Approval and Consent to Participate:

Not applicable.

Consent to Publish:

All the authors approved the final manuscript and agreed on the publishing of the submitted work in the APS journal.

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Competing Interests:

The authors declare that there is no conflict of interest.

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The review idea was by M.F.T; the manuscript was drafted by M.H; All authors reviewed and approved the final manuscript.

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