REVIEW ARTICLE

CAN BAICALEIN BECOME A NEW DRUG FOR COVID-19?

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Summary

The ongoing coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global health crisis. Flavon baicalein, a major bioactive molecule of *Scutellaria baicalensis*, inhibits the replication of SARS-CoV-2 which causes severe acute respiratory syndrome in humans. Animal experiments show that baicalein has the character of a broad-spectrum coronavirus drug. It is non-toxic and can inhibit SARS-CoV-2-induced damage. Baicalein may therefore be a promising therapeutic drug for the treatment of COVID-19.

Key words: Baicalein and baicalin; *Scutellaria baicalensis*; antiviral activity; SARS-CoV-2; COVID-19

Introduction

A new type of coronavirus SARS-CoV-2 (1), which appeared in Wuchan, China in 2019, rapidly infected people around the world and caused a global pandemic (2). Every day in the public media, we are informed about the number of infected people in each country, the number of cases worldwide and the number of deaths. At the same time, methods for coronavirus testing are being intensively sought and new drugs are being developed. Much progress has been made in the development of new vaccines (3–5), but new drugs are also being sought which are easier and cheaper to administer than vaccines (6). New drugs for COVID-19 infection are sought both among known drugs that have already been approved for other diagnoses and among newly discovered ones. Of these newly discovered drugs, a large number are natural compounds, especially phytochemicals (7). High hopes are placed especially in flavonoids (8) because flavonoids are the bioactive compounds obtained from plants with a broad spectrum medicinal properties. Among the flavonoids baicalein (flavone-anthoxanthins subgroup) is one of them.

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Information about baicalein

Chemistry of baicalein

Baicalein (IUPAC name: 5,6,7-trihydroxy-2-phenyl-chromen-4-one; chemical formula: C_{15}H_{10}O_{5}; molar mass: 270.24 g/mol; CAS number: 491-67-8) is a yellow powder compound, sparingly soluble in water, but the solubility can be increased by the addition of ethanol (9). Structurally belongs to flavones (Figure 1), the backbone of baicalein is based upon a fifteen-carbon skeleton that consists of two benzene rings (designated as ring A and B) linked via heterocyclic γ-pyrone ring (ring C) (10).

Sources of baicalein and related compounds

Natural flavone, baicalein is a bioactive compound which was first isolated from the roots of *Scutellaria baicalensis* Georgi (Baikal/Chinese skullcap) and *Scutellaria lateriflora* L. (American skullcap), flowering plants in the family Lamiaceae. However, it is also present in leaves of *Thymus vulgaris* L. (common thyme) as well as in *Oroxylum indicum* (L.) Kurz (Indian trumpet flower) (11).

Flavones are important bioactive compounds that are widely distributed in terrestrial plants. Baicalein and its glycoside baicalin along with wogonin and glycoside wogonoside, are the major biologically active ingredient of the medicinal plant *Scutellaria baicalensis* (Figure 2). These flavones have a wide-number of pharmacological activities (12) and have been extensively studied in recent years (13–16), including their possible use as COVID-19 drugs (17).

Figure 1. Structure of baicalein (left) with carbon numbering according to the IUPAC (blue numbers) and backbone structure of flavones (right) with highlighted ring designation (green letters).

Figure 2. Structures of baicalein, its glycoside baicalin, wogonin and its glycoside wogonoside.
Folk use of Scutellaria baicalensis

The first description of *Scutellaria baicalensis* in China was recorded as early as the Western Zhou Dynasty (1045 BC – 771 BC). The first therapeutic application of the plant is recorded in “Shen Nong Ben Cao Jing”, the earliest existing traditional Chinese medicine book, from the Han Dynasty period (206 BC – 220 AD) (18).

Even today, baicalein and baicalin are important components of the traditional Chinese medicine “Shuang Huang Lian” (SHL) which, in addition to the root of the *Scutellaria baicalensis*, also contains the flower of the *Lonicera japonica* Thunb. (Japanese honeysuckle) and the fruits of the *Forsythia suspensa* (Thunb.) Vahl. (forsythia). The SHL, a commercial antimicrobial formulation is used for the treatment of acute bronchitis, acute upper respiratory tract infection, light pneumonia caused by bacteria/viruses and other illnesses (19). The SHL is also applied to treat acute bronchitis, light pneumonia, and bronchial asthma. In addition, SHL injection is used in the treatment of acute upper respiratory tract infections, various respiratory illnesses caused by different bacteria or viruses with typical symptoms such as headache, cough, sneezing, runny nose, sore throat and others. According to several studies, SHL injections bear potential to relieve some of the typical symptoms like sore throat, cough and can reduce development of the disease (20). In addition, another Chinese herbal medicine “Sho-saiko-to” (SST) is prepared form dried extracts of seven herbs: the root of *Bupleurum falcatum* L., the tuber of *Pinellia ternata* (Thunb.) Breit, the root of *Scutellaria baicalensis*, the fruit of *Ziziphus jujuba* Mill., the root of *Panax ginseng* C. A. Meyer, the root of *Glycyrrhiza* (G. uralenis Fisch. ex DC., G. inflata Batalin or G. globra L.) and the rhizome of *Zingiber officinale* Roscoe. Ethanol extracts of SST were analyzed to evaluate the major active ingredients of the medicine. Approximate concentrations of three major active compounds in the ethanol extracts were determined as follows: 3.5% of baicalin, 1% of glycyrrhizin, and 0.3% of baicalein (21,22). The SST has been used for a long time in the treatment of several inflammatory diseases of the respiratory system (23). Indeed, *Scutellaria baicalensis* has a long tradition in folk treatment of respiratory diseases. In China, the lung-heat syndrome that involves various conditions including cough, breathlessness, hot feeling, etc. was for a long time treated by *Scutellaria baicalensis* (24). Several respiratory infections have been treated by classical prescriptions involving *Scutellaria baicalensis* (18). These beneficial applications of the plant in the folk medicine for treatment of respiratory diseases have also been proved in the modern studies (24). According to the modern studies, baicalein, the constituent of *Scutellaria baicalensis* bears a significant potential to treat respiratory diseases. It has potential to improve respiratory functions as well to inhibit respiratory inflammations. Its antiviral activity against influenza A virus represents a new hope in the fight against respiratory viruses such as SARS-CoV-2 (25).

Biological activities of baicalein

Baicalein itself exhibits interesting biological activities including anti-inflammatory, antioxidative effects, ability to protect against cytotoxicity induced by oxidative stress, beneficial effects in the cardiovascular system. This natural flavone has also been proposed as a neuroprotectant and a suitable candidate for the neurodegenerative diseases treatment such as Alzheimer’s and Parkinson's diseases. An anxiolytic-like effect of baicalein in the elevated plus-maze has been reported (26). In addition, antiviral properties as well as a significant anti-cancer effect against various types of cancer were reported. The anticancer potential of baicalein involves several mechanism of action and its influence on the different signaling pathways (27).

Pharmacokinetics of baicalein and baicalin

**Absorption:** the experiments performed in rats revealed that baicalin was moderately absorbed in the stomach and poorly absorbed from the small intestine and colonic regions. In contrast, baicalein was good absorbed from the stomach and the small intestine, however its absorption from the colon was relatively lower. Therefore, baicalein is more suitable to be administered orally than baicalin. In addition, baicalin is hydrolyzed by bacteria in the intestine to baicalein and after absorption restored to its original form - baicalin, in the body. Subsequently, baicalein formed in the body from absorbed (or intravenously administered) baicalin can be excreted back into the gastrointestinal tract (28,29). **Distribution:** sustained presence of baicalin levels as a result of absorption dynamics may be considered as a significant distribution phenomenon. The protein binding of baicalin in human plasma was in vitro shown to range from 86% to 92%. This suggesting that the drug displacement from plasma protein binding site by the co-administered baicalin may not be an issue (28). The pharmacokinetics investigation of baicalin and baicalein in tumor-bearing mice revealed high concentrations of baicalin in the heart and lung.
tissues, whereas its concentration in the tumor tissues was higher than in kidneys and liver (30). **Metabolism:** after oral administration of baicalein in rats, two main types of metabolites were detected in plasma, specifically glucuronides and sulfate conjugates. However, an intravenous administration of baicalein resulted in almost 76% conversion into the conjugated metabolites. An oral administration of baicalin resulted in detection of the intact baicalin in the systematic circulation, furthermore extensive levels of glucuronide and sulfate conjugates of baicalein were observed as well (28,31). **Excretion:** biliary excretion is the major route that brings the glucuronide and sulfate conjugates of baicalin back into the small intestine to undergo a hydrolytic cleavage mediated by intestinal β-glucuronidase (28,32). Akao et al. earlier reported that a major portion of baicalein administered orally is retained within the intestinal mucosal cells and transformed into baicalin (33). Generally, baicalein and baicalin are both mainly excreted through the bile excretion and fecal excretion (30).

In addition, Song et al. prepared different crystal forms of baicalein to improve its bioavailability (25). The character of crystal form affects not only physical and chemical properties, but also a pharmacokinetic profile of the drug. The experimental data were compared by the authors with an absolute bioavailability of baicalein in rats that was previously reported to be 7.46%. The results revealed, that crystal form α of baicalein reached a comparable bioavailability (7.31%) as reported previously, whereas crystal form β of baicalein showed a significantly higher bioavailability (47.40%). The authors concluded, that the absorption of crystal form β was obviously improved (25).

The clinical trials of baicalein revealed its good tolerance. However, some adverse effects were observed in the group with a higher dose of baicalein such as abdominal distention, constipation, dizziness, hyperactive bowel sounds, somnolence, blurred vision, blood leukocyte decreased, plasma fibrinogen decreased. All of the side effects were rated as mild and resolved without any treatment. During the study, no clinically relevant changes in the blood pressure nor electrocardiogram findings were reported. Further assessments also confirmed no signs of toxicity in the liver or kidney (34,35).

**Baicalein and baicalin, the antiviral activity and activity against SARS-CoV-2**

_Proposed targets for inhibition of SARS-CoV-2_

It is very important to note that the virus will affect the body through multiple pathways and ultimately leads to many complications. The virus prompts a cytokine storm resulting in many complications, such as inflammation, septic shock and multiple organ failure (36,37). Interestingly, it was shown that the levels of inflammatory factors such as interleukins (IL-2, IL-6, IL-7 and IL-10), tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1 α (MIP-1α), monocyte chemoattractant protein-1 (MCP-1) and others were reported to be higher in critically ill COVID-19-positive patients (38,39). Therefore, understanding the role of inflammatory markers in diseases such as COVID-19 may bring a novel therapeutic approach for treatment of the disease (38). Moreover, these facts allow to utilize baicalein as a neuroprotective compound with effects against various neurotoxic agents (40).

Function of central metabolic pathways such as oxidative phosphorylation system (OXPHOS) and mitochondrial permeability transition pore (mPTP) are often changed by viruses for providing energy, biosynthetic resource, or preventing immune surveillance to promote their development (41,42). Viruses also modify mitochondrial metabolism via blunting mPTP to facilitate their production, and suppression of OXPHOS attenuates the viral replication (43). So, OXPHOS has been purposed as a key target for treating viral infection (41,42).

Another assumed target for the inhibition is 3-chymotrypsin-like protease (3CL\textsuperscript{pro}) which plays a central role in viral replication in the posttranslational processing of pp1a and pp1ab replicase polyproteins (44). Indeed, 3CL\textsuperscript{pro} is one of the important targets in the design and development of antivirals effective against COVID-19 (45). It consists of 306 amino acids (46), N-terminal domain-I, N-terminal domain-II and C-terminal domain-III (47). The catalytic center of this enzyme is the amino acid pair Cys145 and His45 (48). A number of substances that may act as the 3CL\textsuperscript{pro} inhibitors have been tested, but there is still no clear antiviral drug for COVID-19.
Baicalein and baicalin as potential antiviral drugs for COVID-19

It has been reported a broad-spectrum of antiviral properties of baicalein in the past against viruses, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) (49), influenza A virus subtype H1N1 (50–53), influenza A subtype H1N1pdm09 (54), influenza A virus subtype H5N1 (55), Chikungunya virus (CHIKV) (56), human immunodeficiency virus (HIV) (57,58), dengue virus (DENV) (59,60), Sendai virus (SeV) (61), Zika virus (ZIKV) (62), Japanese encephalitis virus (JEV) (63), etc. It would therefore probably be a good antiviral against the SARS-CoV-2 virus. The study found that baicalein inhibited the overactivation of the complement system in vivo and enhanced the acute lung damage caused by influenza A virus (64). Mechanistically, baicalein showed the evidence that it inhibits mitochondrial OXPHOS quickly and robustly, and this inhibition is reversibly associated with mPTP activity (43). Another studies reveled that baicalein could inhibit ATPase activity of nonstructural protein 13 (NSP13) (65) and it may also bind to nonstructural protein 14 (NSP14) (46) to exert anti-SARS-CoV-2 activity.

Baicalin, the 7-O-glucuronide analog of baicalein, blocks the respiratory syncytial virus (RSV) infection. Baicalein can reduce the infiltration of T lymphocyte and pro-inflammatory factor gene expression to the antiviral impact (66). Moreover, it was revealed that baicalein can directly develop virus-killing activity against CHIKV in vitro and inhibits different stages of CHIKV replication cycle (56). Baicalein and baicalin were characterized as the first non-peptidomimetic inhibitors of SARS-CoV-2 to exhibit a potent antiviral activity (67,68). The molecular target of these two flavonoids is 3CL\(^{pro}\), the main protease of SARS-CoV-2. Interestingly, the binding of baicalein to 3CL\(^{pro}\) of SARS-CoV-2 was determined by X-ray protein crystallography and revealed that the binding mode is distinctly different from those of known inhibitors (Figure 3). Baicalein is perfectly positioned on the substrate-binding pocket core by its interaction with catalytic residues. The inhibition of SARS-CoV-2 3CL\(^{pro}\) was determined for both, baicalein and baicalin. Both compounds are active inhibitors of the protease with an \(IC_{50}\) of 6.41 μM for baicalein and an \(IC_{50}\) of 0.94 μM for baicalin. These potent in vitro antiviral activities in association with the favorable safety data from clinical trials are according to the authors a great opportunity for development of new drugs against COVID-19 (68).

Figure 3. The crystal complex structure of SARS-CoV-2 3CL\(^{pro}\) (dark green color) with baicalein (bright green color). The key interaction sites (Gly143 and Glu166) are designated. Molecules of water are represented by the individual red spheres. The H-bonds are represented by dashed lines (PDB code 6M2N) (68).

There are preliminary evidences that flavonoids such as baicalein might have other effects on SARS-CoV-2 that block its virucidal effects (25). This could be, for example, its binding to angiotensin-converting enzyme 2 (ACE2), which serves as an entry site for SARS-CoV-2 coronavirus into cells (43) and blocks its replication (69). Baicalein also suppresses neuroinflammation by reducing the production of pro-inflammatory factors including nitric oxide.
(NO), IL-6, TNF-α and, in addition, significantly inhibiting the production of reactive oxygen species (ROS), reducing expression of cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB)/p65 (Table 1) (70). Baicalein also inhibits the transmembrane protease serine 2 (TMPRSS2), which is involved in the spread and pathogenesis of SARS-CoV-2 virus, in in silico studies (71).

Table 1. Summarization of proposed baicalein’s targets.

| Active ingredient | Target | Anti SARS-CoV-2 |
|-------------------|--------|-----------------|
| baicalein         | ACE2, IL6, NO, TNF-α, ROS, COX-2, NF-κB/p65, OXPHOS/ mPTP, NSP13 protein, NSP14 protein | inhibiting the virus replication |

**Conclusion and perspectives**

COVID-19 is a pandemic viral disease whose termination is not yet predictable (72–75). Research is currently underway around the world to develop vaccines and treatments to deal with the disaster. Although high hopes are placed on vaccines, their effectiveness is not yet well documented and the vaccination campaign is accompanied by a number of organizational complications, ambiguities with efficacy in the mutated virus, and uncharted allergic and other adverse reactions (76). In addition, the vaccination campaign is accompanied by a number of vaccines with different mechanisms of action and their deficiency (77–79).

Since both SARS and COVID-19 were caused via binding spike protein (S protein) to ACE2 (80,81), current research into suitable antivirals focuses in particular on the substances whose target site is the major protease of SARS-CoV-2, the 3CLpro, which is one of the good targets for finding an effective drug. This protease is known to be inhibited by some flavonoids, including baicalein (82). Baicalein further prevented SARS-CoV-2-induced cell damage and significantly inhibited virus replication. This well tolerated compound showed no signs of toxicity in the liver or kidney (35). Administration of crystalline baicalein p.o. has been shown to inhibit SARS-CoV-2-induced damage both in vitro and in vivo experiments. The results of all tests performed so far suggest that baicalein may be a promising therapeutic drug for the treatment of the COVID-19 (25). Even if baicalein will not avoid an infection, there are significant indications that it can help to attenuate progression of the COVID-19. Therefore, we suspect that the anti-SARS-CoV-2 activity induced by the baicalein could be valuable for further study.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Adherence to Ethical Standards**

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

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