The Golden Root: Clinical Applications of *Scutellaria baicalensis GEORGI* flavonoids as Modulators of the Inflammatory Response

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Abstract:

Scutellaria baicalensis GEORGI has been used to treat inflammatory-related disorders in China and Japan for centuries. The plant root has a particularly high flavonoid content, over 35 percent, giving it a yellow color, and its traditional name of golden root. These flavonoids selectively inhibit enzymes in the arachidonic acid cascade, in particular lipoxygenases, as well as possessing antioxidant, antiviral, antiretroviral, antitumor, antibacterial, and sedative properties. Scutellaria is used in traditional Chinese medicine to "cleanse heat," "dry moisture," and "remove toxins."
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Introduction

Cultural exchange has contributed greatly to the development of ideas and technologies throughout history, and medicine is no exception. The West has much to learn in this respect, and has barely begun to scientifically examine the traditional use of botanical medicines from other cultures. In particular, Traditional Chinese Medicine (TCM) has developed in a culture with a rich history of thousands of years of botanical use. Now, bus shelters everywhere carry advertisements for Tiger Balm, and ginseng gum shares shelf space with the likes of beef jerky and chocolate bars at the gas station candy counter. Chinese and Japanese scientists have been closely investigating many of their traditionally used botanicals. The West, however, is only beginning to appreciate and understand TCM, and little is known of the clinical applications of even the most common of Chinese herbs, one of which is *Scutellaria baicalensis GEORGI* .[1] Baical or Chinese skullcap, as it is also known, has a very high flavonoid content,[2] and it is not surprising that the active components most studied are all flavonoids. Currently, Scutellaria's flavonoids are receiving scientific attention as modifiers of inflammatory processes, as well as for antiviral, antiretroviral, antitumor, and antibacterial properties.[3-6] While these studies are generally *in vitro* or on animals, much of the evidence supports the centuries of traditional use in China and Japan.

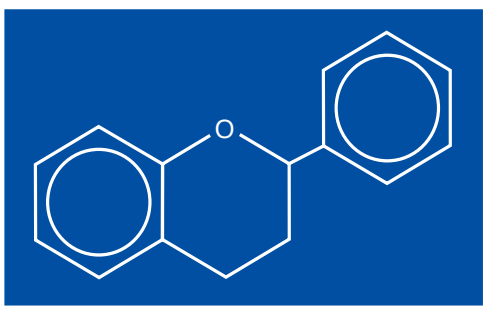
It is beyond the scope of this paper to address all of the actions of *Scutellaria baicalensis GEORGI*, and so, recognizing it is by no means the only important and useful application, this paper will focus on its use as a modulator of inflammation.

Constituents of Scutellaria

Scutellaria baicalensis GEORGI is known to the Chinese as Huang qin and the Japanese as Ogon. Huang qin is referred to in China as one of the "three cold brothers" and has traditionally been used to "cleanse heat," "dry moisture," and "remove toxins."[7] Conditions in which Huang qin is useful are caused by an excess of heat and moisture, and are characterized by symptoms such as fever, inability to sleep, and copious perspiration.[8] The patient may have a red face, a dislike of heat, feel better with cold, have a desire for cold drinks, and have an "outgoing nature."[9] In Western terms it has traditionally been used to treat inflammation, respiratory tract infections, diarrhea, dysentery, jaundice and liver disorders, hypertension, hemorrhage, and insomnia.[7,10]

Huang qin, literally translated, means yellow gold, describing the color of the plant's bitter root,[7] the part most often used traditionally. Interestingly, flavus, from which the word flavonoid is derived, itself means yellow.[11] The root of Huang qin is rich in flavonoids,[2] a class of botanically-derived molecules with a particular structural framework, as shown in Figure 1. There are many subcategories within this broad classification, and varying activities both within and between subcategories.

Figure 1. Structural framework of Huang qin flavonoids



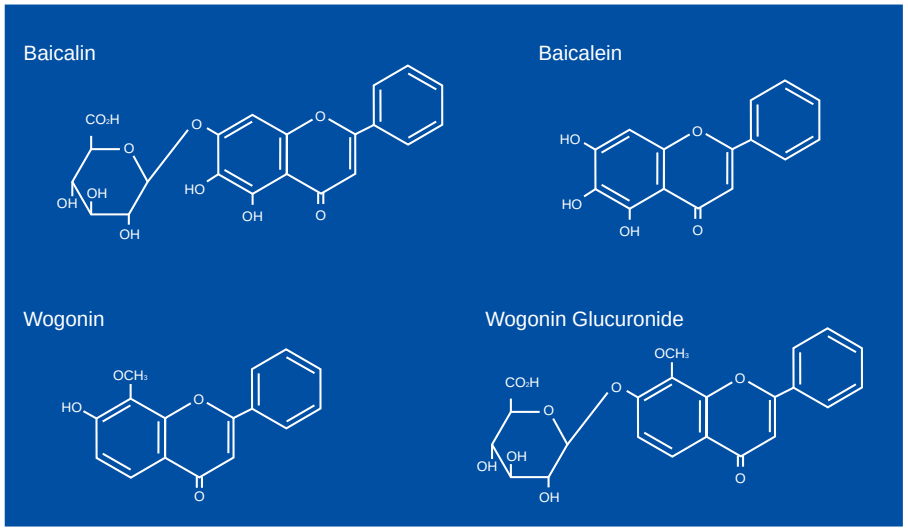
Biological activity relates to variations in the structure and substituent groups;[12] but, with a common backbone, flavonoids share many properties. Flavonoids are derived from plants where they have evolved as pigments and protective substances.[13] They have many actions in the plant, including as antimicrobial agents and strong antioxidants.[14] Their actions often relate to particular enzyme systems and environmental stresses, and can therefore be very selective. While flavonoids are not endogenous to animals, they have been promoted as having tissue specificity in humans.[15] Generally, flavonoids are nontoxic, and with universal distribution in vascular plants, are common constituents of the human diet.[16,17]

The most commonly studied flavonoids in *S. baicalensis GEORGI* include baicalin, baicalein, wogonin, and wogonside (Figure 2); and well over 35 others have been isolated. Baicalin, a flavone glycoside, is the predominant flavonoid, varying from 12-17 percent in the root, and can be extracted in 50 percent ethanol. On acid hydrolysis the corresponding aflavone baicalein and glucuronic acid are formed.18 Hot water extraction of *S. baicalensis* yields 26.2 percent baicalin, 9.9 percent wogonin glucuronide, 1.9 percent baicalein, and 0.2 percent wogonin.[2]

Flavonoid glycosides are hydrolyzed in the body by intestinal microflora.[19] A recent study examined the relationship of oral administration of a botanical formula containing Huang qin to plasma levels of baicalin and baicalein in humans. Baicalin was not detected in plasma, indicating it is not absorbed intact. However, plasma levels of the corresponding aglycone, baicalein, peaked twice: the first between two and four hours, and the second at 12 hours. The earlier peak is thought to be due to initial absorption of baicalein, and the second peak represents baicalein released from baicalin by intestinal microflora. By 24 hours baicalein was still detectable in plasma at approximately 3 µg/ml, down from an earlier peak level of 6 µg/ml.[20]

Flavonoid metabolites of *S. baicalensis GEORGI* are excreted in bile and urine. Those excreted in bile may enter the enterohepatic

Figure 2. Flavonoid compounds in Scutellaria.



circulation. This is therapeutically relevant because of increased exposure of metabolites to the enterohepatic system and for dosage determinations. Unhydrolyzed baicalin has been recovered in human urine 0.4 hours after IM injection,[18] demonstrating that at least some baicalin is excreted intact by the kidneys. Many tissue cells are able to metabolize flavonoids, and the liver is particularly active.[21] In animal models the intestinal wall and the kidney are also known sites of metabolism.[19] Flavonoids are not believed to accumulate in the body.[21] While studies are not yet published detailing the exact nature of these flavonoids in human metabolism, traditional use of this plant in some forms of liver disease[22] and as a diuretic[23] supports that, as in animals, the liver and kidneys are sites of their activity in humans.

Indicated Dosage

The average oral dose for Huang qin is 6-15 grams per day, according to Bensky[10] and Hsu,[7] while other sources advise a daily dose of 5-8 grams of the dried root.[24,25] For children less than two years old, Hsu recommends 1.5-5 grams per day.7 It can be administered as a hot water extract, in tablets, granules or as an alcohol extract. Tablets and solutions were found to yield a bioavailability of 22-36 percent, as opposed to IM injection which had a bioavailability of 89 percent but a short half life of 0.6 hours.[18] From the absorption experiment discussed previously,[20] Scutellaria appears to have a much longer half life when taken orally, although most flavonoids are generally considered to have relatively short half lives.[19,26] Clinical trials showed intramuscular injection of 150 mg of baicalin caused myalgia and fever, and administration of 27 mg of baicalin intravenously resulted in fever and a sudden decrease in white blood cell count in humans.[27] While oral doses at the stated levels appear safe, as with other flavonoids, TCM contraindications include any condition caused by excess cold or deficient heat,[10] characterized by symptoms including lack of energy, feeling cold, clear discharges, or night sweats.[8] Recently, two cases of pneumonitis have been recorded related to intake of Sho-saiko-to, an herbal formula containing *S. baicalensis GEORGI*; but the causative agents have not been isolated.[28,29]

Physiology of Inflammation

Like many plants with a substantial flavonoid content, Huang qin has many traditional uses, with one of its main applications being as an anti-inflammatory in "heat" conditions. Even from a Western perspective it is not difficult to see how inflammation can be characterized as hot and moist, with its associated heat and edema. In particular, traditional use has focused on its application in respiratory tract and epigastric disorders, and further research might demonstrate tissue specificity in these areas. While the plant is generally used in combination with other herbs, its high

flavonoid composition is proving to be active in modulating the inflammatory process, according to scientific studies supporting traditional use.

Inflammation, the means by which our bodies deal with insult/injury, is a very delicate and not fully understood communication between cellular and humoral elements in which the vascular system is integral to ultimate containment of the injury and to destruction of the offending stimulus as required. Inflammation is necessary, and yet it is not always benign. Vasoconstriction can lead to ischemic injury; vasodilation can result in increased local blood flow and reperfusion injury; increased vascular permeability can lead to excess fluid in the tissue space; and migration and activation of leukocytes can damage healthy tissues. Otherwise healthy cells can be injured by free radicals and enzymes generated in the inflammatory process itself, as well as by alterations in the interstitial fluid and vascular flow. Cells actively involved are primarily endothelial cells, white blood cells and resident phagoctyes, and platelets. Various biochemical mediators take part, some of which activate cells, and some which are, in turn, products of this activation. Notable among these biochemical mediators are the metabolites of the arachidonic acid cascade. Free radicals are generated during inflammation in the arachidonic cascade itself, by activated leukocytes, and by the inflammatory stimulus.[30] There is considerable evidence that *S. baicalensis* flavonoids are effective at the level of enzymes in arachidonic acid metabolism, as well as in leukocyte migration and activation, free radical scavenging, and the prevention of lipid peroxidation.

Anti-inflammatory Mechanisms of Scutellaria

A major inflammation-modulating action of *S. baicalensis GEORGI* is via its effects on lipoxygenase in arachidonic acid metabolism. Arachidonic acid, which is esterified in membrane phospholipids,[30] is released in the initial stages of inflammation, generally in response to mediators from activated platelets.[31] Platelets themselves are activated by contact with substances relating to the initial injury such as collagen, thrombin, and bradykinin.[32] Some flavonoids, at high concentrations, directly inhibit the enzyme phospholipase A2, which releases esterified arachidonic acid,[33] but it is not known if Huang qin shares this ability. Free arachidonic acid is broken down by either lipoxygenase or cyclooxygenase, forming metabolites with varying roles in inflammation. In leukocytes, 5-lipoxygenase leads to the formation of leukotrienes via 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), a strong chemotactic agent for neutrophils and leukotriene B4 (LTB4), which is a powerful attractor and activator of neutrophils.[34] Platelets utilize 12-lipoxygenase to produce 12-HPETE, an inhibitor of platelet aggregation,[35] and other inflammatory metabolites. Baicalein selectively inhibits lipoxygenase, and the whole herb shows limited inhibitory effects on cycloxygenase.[36]

Animal studies confirm the traditional use of Huang qin to reduce local inflammation. Oral doses of a 70 percent root extract and isolated constituents bacalein, baicalin, and wogonin have been shown to dose-dependently inhibit acetic acid-induced vascular permeability in mice. The whole plant, and both baicalin and baicalein also decreased edema produced by carrageenan injection, while wogonin had no effect.[37] A later study looking specifically at bacalein confirmed oral baicalein dose-dependently inhibited carrageenan-induced rat paw edema to a maximum of 45 percent inhibition at 200 mg/kg.[38] Granulomatous inflammation induced by subcutaneous implantation of cotton pellets in mice was not prevented at oral levels tested—500 mg/kg of 70 percent methanol root extract and

100 mg/kg each of baicalin, baicalein, and wogonin.[37] Granulomatous inflammation is a result of cell-mediated immunity,[30] which suggests Huang qin is ineffective against this type of inflammation.

Bone destruction in chronic arthritis, induced by injection of adjuvant *Mycobacterium butyricum*, was decreased in rats given oral daily doses of 70 percent methanol root extract, as well as the isolated flavonoids baicalein, baicalin, and wogonin, when compared to controls.[37] Baicalein's effect in reducing chronic inflammation in this model was later confirmed, and an increased weight gain in rats given baicalein versus other test substances was taken as a reflection of baicalein's lack of toxicity. This later report also examined dose-dependent inhibition of LTC4 production by rat peritoneal macrophages *in vitro*, and demonstrated up to 75 percent inhibition at a concentration of 100 μM baicalein. Since LTC4 is produced via the 5-lipoxygenase pathway, the researchers concluded baicalein blocks 5-lipoxygenase and the resultant formation of proinflammatory LTC4 and possibly LTB4.[38]

Yasuo et al examined LTB4 production in human alveolar macrophages isolated from patients with various respiratory conditions, including bronchial asthma, chronic bronchitis, lung cancer, sarcoidosis, and idiopathic pulmonary fibrosis. Baicalein dose-dependently inhibited production of LTB4. At 1 μM, LTB4 synthesis was inhibited by 40 percent, and at 100 μM baicalein inhibited LTB4 synthesis by 80 percent, confirming this as one of the anti-inflammatory mechanisms of Huang qin.[34] Inhibitors appear to act via free radical scavenging, as a catechol structure appears necessary,[39,40] but the exact method of inhibition is still under study.

Baicalein inhibited chemiluminescence, a measure of oxygen radical production, in human alveolar macrophages, without cytotoxicity, at concentrations as high as 100 M baicalein.[34] Reactive oxygen species and other free radicals damage proteins, nucleic acid, and lipids.[30] When free radicals initiate lipid peroxidation, they damage cell membranes and organelles, and lead to further release of peroxides which in turn act as free radicals. A hot water extract of the root inhibited lipid peroxidation *in vitro* in a rat model,[41] and baicalin inhibited lipid peroxidation in rat brain homogenate almost three times more than the flavonoid quercetin, and almost 375 times more than vitamin E, both known inhibitors of lipid peroxidation.[42] Furthermore, testing with a stable free radical, 1-diphenyl-2-picrylhydrazyl (DPPH), showed baicalein to be a more potent free radical scavenger *in vitro* than vitamin E, though slightly less potent than quercetin.[42] This strong *in vitro* free radical scavenging ability was confirmed in an experiment showing DPPH and superoxide radicals similarly inhibited at baicalein concentrations of 4.4 μM and 50 μM, respectively. Baicalein only weakly inhibited hydroxyl radicals *in vitro*, but further experimentation on rats led Hamada to conclude baicalein quenches superoxide, hydroxyl, and other radicals generated by FeCl3 injection.[43]

Free radical scavenging is not the only anti-inflammatory mechanism by which *S. baicalensis* inhibits lipid peroxidation. 12-O-tetradecanoylphorbol-13-acetate (TPA) activates phospholipase A2, and thus initiates the arachidonic acid cascade. In TPA-induced mouse ear edema, baicalein was almost as effective as quercetin in reducing edema. There was also a histological decrease in edema and neutrophil infiltration in test subjects versus controls, confirming *in vivo* inhibition of leukocyte migration and reduction of edema.[42]

Another flavonoid from *S. baicalensis*, wogonin, has no DPPH scavenging ability, and thus appears only to block enzyme-induced lipid peroxidation, as opposed to non-enzymatic induction. Wogonin inhibited

the activity of cytochrome P-450 reductase and the resultant formation of Fe^{2+}, a free radical initiator.[44] An earlier experiment by Miyahara confirmed this action, and determined baicalein and baicalin are the active components inhibiting iron-induced lipid peroxidation in rat mitochondria and microsomes.[45]

Indirectly, Huang qin modulates inflammation by modifing the inflammatory stimulus itself. Broad spectrum antimicrobial activities of *S. baicalensis* can decrease initial stimuli in infective processes by direct disruption of metabolism and destruction of infectious agents, including many viruses, retroviruses, bacteria, and fungi.[3,46-49]

Research on adaptogenic properties of S. *baicalensis* raises interesting questions. In stressed rats most hormonal parameters measured, including ACTH, insulin, urea, and glucose were normalized by administration of either the whole plant or baicalin.[50] This is an intriguing observation and follow-up research would be useful to determine its relationship to the inflammatory process in humans. Inflammation and the resulting pain and decrease in function are stressful in themselves, and if Huang qin proves to be effective on this axis, it would indeed be a useful addition to an anti-inflammatory protocol. Scutalleria's properties as a sedative[10] may also enable patients to better cope with inflammatory conditions.

Other research suggests additional mechanisms by which Huang qin modulates inflammation. Beta glucuronidase is a lysosomal enzyme released by activated neutrophils which can potentially damage healthy tissue.[14] The glucuronide baicalin inhibits *E. coli* beta glucuronidase directly.[51] Quercetin has been shown to inhibit beta-glucuronidase release from human neutrophils,[34] but it is not yet determined if Huang qin shares this ability. Baicalein, at 10 μM inhibited xanthine oxidase by 64 percent *in vitro,* while the standard gout medication allopurinol showed 43 percent inhibition at this concentration; therefore, Huang qin could be useful in inflammation due to gout.[52] Baicalin inhibits thromboxane synthetase *in vitro,*[53] and might inhibit vasoconstriction and leukocyte migration[54] caused by the product thromboxane. Baicalein inhibits platelet aggregation[18] which could relate to platelet activation and initiation of inflammation. The inflammatory process itself is not entirely understood, and as it is clarified, the implications of these effects will be elucidated.

Other Actions of Scutellaria

In addition to its general anti-inflammatory properties, *S. baicalensis* demonstrates activities which can affect specific conditions. Baicalein inhibits type I and II hypersensitivity reactions, confirming its traditional use in asthma[55] and allergic dermatitis.[18] *In vitro* evidence indicates baicalin stimulates recombination and repair of damaged DNA,[56] supporting its traditional inclusion in cancer formulas, and suggesting possible use in sunburn and radiation damage. Arachidonic acid metabolites play a part in hypertension as well as inflammation; and, via its effect on arachidonic metabolism, baicalein has been shown to promote vasodilation, reducing blood pressure.[57,58] *S. baicalensis* flavonoids have received attention lately for their inhibition of reverse transcriptase and a strong *in vitro* inhibition of HIV infection.[19] Apparently, without being toxic to host cells,[5] these flavonoids are most active in earlier stages of infection, although their clinical use is being evaluated.[59] Huang qin has demonstrated inhibition of many viruses,[46-48,60] and has traditionally been used to treat acute febrile and inflammatory disease. Huang qin flavonoids have also been proven to be strong anti-coagulants,[61] opening future possibilities for clinical applications in this area. Although it has a long tradition of use, and studies detailing the efficacy of TCM formulations exist, scientific efficacy is yet to be determined

for clinical use of the isolated herb in particular conditions. In fact, as more is known, it may be shown to work best in individualized combinations, following traditional use.

Conclusion

Because *Scutellaria baicalensis* is high in active flavonoids, and because flavonoids have many functions, there are far reaching implications for clinical application. Scientific evidence to date confirms the traditional use of Huang qin as an inflammatory modulator, and begins to explain the mechanism of action. There are many questions not yet answered, and efficacy studies are much needed. However, despite the incomplete research base, its wide range of known actions and low toxicity make Huang qin a useful consideration in anti-inflammatory protocols. As our understanding of medicinal uses of flavonoids, particularly the flavonoids of Scutell*aria baicalensis*, grows, this plant may find a valued place in Western clinical botanical practice.

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