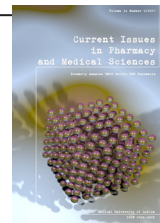


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# *Scutellaria baicalensis* – a small plant with large pro-health biological activities

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### ABSTRACT

*Scutellaria baicalensis*, known also as Huang-Qin is a traditional Chinese plant used in medicine for at least 2000 years. The plant is widely distributed in Japan, Korea, Mongolia and Russia, and is listed in Chinese Pharmacopoeia, European Pharmacopoeia and British Pharmacopoeia. The interest in Huang-Qin results from various biological activities which are primarily related to secondary plants metabolites consisting of flavonoids, phenolic compounds and terpenes. It is known that the compounds are active against numerous diseases and protect the organism against harmful pathogenic agents. Particular attention is paid to baicalein, wogonin and oroxylin A – which are characteristic secondary metabolites of the plant. In this paper, we focused on phytochemical analysis and selected biological activities used in periodontal and cardiovascular problems. The presented studies confirm the ability of Huang-Qin to scavenge free radicals, moreover, that it presents anti-bacterial, anti-inflammatory and enzyme inhibitory activities.

### INTRODUCTION

Herbal medicine is the raw or extracted products isolated from natural substances that have medicinal or life enhancing properties. In most cases, the substances are safer and less toxic than synthesized drugs and their pro-health properties significantly exceed side effects [1]. Today, scientists are focused on searching substances have effectiveness against cancer, neurodegeneration, viruses, especially SARS-CoV-2 and a lot of more. Nevertheless, such activity demands long and hard work involving a lot of people around the World.

Among the intensively studied plants is *Scutellaria*, a wide-spread genus commonly used in traditional Asiatic medicine. *Scutellaria baicalensis* belongs to the *Lamiaceae* family. It is a flowering plant with bitter taste and cold nature. The roots of the plant are widely used in traditional Chinese medicine, especially against viruses, microbials and inflammation [2,3]. Detail studies have revealed diverse biological activities which result from its rich composition of secondary plant metabolites (terpenes and flavonoids) [4]. In this paper, particular attention is paid to baicalin (C<sub>21</sub>H<sub>18</sub>O<sub>11</sub>; 7-D-glucuronic acid-5,6-dihydroxyflavone) derived from the roots of *Scutellaria baicalensis* Georgi. Detail analysis of the compound has indicated that it holds

antiviral, anti-tumor, anti-apoptotic, antioxidative, neuronal protective and anti-thrombotic properties [5-7]. Furthermore, recent, in-depth studies have demonstrated the significant biological activity of the plant, especially from derivatives from its stems and leaves, towards the protection of hippocampal neurons, which result in improvement in learning and memory, as well as reduction of oxidative damage [8].

This paper outlines the phytochemistry and biological activity of *Scutellaria baicalensis*.

#### Phytochemistry

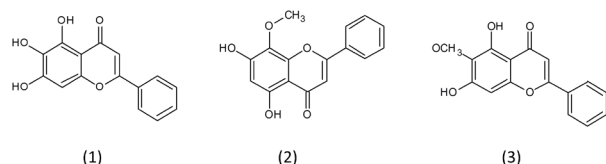
*Scutellaria baicalensis* is a plant rich in secondary plant metabolites. These can be classified into four types: free flavonoids, flavonoid glycosides, phenylethanoid glycosides and other small molecules such as steroids, diterpenes, amides and phenolic compounds. Polysaccharides are an additional group that can be found in the plant [9]. It is known that the main source of active compounds is found in the plant's root, whereas its aerial parts are less affluent [3].

Among the aforementioned flavonoids, which include flavones, flavonols, flavonones, flavonol, chalcone and biflavonoid, the most intensively studied are baicalein, wogonin and oroxylin A (Fig. 1) of these, baicalin, a flavonoid glycoside, is of the greatest abundance, and was the first pure compound reported from the plant. An equally interesting

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secondary metabolite is wogonin – which was the first free-flavonoid isolated from *Scutellaria baicalensis* [3]



**Figure 1.** Structures of baicalein (1), wogonin (2) and oroxylin A (3), the most intensively studied secondary plant metabolites of *Scutellaria baicalensis*.

**Table 1.** Selected compounds identified in root and aerial parts of *Scutellaria baicalensis*

Name	Plant part	References
Free flavonoids		
baicalein	root, hairy root	[10], [11]
Scutellarein	root	[10]
Oroxylin A	root	[11]
Tenaxin II (5,7,2'-Trihydroxy-6-methoxyflavone)	root	[12]
5,7,4'-Trihydroxy-6-methoxyflavone	aerial part	[9]
5,7-Dihydroxy-6,8-dimethoxyflavone	root	[13]
Chrysin (5,7-Dihydroxyflavone)	root	[14]
Norwogonin (5,7,8-Trihydroxyflavone)	root	[12]
Apigenin (5,7,4'-Trihydroxyflavone)	root	[13]
Wogonin (5,7-Dihydroxy-8-methoxyflavone)	root	[9]
Scutevulin (5,7,2'-Trihydroxy-8-methoxyflavone)	root	[15]
5,7-Dihydroxy-8,2',3',6'-tetramethoxyflavone	root	[16]
Genkwanin (5,4'-Dihydroxy-7-methoxyflavone)	aerial part	[17]
Flavonoid glycosides		
Apigenin 7-O-β-D-glucoside	aerial part	[9]
Baicalein 7-O-β-D-glucoside	root	[15]
Oroxylin A 7-O-β-D-glucoside	aerial part	[9]
5,6'-Dihydroxy-7,8-dimethoxyflavone 2'-O-β-D-glucoside	root	[18]
Wogonin 5-O-β-D-glucoside	root	[19]
3,5,7,6'-Tetrahydroxyflavone 2'-O-β-D-glucoside	root	[18]
Kaempferol 3-O-β-D-glucoside	aerial part	[20]
Wogonoside (Wogonin 7-O-β-D-glucuronide)	root, hairy root	[21]
Apigenin 7-O-β-D-glucuronide	aerial part	[20]
Chrysin 8-C-β-D-glucoside	root	[18]
Phenylethanoid glycosides		
Darendoside B	root	[18]
Acteoside	hairy root	[22]
Isomartynoside	root	[23]
Leucosceptoside A	hairy root	[23]
Cistanoside D	root	[24]
Others		
Stigmasterol	root	[13]
β-Sitosterol	root	[25]
Pellitorine	root	[26]
Benzoic acid	root	[25]
Vanillin	root	[27]

## Antioxidant activity

The most characteristic compounds of *Scutellaria baicalensis* are baicalein, baicalin and scutellarin. These are responsible for a variety of biological-medicinal activities, including antioxidant and free radical scavenging. Studies demonstrating the effectiveness of these compounds on free radicals are listed in Table 2.

**Table 2.** Antioxidant activity of baicalein, baicalin and scutellarin

Compound	Studies confirming antioxidant activities	References
baicalein	Prevention of diabetes-related periodontal tissue destruction by regulation of the Nrf2 signaling pathway	[28]
	Determination of antioxidant activity of baicalein-p-sulfonatoacalix[n]arenes inclusion complexes	[29]
	Determination of beneficial effect of oral administration of flavone baicalein in streptozotocin-nicotinamide-induced diabetic rats by measuring oxidative stress markers, antioxidant enzyme activities and expression analysis of antioxidant genes	[30]
	Protective mechanism of the antioxidant baicalein toward hydroxyl radical-treated bone marrow-derived mesenchymal stem cells	[31]
baicalin	Studies towards baicalin suppression of apoptosis, reactive oxygen species (ROS) generation, NO production, foam cell formation, protein expression of inducible nitric oxide synthase and cyclooxygenase-2 in MØ-MP-induced RAW264	[32]
	Enhancement of antioxidant activity of the inclusion complexes of baicalin with p-sulfonatoacalix[n]arenes	[33]
	Antioxidant activity against superoxide and peroxy radical of baicalin and its oxidovanadium(IV) complex	[34]
scutellarin	Dual effect of glucuronidation of a pyrogallol-type phytophenol antioxidant	[35]
	Investigation of the effects of Sc on IR and oxidative stress and explored the underlying mechanisms of action <i>in vivo</i> and <i>in vitro</i>	[36]
	Examination of the effects of scutellarin on oxidative stress-induced vascular endothelial dysfunction and endothelial cell damage	[37]

The harmful activity of free radicals leads to numerous disorders such as cancer, neurodegeneration or tissue damage. One of several possible antioxidant mechanisms of *Scutellaria baicalensis*-based medicinals is based on NO production-inhibition. Studies performed towards the activity of compounds isolated from MeOH extracts of *Scutellaria baicalensis* have revealed that three contained show inhibition levels above 83% [38]. Another study, based on EtOH extract of the plant confirmed the contained antioxidant activity by demonstrating its ability to scavenge DPPH. The obtained results were correlated with the amount of total polyphenol content, and this correlation demonstrated significant values in the relationship between the investigated phenolic compounds and the reducing power of the plant's extracts [39]. Similar activity was observed for baicalein, baicalin and scutellarin when analyzed via DPPH, ABTS and CAA assays. The three flavonoids made contributions of 58.33%, 60.36% and 51.41% (respectively) to the overall antioxidant activity of a flavonoid-rich extract [40]. Of note, a study of the comparison of the antioxidant activity of extracts obtained from root, leaf, stem and flower performed by Seo *et al.* revealed high antioxidant activity for all used methods (DPPH, ABTS and RP), nevertheless, the highest activity was observed for root, followed by leaf, stem and flower [41].

Beside *in vitro* studies, antioxidant activity was also evaluated in *in vivo* conditions. For example, Peng *et al.* [42] performed an assay based on mice bearing U14 cervical cancers. Here, the researchers observed an increase in activity of SOD and a decrease in MDA level. This outcome demonstrated the significant antioxidant activity of *S. baicalensis* extract and revealed that the plant's extracts can be considered as potential inhibitors of tumor growth. Confirmation of the effect resulted from studies performed with use of D-galactose and NaNO<sub>2</sub>-injected mice. In this case, high dose of extract (100 mg/kg) showed significant influence on SOD, catalase activities and MDA levels [43].

### Influence on periodontal tissues

Due to its biological activities, derivatives of *S. baicalensis* have been investigated for their usefulness in various branches of pharmacy and medicine. For example, in dentistry, extracts of the plant are applicable due to their high antioxidant, antibacterial, protective and anti-inflammatory activities. A significant source of periodontal problems is the oral bacteria that is present in dental plaque. The pathogenic bacteria activate immunological cells that produce various mediators and effectors of tissues breakdown [44]. One possible way to counteract the problem is antibacterial therapy. Currently, numerous toothpastes and mouth rinse are rich in natural herbal ingredients. Among these are derivatives of *S. baicalensis*, as these have revealed anti-bacterial effect on oral pathogens. The studies performed by Leung *et al.*, for example, aimed at encapsulating *S. baicalensis* with chlorhexidine. The resulting nanoparticles revealed a synergistic effect against mixed oral bacterial biofilms [45].

Baicalin, one of the secondary metabolite of *S. baicalensis*, has important influences upon periodontal tissues, and numerous animal studies have shown the positive impact of the compound on periodontitis. The periodontal ligament cells (PDLC) are the main cells of the periodontal ligament. Cao *et al.* [46] focused on type I collagen and the effect of baicalin upon these, particularly, the expression of type I collagen mRNA in PDLC. They noted a positive effect. In Li *et al.* [47] investigation of the activity of baicalin towards periodontitis lesions, baicalin turned out to be active towards reducing the number of osteoclasts increased by LPS. The positive influence of baicalin was also recorded in the synthesis of collagen, while baicalin exhibited a prominent impact on the process, as well as on the synthesis of total protein from human gingival fibroblasts. This activity is connected with the inhibitory impact of the secondary metabolites on collagenase – which is able to destroy collagen tissue [48].

Additionally, the positive effect of baicalin application was observed towards pro-inflammatory mediators. It is known that one of possible way of treating chronic inflammation is down-regulation of over-expressed TNF- $\alpha$  and IL-1 $\beta$ , both of which are responsible for activating NF- $\kappa$ B [49]. Another important enzyme linked with inflammation is cyclooxygenase-2 (COX-2). In the case of periodontal disease, the problem could be resolved by inhibiting the enzyme. The issue was considered by Cai *et al.* [50], whose studies revealed the positive influence of baicalin on up-regulation of COX-2 protein expression in macrophages,

plasma cells, fibroblasts and gingival tissues in an animal model of ligature-induced periodontitis. Considering periodontal disease, attention should be also paid to cyclooxygenase, nitrogen metabolites, reactive oxygen and cytokines. Here, by means of baicalin application, iNOS, an inducible nitric oxide synthase responsible for overproduction of nitric oxide in periodontitis, inhibition was observed [50].

### Cardiovascular and cerebrovascular diseases

It has been demonstrated that the *Scutellaria baicalensis* can influence the course of cardiovascular and cerebrovascular diseases [3]. Factors involved in the pathogenesis of many cardiovascular diseases include abnormal mitochondrial fission and mitophagy. Baicalein inhibits mitochondrial apoptosis induced by oxidative stress in cardiomyocytes by stabilizing MARCH5 expression. In addition, it may counteract cardiotoxicity. One of the mechanisms of such action is the inhibition of mitochondrial apoptosis induced by oxidative stress in cardiomyocytes by stabilizing MARCH5 expression. Overexpressed MARCH5 reduces apoptosis of myocardial cells by countervailing oxidative stress as well as ischaemia and reperfusion [51].

Source data indicate that baicalein has antiatherosclerotic properties, such as macrophage lipid regulation [52]. Accordingly, *Scutellaria baicalensis* Georgi extract (containing baicalin, baicalein and wogonin) has demonstrated antioxidant and anti-inflammatory properties against macrophages. It has also been shown that it inhibited the Cu<sup>2+</sup> – induced oxidation of LDL, the expression of NO generation and inducible NO synthase, and exhibited an anti-inflammatory property partly via the induction of HO<sup>-1</sup> [53].

Tissue factor (TF) is the most common cause of arteriosclerotic thrombosis, and plaque atherosclerotic rupture, followed by thrombosis. TF can cause a heart attack or stroke. Wogonin is a biologically active compound that is active in countering the effects of inflammatory diseases, atherosclerosis and hyperlipidemia. Wogonin is known to affect TF expression. In addition, Wogonin acts as an anticoagulant on the basis of various mechanisms of action. For example, it dose dependently inhibits mRNA, protein and PMA-enhanced TF activity at EC. This inhibition was attributed to the decreasing nuclear accumulation of transcription factors phospho-c-Jun and early growth-1 (Egr-1) responses. Furthermore, it showed anticoagulant activity by inhibiting TF expression and activity in tumor necrosis factor-alpha (TNF- $\alpha$ ) – and lipopolysaccharide (LPS) -treated ECs and THP-1 cells. It is also possible that wogonin limits the transactivation of TF promoter activity, leading to regulation of TF expression and activity induced by inflammatory mediators [54].

Diabetes mellitus initiates many metabolic disorders in various tissues and organs, including the cardiovascular system. Such disorders can lead to heart failure, even in the absence of ischemic heart disease. This is known as ‘diabetic cardiomyopathy’. Research on the effectiveness of wogonin in controlling diabetic cardiomyopathy is ongoing [55].

Wang *et al.* [56] investigated the effect of baicalin on hyperglycemia-induced cardiovascular malformations during embryonic development. For this purpose, they used early chicken embryos – they estimated the optimal

concentration of baicalin for preventing these defects as 6  $\mu$ M. This research indicated that Baicalin reduced hyperglycemia-induced cell apoptosis, inhibited excessive ROS (reactive oxygen species) production, as well as regulated SOD (superoxide dismutase), d GSH-Px (glutathione peroxidase) and GABAA (c-aminobutyric acid) levels [56].

Inflammatory processes are an important aspect in the pathogenesis of different heart diseases such as myocardial fibrosis, atherosclerosis and myocardial depression. BNP (brain natriuretic peptide) level is considered as a diagnostic marker of hypertrophy and heart failure. An experiment in an animal model with spontaneously hypertension (rats) has shown that baicalein (200 mg/kg/day, intraperitoneally) protects myocardial fibrosis by significantly reducing collagen deposition in left ventricular tissue. Moreover, its administration alleviated elevated systolic blood pressure and BNP levels in plasma by suppressing the expression of 12-LOX, p-ERK and MMP-9 in heart tissue. In addition, there was a decrease in the thickness of the interventricular septum and the body weight/heart ratio. The anti-fibrotic effect of baicalein in the experiment was compared to that of valsartan at a dose of 20 mg/kg/day [57].

## CONCLUSION

*S. baicalensis* is a well-known and commonly used plant in Chinese traditional medicine. The various recognized biological activities have encourage the dissemination of the plant into European medicine and pharmacy. Phytochemical analysis has revealed that it contains various secondary plant metabolites that are active against numerous factors leading to diseases such as neurodegenerations, cardiovascular and cerebrovascular or periodontal problems. We can, therefore, observe an increase in interest in the potential use of *S. baicalensis*, as well as its inclusion in more and more natural medicaments and cosmetics. What is more, the multi-directional activity of Huang-Qin has given hope that it can be active against neurodegeneration or cancer.

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## CONFLICTS OF INTEREST

Authors of this work have no conflicts of interest.

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