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REVIEW

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Applications, phytochemistry, pharmacological effects, pharmacokinetics, toxicity of *Scutellaria baicalensis* Georgi. and its probably potential therapeutic effects on COVID-19: a review

Jia-Wen Song, Jia-Ying Long, Long Xie, Lin-Lin Zhang, Qing-Xuan Xie, Hui-Juan Chen, Mao Deng and Xiao-Fang Li*

Abstract

Scutellaria baicalensis Georgi. (SB) is a common heat-clearing medicine in traditional Chinese medicine (TCM). It has been used for thousands of years in China and its neighboring countries. Clinically, it is mostly used to treat diseases such as cold and cough. SB has different harvesting periods and processed products for different clinical symptoms. Botanical researches proved that SB included in the Chinese Pharmacopoeia (1st, 2020) was consistent with the medicinal SB described in ancient books. Modern phytochemical analysis had found that SB contains hundreds of active ingredients, of which flavonoids are its major components. These chemical components are the material basis for SB to exert pharmacological effects. Pharmacological studies had shown that SB has a wide range of pharmacological activities such as antiinflammatory, antibacterial, antiviral, anticancer, liver protection, etc. The active ingredients of SB were mostly distributed in liver and kidney, and couldn't be absorbed into brain via oral absorption. SB's toxicity was mostly manifested in liver fibrosis and allergic reactions, mainly caused by baicalin. The non-medicinal application prospects of SB were broad, such as antibacterial plastics, UV-resistant silk, animal feed, etc. In response to the Coronavirus Disease In 2019 (COVID-19), based on the network pharmacology research, SB's active ingredients may have potential therapeutic effects, such as baicalin and baicalein. Therefore, the exact therapeutic effects are still need to be determined in clinical trials. SB has been reviewed in the past 2 years, but the content of these articles were not comprehensive and accurate. In view of the above, we made a comprehensive overview of the research progress of SB, and expect to provide ideas for the follow-up study of SB.

Keywords: SB applications, Phytochemistry, Pharmacological effects, Pharmacokinetics, Toxicity, Treating COVID-19

Background

SB, a species in the genus *Scutellaria* (family *Lamiaceae*) which its dried root is a TCM recorded in ChP (1st, 2020) [1], often been called Huangqin or Skullcap. SB has been widely used for thousands of years by China and its neighbors. It mainly grows in temperate regions and tropical mountains (with an altitude of about 1300–3000 m), including China, Russia's Eastern Siberia, Mongolia, North Korea, Japan, etc. [2]. The traditional therapeutic effects have been first recorded in the *Shennong Bencaojing (The Classic of Herbal Medicine)* [3], an existing original pharmacological monograph of China

*Correspondence: lixiaofang@cdutcm.edu.cn
School of Pharmacy, Chengdu University of Traditional Chinese Medicine, No. 1166, Liutai Avenue, Chengdu 611137, China

written by many medical scientists together during the Han dynasty. It narrated in detail that SB has "the effects of clearing away the pathology of heat and dampness, eliminating fire pathology, detoxifying, and preventing bleeding and fetal restlessness" [1].

SB contains various chemical components, such as various flavonoids, diterpenes, polyphenols, amino acids, volatile oils, sterols, benzoic acids, etc. [4, 5]. Flavonoids are the main components of SB. There are more than 110 kinds of flavonoids in its dried roots, including baicalin, baicalein, wogonoside, wogonin, etc. These are the main material basis for SB to play clinical effects. SB has antibacterial, antiviral, anti-inflammatory, anticancer, liver and nerve protective functions, etc. [6–8]. Because SB has a very wide range of pharmacological effects and clinical applications, more and more in-depth researches had been implemented. This paper is a comprehensive summary of the current researches on SB, including clinical and non-clinical applications, medicinal materials, botany, phytochemistry, pharmacology, pharmacokinetic characteristics, and toxicity. And then, we also discussed that SB has a certain potential effects in the treatment of the current major disease-COVID-19 based on the current network pharmacology researches. Its possible prevention and treatment mechanisms were discussed, but the exact therapeutic effects still need to be determined in the next step.

Applications

Clinical applications

SB is one of the 40 bulk medicinal materials and one of the famous "three yellow" in TCM [9]. It is a common medicine for treating cold, flu, fever, diarrhea, jaundice, headache, abdominal pain, drenching, etc. SB is frequently used in classical prescription, such as Mahuang Shengma decoction, Xiexin decoction and Huangqin decoction, ect [10]. In modern clinical applications, the quantity or dosage of TCM in prescriptions can be added or reduced to clearing away heat with different symptoms [11]. Compared with other antipyretic TCM, SB is more suitable for heat syndrome with fetal restlessness. There are about 477 prescriptions containing SB [12] for treating 153 main diseases, cough and cold are more frequently used. And after searching ChP. (4th, 2020) [13], for the treatment of cold, more than 30% of Chinese patent medicine contained SB active ingredients, and for clearing away heat and detoxifying more than 70% of them contained SB and its active ingredients. Common forms of these preparations include granule, pill, tablet, liquid preparation, capsule, etc. [14]. The same prescription may have different preparation forms, and the appropriate form should be selected according to the development of the disease.

Non-clinical applications

A composite material contained SB had good biocompatibility and strong antibacterial activity [15]. Many components (e.g. baicalin, baicalein and wogonin) had reversible electronic shuttle activity for the extraction of bioenergy [16]. Microbial fuel cells contained baicalin and baicalein had higher ability of bioelectricity generation, and showed weaker biological toxicity during the process of generating electricity. Feed contained SB flavonoids improved the meat quality and antioxidant capacity of broilers and increased the activity of SOD, GSH and peroxidase in liver [17]. It is suggested that SB flavonoids can be added into agricultural feed to improve meat quality. A silk product contained baicalin was successfully prepared [18], and it had antibacterial, anti-oxidation and UV protection effects. In addition, it also showed an electrostatic effect. SBE had the effect of inhibiting the synthesis of melanin, and had good safety to the skin [19]. It can be used as a whitening ingredient in the beauty industry after more clinical trials based on human skin safety.

Botanical researches

Textual researches of botany

Genuine SB is the dried root of perennial herb SB of the *Labiaceae* family. It is widely distributed in Hebei, Shandong, Shanxi and other regions in China. It is suitable for growing in the dry sunny places such as the mountain top, hillside, forest edge and roadside with an altitude of 500–1500 m [20]. *Illustrated Pharmacopoeia* (*Ben Cao Tu Jing*) narrated that "The seedling is more than foot-long, the stem is as thick as chopsticks, and the leaves are clustered from all sides of the ground". *Compendium of Materia Medica* (*Ben Cao Gang Mu*) also narrated that "Kuqin (rotten xylem) is an old root with hollow and yellow outside and black inside. Ziqin (strip types) is a new root with more compact inside. SB in southwest is hollow and black, contrast to SB in north is solid and deep yellow". The former is mainly used to treat lung heat cough and the latter is mainly used to treat damp heat dysentery. However, there is no excessive differentiation in clinical use [21]. Therefore, the plant morphology of SB described by the ancients is consistent with that of SB used now [22].

Harvesting and processing

In addition to the regulation of genetic factors and the influence of environmental conditions [23], the quality of effective components of TCM is also affected by harvesting and processing [24]. Studies have shown that there are differences in the content of SB in spring and autumn [25]. The best harvest time of SB is determined

by the highest content of baicalin, wogonoside, baicalein and scutellarin, most of which are concentrated in September [26]. According to the growth condition of SB and the dynamic accumulation of baicalin, there was a significant increase of baicalin in triennial compared with biennials in the root [20]. Therefore, the harvest time of SB is mainly concentrated in autumn, and the quality of triennial one is the best.

The traditional processing of SB needs to bump away the rough skin. However, the key enzymes for the synthesis of flavonoids were found to be mainly concentrated in the phloem of the root according to spatial imaging [27]. The content of baicalin in cortex is the highest, which affects the quality of SB. Therefore, it is suggested that the above-mentioned step should be cancelled in the modern processing of SB, so as to ensure the quality of SB [28, 29]. The total amount of baicalin and flavonoids in the process of drying shows a change trend of inverted "V", which may be related to the physiological mechanism of anti-drought stress of SB root itself [26, 30]. This showed that the drying time should not be too long, otherwise the content of active ingredients will be reduced. At present, there are different processed products of SB, such as wine, fried and charcoal SB respectively. Different processed products of SB play different roles in the prescription [31]. The commonly used processed products of SB are raw materials, which can play the role of clearing away heat and detoxification. Wine SB can play the role of tonifying and moistening in addition to clearing away heat.

Cultivation conditions

By controlling the cultivation conditions, the content of the effective components of planted SB can be improved. Yuan et al. found that the lack of water can cause the hormone metabolism in SB and affect the synthesis of baicalin and other flavonoids [32]. The synthesis of different flavonoids in SB will change differently under UV-B irradiation [33]. For example, the content of chrysin, scutellarin, baicalin and tectoridin would changed under different intensity UV-B irradiation. Free salicylic acid has a great effect on the accumulation of baicalin in the growth of SB, but it has little effect on baicalein [34]. Blue, white and red light has different effects on the content of flavonoids [35]. The content of baicalin increased with the extension of illumination time, and its content reached the maximum under blue light. These studies indicated that the content of water, free salicylic acid, UV-B irradiation, and different light time and intensity could be regulated to change the content of flavonoids in the cultivation process of SB.

Phytochemistry

In 1970s, many chemical components of SB had been separated one after another. These components are the material basis for SB to play a wide range of pharmacological actions [36]. There are hundreds of ingredients in SB (shown in Table 1 and Fig. 1), in addition to flavonoids, it also contains volatile oils, terpenoids, polysaccharides, phenylethyl, amino acids, sterols, starch, alkaloids, organic acids and trace elements [40]. Flavonoids are the major components of SB. There are more than 100 kinds of flavonoids in SB, it is important to note that pharmacological activities of SB take place due to the presence of specific 4′-deoxyflavones such as chrysin, baicalein, wogonin and their glycosides (baicalin and wogonoside) [41]. The key enzymes for the synthesis of these compounds are mainly found in roots, including PAL, C4H, CLL, CHS, CHI, FNSII, MT, GT, FH and OMT, different flavonoid synthetases are encoded by different genes [6, 42, 43]. The main synthetic routes of flavonoids were shown in Fig. 2.

Volatile oils, as secondary metabolites of plants, are widely distributed in the whole plant. Acetophenone, 1-phenyl-1,3-butanediol, palmitic acid and oleic acid are the most abundant [44]. The content and composition of volatile oils in different parts are different [45]. For example, germacrene D, bornyl acetate, diphenylamine and hexadecanoic acid are the primary oils in flowers, stem leaves, roots and seeds respectively. Terpenoids are mainly distributed in the aboveground part and not exist in seeds [46]. They have antibacterial, antiviral, antipyretic, analgesic and anti-inflammatory effects [47].

The polysaccharides of SB are water-soluble, mainly composed of arabinose, galactose, glucose and some differential branched dextran [48–50]. At present, a group of new polysaccharides SP1-1 with molecular weight of 4.56×10^5 Da was identified and had anti-inflammatory effect [51], which is mainly composed of mannose, ribose, glucuronic acid, glucose, xylose and arabinose (the molar ratio were 2.14:3.61:1:2.86:5.98:36.39).

There are 14 kinds of amino acids in SB, of which proline is the highest, accounting for 80% [52]. Sterols contain α-spinasterol and β-sitosterol [40], among them, β-sitosterol has been proved to be effective for anorexia. Phenolic compounds, as organic acid components of medicinal plants, such as citric acid, tartaric acid, malonic acid, etc., have influence on the growth of plants [53]. Exception for lutein and β-carotene [54], there also are phytoene, zeaxanthin and ξ-carotene. And there are 3 lignin glycosides in SB [55]. Platinum is is mainly concentrated in roots, which its content related to the growth of SB [56]. Recently, a new actinomycete isolated from the cortex of SB [57], named *Brachybacterium endophyticum* sp. nov., was identified as a gram-positive, aerobic,

Table 1 The components of SB

No.	Name	Molecular formula	Weight	Plant part	Ref.
1	Baicalein (5,6,7-Trihydroxyflavone)	$C_{15}H_{10}O_5$	270	Root Hairy Root	[37]
2	Methoxybaicalein (5,6-Dihydroxy-7-methoxyflavone)	$C_{16}H_{12}O_5$	284	Root	[117]
3	Scutellarein (5,6,7,4′-Tetrahydroxyflavone)	$C_{15}H_{10}O_6$	286	Root	[39]
4	5,6,7-Trihydroxy-4′-methoxyflavone	$C_{16}H_{12}O_6$	300	Aerial part	[38]
5	Oroxylin A (5,7-Dihydroxy-6-methoxyflavone)	$C_{16}H_{12}O_5$	284	Root	[37]
6	Tenaxin II (5,7,2′-Trihydroxy-6-methoxyflavone)	$C_{16}H_{12}O_6$	300	Root	[38]
7	5,7,4′-Trihydroxy-6-methoxyflavone	$C_{16}H_{12}O_6$	300	Aerial part	[38]
8	5,7-Dihydroxy-6,8-dimethoxyflavone	$C_{17}H_{14}O_6$	314	Root	[38]
9	5,7,2′-Trihydroxy-6,8-dimethoxyflavone	$C_{17}H_{14}O_7$	330	Root	[38]
10	5,8-Dihydroxy-6,7-dimethoxyflavone	$C_{17}H_{14}O_6$	314	Root	[38]
11	5,8,2′-Trihydroxy-6,7-dimethoxyflavone	$C_{17}H_{14}O_7$	330	Root	[38]
12	Tenaxin I (5,2′-Dihydroxy-6,7,8-trimethoxyflavdne)	$C_{18}H_{16}O_7$	344	Root	[38]
13	5,2′,5′-Trihydroxy-6,7,8-trimethoxyflavone	$C_{18}H_{16}O_8$	360	Root	[38]
14	Skullcapflavone II (5,6′-Dihydroxy-6,7,8,2′-tetramethoxyflavone)	$C_{19}H_{18}O_8$	374	Root Hairy Root	[37]
15	5,4′-Dihydroxy-6,7,3′,5′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374	Aerial part	[38]
16	5,2′-Dihydroxy-6,7,8,3′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374	Hairy Root	[38]
17	Chrysin (5,7-Dihydroxyflavone)	$C_{15}H_{10}O_4$	254	Root Aerial part	[37]
18	Norwogonin (5,7,8-Trihydroxyflavone)	$C_{15}H_{10}O_5$	270	Root	[38]
19	Isoscutellarein (5,7,8,4′-Tetrahydroxyflavone)	$C_{15}H_{10}O_6$	286	Aerial part	[38]
20	Apigenin (5,7,4′-Trihydroxyflavone)	$C_{15}H_{10}O_5$	270	Root Aerial part	[39]
21	4′-Hydroxywogonin (5,7 4′-Trihydroxy-8-methoxyflavone)	$C_{16}H_{12}O_6$	300	Root	[38]
22	2′-Hydroxychrysin (5,7,2′-Trihydroxyflavone)	$C_{15}H_{10}O_5$	270	Root	[38]
23	5,7,2′,3′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286	Root	[38]
24	6-Hydroxyluteolin	$C_{15}H_{10}O_7$	292	Whole plant	[39]
25	Salvigenin	$C_{18}H_{16}O_7$	344	Root	[38]
27	Luteolin	$C_{15}H_{10}O_6$	286	Whole plant	[39]
26	5,7,2′,5′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286	Root	[38]
28	5,7,2′,6′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286	Root	[38]
29	5,7,6′-Trihydroxy-2′-methoxyflavone	$C_{16}H_{12}O_6$	300	Root	[38]
30	5,7-Dihydroxy-6,8,2′,3′-tertramethoxyflavone	$C_{19}H_{18}O_7$	358	Root	[38]
31	Wogonin (5,7-Dihydroxy-8-methoxyflavone)	$C_{16}H_{12}O_5$	284	Root Aerial part Hairy Root	[37]
32	3,5,4′-Trihydroxy-6,7,8-trimethoxyflavone	$C_{18}H_{16}O_8$	360	Whole plant	[39]
33	Scutevulin (5,7,2′-Trihydroxy-8-methoxyflavone)	$C_{16}H_{12}O_6$	300	Root	[38]
34	5,7,6′-Trihydroxy-8,2′-dimethoxyflavone	$C_{17}H_{14}O_7$	330	Root	[37]
35	Viscidulin III (5,7,3′,6′-Tetrahydroxy-8,2′-dimethoxyflavone)	$C_{17}H_{14}O_8$	346	Root	[38]
36	5,7,2′-Trihydroxy-6′-methoxyflavone	$C_{16}H_{12}O_6$	300	Root	[38]
37	5,7-Dihydroxy-8,2′,3′,6′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374	Root	[38]
38	7-Methoxychrysin (5-Hydroxy-7-methoxyflavone)	$C_{16}H_{12}O_4$	268	Aerial part	[38]
39	5,8-Dihydroxy-7-methoxyflavone	$C_{16}H_{12}O_5$	284	Root	[38]
40	Genkwanin (5.,4′-Dihydroxy-7-methoxyflavone)	$C_{16}H_{12}O_5$	284	Aerial part	[38]
41	5,8,2′-Trihydroxy-7-methoxyflavone	$C_{16}H_{12}O_6$	300	Root	[38]
42	7-O-Methylwogonin (5-Hydroxy-7,8-dimethoxyflavone)	$C_{17}H_{14}O_5$	298	Root	[38]
43	5,7,4′-Trihydroxy-8-methoxyflavone	$C_{17}H_{12}O_6$	312	Root	[38]

Table 1 (continued)

No.	Name	Molecular formula	Weight	Plant part	Ref.
44	Skullcapflavone I (5,2′-Dihydroxy-7,8-dimethoxyflavone)	$C_{17}H_{14}O_6$	314	Root Hairy Root	[38]
45	Viscidulin II (5,2′,6′-Trihydroxy-7,8-dimethoxyflavone)	$C_{17}H_{14}O_7$	330	Root	[38]
46	Rivularin (5,6′-Dihydroxy-7,8,2′-trimethoxyflavone)	$C_{18}H_{16}O_7$	344	Root Hairy Root	[38]
47	6′-Hydroxy-5,6,7,8,2′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388	Root	[38]
48	6,6′-Dihydroxy-5,7,8,2′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374	Root	[38]
49	5,7,3′4′,5′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372	Aerial part	[38]
50	Viscidulin I (5,7,2′,6′-Tetrahydroxyflavonol)	$C_{15}H_{10}O_7$	302	Root	[37]
51	5,7,6′-Trihydroxy-2′-methoxyflavonol	$C_{16}H_{12}O_7$	316	Root	[38]
52	Baicalein 6-O-glucuronide	$C_{21}H_{18}O_{11}$	446	Whole plant	[39]
53	6-Hydroxyluteolin 7-O-glucoronide	$C_{21}H_{18}O_{13}$	478	Whole plant	[39]
54	Luteolin 7-O-glucuronide	$C_{21}H_{18}O_{12}$	462	Whole plant	[39]
55	Apigenin 7,4′-di-O-rhamnoside	$C_{21}H_{20}O_8$	400	Whole plant	[39]
56	8-Methoxy-5-O-glucosideflavone	$C_{22}H_{20}O_{10}$	444	Root	[38]
57	Apigenin 7-O-β-D-glucoside	$C_{21}H_{20}O_{10}$	432	Aerial part	[39]
58	Baicalein 7-O-β-D-glucoside	$C_{21}H_{20}O_{10}$	432	Root Aerial part	[37]
59	Oroxylin A 7-O-β-D-glucoside	$C_{21}H_{20}O_{10}0$	446	Aerial part Root	[37]
60	Apigenin 6-C-glucosyl-8-C-arabinoside	$C_{26}H_{28}O_{14}$	564	Whole plant	[39]
61	5,6′-Dihydroxy-7,8-dimethoxyflavone 2′-O-β-D-glucoside	$C_{23}H_{24}O_{12}$	492	Root Hairy Root	[37]
62	5,6′-Dihydroxy-6,7,8-trimethoxyflavone 2′-O-β-D-glucoside	$C_{24}H_{26}O_{13}$	522	Root	[38]
63	5,6′-Dihydroxy-6,7-dimethoxyflavone 2′-O-β-D-glucoside	$C_{23}H_{24}O_{12}$	492	Root Hairy Root	[38] [38]
64	5,7,6′-Trihydroxyflavone 2′-O-β-D-glucoside	$C_{21}H_{20}O_{11}$	448	Hairy Root	[37]
65	Viscidulin III 6′-O-β-D-glucoside	$C_{23}H_{24}O_{13}$	508	Root Hairy Root	[37]
66	Wogonin 5-O-β-D-glucoside	$C_{22}H_{22}O_{10}$	446	Root	[37]
67	3,5,7,6′-Tetrahydroxyflavone 2′-O-β-D-glucoside	$C_{21}H_{20}O_{12}$	464	Root	[38]
68	Kaempferol 3-O-β-D-glucoside	$C_{21}H_{20}O_{11}$	448	Aerial part	[38]
69	Chrysin 7-O-β-D-glucuronide	$C_{21}H_{18}O_{10}$	430	Root Aerial part	[37]
70	Baicalin (5,6-Dihydroxyflavone 7-O-β-D-glucuronide)	$C_{21}H_{18}O_{11}$	446	Root Aerial part Hairy Root	[37]
71	5,2′-Dihydroxy-6-methoxyflavone 7-O-β-D-glucuronide	$C_{22}H_{20}O_{12}$	476	Root	[37]
72	Wogonoside (Wogonin 7-O-β-D-glucuronide)	$C_{22}H_{20}O_{11}$	460	Root Hairy Root	[37]
73	Oroxyloside (Oroxylin A 7-O-β-D-glucuronide)	$C_{22}H_{20}O_{11}$	460	Root	[37]
74	Norwogonin 7-O-β-D-glucuronide (5,8-dihydroxyflavone 7-O-β-D-glucuronide)	$C_{21}H_{18}O_{11}$	446	Root	[37]
75	Isoscutellarein 8-O-β-D-glucuronide	$C_{24}H_{24}O_{12}$	504	Leaf	[38]
76	5-Hydroxy-7,8,6′-trimethoxyflavone 2′-O-β-D-glucuronide	$C_{24}H_{24}O_{13}$	520	Hairy Root	[38]
77	Scutellarin	$C_{21}H_{18}O_{12}$	462	Root	[37]
78	Apigenin 7-O-β-D-glucuronide	$C_{21}H_{18}O_{11}$	446	Aerial part	[39]
79	Patuletin 7-O-β-D-glucuronide (3,5,3′,4′-Tetrahydroxy-6-methoxyflavone 7-O-β-D-glucuronide)	$C_{22}H_{20}O_{14}$	508	Root	[38]
80	Chrysin 8-C-β-D-glucoside	$C_{21}H_{20}O_9$	416	Root	[37]
81	Chrysin 6-C-β-D-glucoside	$C_{21}H_{20}O_9$	416	Root	[38]
82	Chrysin 6-C-β-D-glucoside-8-C-α-L-arabinopyranoside	$C_{26}H_{28}O_{13}$	548	Root Hairy Root	[37]

Table 1 (continued)

No.	Name	Molecular formula	Weight	Plant part	Ref.
83	Chrysin 6-C-α-L-arabinopyranoside-8-C-β-D-glucoside	$C_{26}H_{28}O_{13}$	548	Root Hairy Root	[37]
84	Chrysin 6-C-β-L-arabinopyranoside-8-C-β-D-glucoside	$C_{26}H_{28}O_{13}$	548	Root	[39]
85	Chrysin 6-C-β-D-glucoside-8-C-β-L-arabinopyranoside	$C_{26}H_{28}O_{13}$	548	Root	[39]
86	Chrysin 6-C-β-arabinofuranoside-8-C-β-D-glucoside	$C_{26}H_{28}O_{13}$	548	Root	[39]
87	Chrysin 6-C-β-D-glucoside-8-C-β-arabinofuranoside	$C_{26}H_{28}O_{13}$	548	Root	[39]
88	Chrysin 3-C-α-arabinopyranoside-8-C-β-D-glucoside	$C_{26}H_{28}O_{13}$	548	Root	[39]
89	Apigenin 6-C-α-L-arabinopyranoside-8-C-β-D-glucoside(isoschaftoside)	$C_{26}H_{28}O_{14}$	564	Aerial part	[39]
90	Viscidulin III-2′-O-β-D-glucopyranoside	$C_{23}H_{22}O_{14}$	522	Root	[38]
91	Quercetin 3-glucuronide	$C_{21}H_{18}O_{13}$	478	Whole plant	[39]
92	Naringenin	$C_{15}H_{12}O_5$	272	Whole plant	[39]
93	Pinocembrin	$C_{15}H_{12}O_4$	256	Whole plant	[39]
94	Isocarthamidin ((2S)-5,7,8,4′-Tetrahydroxyflavanone)	$C_{15}H_{12}O_6$	288	Leaf Root	[39]
95	Carthamidin (2S)-5,6,7,4′-Tetrahydroxyflavanone)	$C_{15}H_{12}O_6$	288	Leaf Root	[39]
96	(2S)-5,7,4′-Trihydroxy-6-methoxyflavanone	$C_{16}H_{14}O_6$	302	Root	[38]
97	(+)-Eriodictyol ((2S)-5,7,3′,4′-Tetrahydroxyflavanone)	$C_{15}H_{12}O_6$	288	Root	[38]
98	(2S)-5,4′-Dihydroxy-7-methoxyflavanone	$C_{16}H_{14}O_5$	286	Aerial part	[38]
99	Dihydrooroxylin A ((2S)-5,7-Dihydroxy-6-methoxyflavanone)	$C_{16}H_{14}O_5$	286	Root	[38]
100	(2S)-7-Hydroxy-5-methoxyflavanone	$C_{16}H_{14}O_4$	270	Root	[38]
101	(2S)-5,7,2′,5′-Tetrahydroxyflavanone	$C_{15}H_{12}O_6$	288	Root	[38]
102	(2S)-5,7,2′,6′-Tetrahydroxyflavanone	$C_{15}H_{12}O_6$	288	Root	[37]
103	(2S)-7,2′,6′-Trihydroxy-5-methoxyflavanone	$C_{16}H_{14}O_6$	302	Root	[38]
104	(2R,3R)-3,5,7,2′,6′-Pentahydroxyflavanone	$C_{15}H_{12}O_7$	304	Root	[37]
106	Naringenin 7-O-glucoronide	$C_{21}H_{20}O_{11}$	448	Whole plant	[39]
107	Pinocembrin 7-O-glucoronide	$C_{21}H_{20}O_{10}$	432	Whole plant	[39]
108	(2S) -5,7,2′,5′-Tetrahydroxyflavanone-7-O-β-D-glucopyranoside	$C_{21}H_{22}O_{10}$	434	Root	[38]
109	(2S)-5,7-Dihydroxy-6-methoxyflavanone-7-O-β-D-glucopyranoside	$C_{22}H_{22}O_{10}$	446	Root	[38]
110	(2S)-5-Hydroxy-6-methoxyflavanone 7-O-β-D-glucoside	$C_{22}H_{24}O_{10}$	448	Root	[38]
111	(2S)-5,7,6′-Trihydroxyflavanone 2′-O-β-D-glucoside	$C_{21}H_{22}O_{11}$	450	Root	[37]
112	Dihydrobaicalin ((2S)-5,6-Dihydroxyflavanone 7-O-β-D-glucuronide)	$C_{21}H_{20}O_{11}$	448	Root	[38]
113	(2S)-5-Hydroxy-6-methoxyflavanone 7-O-β-D-glucuronide	$C_{22}H_{22}O_{11}$	462	Root	[37]
114	(2S)-5,6,3′,4′-Tetrahydroxyflavanone 7-O-β-D-glucuronide	$C_{21}H_{20}O_{13}$	480	Aerial part	[38]
115	Isocarthamidin-7-O-β-D-glucuronide ((2S)-5,8,4′-Trihydroxyflavanone 7-O-β-D-glucuronide)	$C_{21}H_{20}O_{12}$	464	Aerial part	[39]
116	Carthamidin 7-O-β-D-glucuronide (Dihydroscutellarein 7-O-β-D-glucuronide, Scutellarin B)	$C_{21}H_{20}O_{12}$	464	Aerial part	[39]
117	(2S)-5,8,3′,4′-Tetrahydroxyflavanone 7-O-β-D-glucuronide	$C_{21}H_{20}O_{13}$	480	Aerial part	[38]
118	4′,5,7-Trihydroxy-6-methoxyflavanone	$C_{16}H_{15}O_5$	287	Root	[38]
119	2′,6′,5,7-Tetrahydroxyflavanone	$C_{15}H_{13}O_5$	273	Root	[38]
120	Sinapoyl hexoside	$C_{27}H_{22}O_{10}$	386	Whole plan	[39]
121	Verbascoside	$C_{29}H_{36}O_{15}$	624	Whole plant	[39]
122	7-O-Acetylloganic acid	$C_{28}H_{26}O_{10}$	402	Whole plant	[39]
123	N^1,N^5,N^{10}-Tri-p-(E,E,E)-coumaroylspermidine	$C_{33}H_{33}O_6N_3$	567	Whole plant	[39]
124	Benzyl alcohol	C_7H_8O	108	Root	[36]
125	4′-(β-D-glucopyranosyloxy)-3,3′,5,5′-tetramethoxy-9,9′-epoxylignane-4, 7′-diol	$C_{30}H_{45}O_{13}$	613	Root	[36]
126	4′-(β-D-glucopyranosyloxy)-3,3′,5′-trimethoxy-9,9′-epoxylignane-4, 7′-diol	$C_{29}H_{43}O_{12}$	583	Root	[36]
127	4′-(β-D-glucopyranosyloxy)-3,3-dimethoxy-9,9′-epoxylignane-4,7′-diol	$C_{28}H_{41}O_{11}$	553	Root	[36]
128	Lutein	$C_{40}H_{55}O_2$	567	Root	[36]
129	β-Carotene	$C_{40}H_{56}$	536	Root	[36]
130	2,6,2′,4′-Tetrahydroxy-6′-methoxychalcone	$C_{16}H_{14}O_6$	302	Root	[38]

Table 1 (continued)

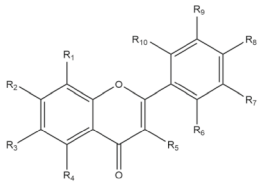
No.	Name	Molecular formula	Weight	Plant part	Ref.
131	8,8″-Bibaicalein	$C_{30}H_{18}O_{10}$	538	Root	[38]
132	5,6,8-Trimethoxy-3′,4′-methylenedioxyflavone 7-O-β-D-glucoside	$C_{26}H_{28}O_{12}$	532	Root	[38]
133	3,5,8-Trimethoxy-3′,4′-methylenedioxyflavone 7-O-β-D-glucoside	$C_{26}H_{28}O_{12}$	532	Root	[38]
134	Delphinidin 3-O-(6-O-malonyl)-β-D-glucoside-5-O-β-D-glucoside	$C_{30}H_{33}O_{20}$	713	Flower	[38]
135	Salidroside (4-Hydroxy-β-phenylethyl-β-D-glucoside)	$C_{14}H_{20}O_7$	300	Hairy Root	[38]
136	Darendoside B	$C_{21}H_{32}O_{12}$	476	Root	[38]
137	Martynoside (2-(3-Hydroxy-4-methoxyphenyl) ethyl-1-O-α-L-rhamnosyl(1 → 3)-β-D-(4-feruloyl)-glucoside)	$C_{31}H_{40}O_{15}$	652	Hairy Root Root	[38]
138	Acteoside	$C_{29}H_{36}O_{15}$	624	Hairy Root Root	[37]
139	Isomartynoside	$C_{31}H_{40}O_{15}$	652	Root	[38]
140	Leucosceptoside A	$C_{30}H_{38}O_{15}$	638	Hairy Root Root	[38]
141	Cistanoside D	$C_{31}H_{40}O_{15}$	652	Root	[37]
142	Darendoside A	$C_{19}H_{28}O_{11}$	432	Root	[38]
143	Stigmasterol	$C_{29}H_{48}O$	412	Root	[38]
144	β-Sitosterol	$C_{29}H_{50}O$	414	Root	[36]
145	Daucosterin	$C_{35}H_{60}O_6$	576	Root	[38]
146	Scutebaicalin (6α,7β-dibenzoyloxy-8β-hydroxy-neo-cleroda-4(18),13-dien-15,16-olide)	$C_{34}H_{38}O_7$	558	Aerial part	[38]
147	Pellitorine	$C_{14}H_{25}NO$	223	Root	[38]
148	(E)-4-[(2-methylpropyl) amino]-4-oxo-2-butenoic acid	$C_8H_{13}NO_3$	171	Root	[38]
149	Dihydropiperlonguminine	$C_{16}H_{21}NO_3$	275	Root	[38]
150	Futoamide	$C_{18}H_{23}NO_3$	301	Root	[38]
151	Piperlonguminine	$C_{16}H_{19}NO_3$	273	Root	[38]
152	Benzoic acid	$C_7H_6O_2$	122	Root	[38]
153	Phenyl acetic acid	$C_8H_8O_2$	136	Root	[38]
154	Syringaldehyde	$C_9H_{10}O_4$	182	Root	[38]
155	4-O-β-D-glucosyl-trans-p-coumaric acid	$C_{15}H_{18}O_8$	326	Root	[38]
156	Ferulic acid methyl ester	$C_{11}H_{12}O_4$	208	Root	[38]
157	4-O-β-D-glucosyl-cis-p-coumaric acid	$C_{15}H_{18}O_8$	326	Root	[38]
158	Vanillin	$C_8H_8O_3$	152	Root	[38]
159	(+)-Crotepoxide	$C_{18}H_{18}O_8$	362	Root	[38]
160	(+)-Syringaresinol-O-β-D-glucoside	$C_{28}H_{36}O_{13}$	580	Root	[38]

coccus-shaped, non-spore-forming actinobacterium. Whether the existence and growth of the bacteria will affect the synthesis of active ingredients, it maybe as a new research point of SB.

Pharmacological effects (Shown in Table 2)

Anti-inflammatory

According to clinical applications, SB is widely used in anti-inflammatory effect. Many diseases can lead to inflammation. In the process of inflammation, all kinds of inflammatory mediators will be produced, such as iNOS, COX-2, IL-6, TNF-α, etc. These mediators can aggravate the inflammatory and then further expand into a vicious cycle [58]. It has been confirmed that the flavonoids of SB can inhibit the release of many inflammatory factors [59]. A new polysaccharide was extracted from SB, and it also could significantly inhibit the level of pro-inflammatory cytokines in serum, including TNF-α, IL-1 β, IL-18, etc. [51]. For inflammatory cells, baicalein can induce their apoptosis, thus reducing the release of inflammatory factors and the invasion of normal cells under the infiltration of inflammatory cells [60]. Inflammation is associated with the expression of many proteins, such as COX-2, vimentin, annexin A1, annexin A2, etc. And flavonoids in SB can inhibit the expression of these proteins to achieve anti-inflammatory effect [61]. The signaling pathways of PPARγ and NF-κB were also associated with the occurrence of inflammatory. SBE could inhibit LPS induced AET II cell inflammatory response



1	R_1=H	R_2=OH	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
2	R_1=H	R_2=OCH_3	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
3	R_1=H	R_2=OH	R_3=OH	R_4=OH	R_5=OH	R_6=H	R_7=H	R_8=H	R_9=OH	R_{10}=H
4	R_1=H	R_2=OH	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OCH_3	R_9=H	R_{10}=H
5	R_1=H	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
6	R_1=H	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
7	R_1=H	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
8	R_1=OCH_3	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
9	R_1=OCH_3	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
10	R_1=OH	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=OH	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
11	R_1=OH	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
12	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
13	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=OH	R_8=H	R_9=H	R_{10}=OH
14	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
15	R_1=H	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=OCH_3	R_8=OH	R_9=OCH_3	R_{10}=H
16	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=OH	R_7=OCH_3	R_8=H	R_9=H	R_{10}=H
17	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
18	R_1=OH	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
19	R_1=OH	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
20	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
21	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
22	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
23	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=OH	R_{10}=OH
24	R_1=H	R_2=OH	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
25	R_1=H	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=OCH_3	R_8=H	R_9=H	R_{10}=H
26	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=OH	R_8=H	R_9=H	R_{10}=OH
27	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
28	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
29	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
30	R_1=OCH_3	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=OCH_3	R_7=OCH_3	R_8=H	R_9=H	R_{10}=H
31	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
32	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=OH	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
33	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
34	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH

Fig. 1 Chemical structure of components of SB

by inhibiting NF-κB, MAPK and phosphatidylinositol-3 kinase signaling pathways [62], and increased the cell viability. To sum up, SB play an anti-inflammatory role mainly by inhibiting the release of inflammatory factors and the expression of inflammatory related proteins.

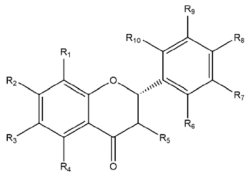
Antibacterial and antimicrobial

There were studies showed that SB also has antibacterial and anti microbial effects. The SBWE could significantly inhibit the reproduction of *Toxoplasma gondii* in 24, 48 and 72 h [63]. Norwogonin has strong inhibitory effect on multidrug resistant *Acinetobacter baumannii* [64]. SB

35	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=OH	R_8=H	R_9=H	R_{10}=OH
36	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
37	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=OCH_3	R_{10}=OCH_3
38	R_1=H	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
39	R_1=OH	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
40	R_1=H	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
41	R_1=OH	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
42	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
43	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
44	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
45	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
46	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
47	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OCH_3	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
48	R_1=OCH_3	R_2=OCH_3	R_3=OH	R_4=OCH_3	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
49	R_1=H	R_2=OCH_3	R_3=H	R_4=OCH_3	R_5=H	R_6=H	R_7=OCH_3	R_8=OCH_3	R_9=OCH_3	R_{10}=H
50	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=OH	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
51	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=OH	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OH
52	R_1=H	R_2=OH	R_3=OGluA	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
53	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
54	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
55	R_1=H	R_2=ORha	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
56	R_1=OCH_3	R_2=H	R_3=H	R_4=OGluA	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
57	R_1=H	R_2=OGlc	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
58	R_1=H	R_2=OGlc	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
59	R_1=H	R_2=OGlc	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
60	R_1=Ara	R_2=OH	R_3=Glc	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
61	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
62	R_1=OCH_3	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
63	R_1=H	R_2=OCH_3	R_3=OCH_3	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
64	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
65	R_1=OCH_3	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=OH	R_8=H	R_9=H	R_{10}=OGlc
66	R_1=OCH_3	R_2=OH	R_3=H	R_4=OGlc	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
67	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=OH	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
68	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=OGlc	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
69	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
70	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
71	R_1=H	R_2=OGluA	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=OH
72	R_1=OCH_3	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
73	R_1=H	R_2=OGluA	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
74	R_1=OH	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H

Fig. 1 continued

can significantly inhibit the up-regulation of IL-1β and IL-8 level caused by *Propionibacterium acnes* via inactivation of the MAPK and NF-κB signaling pathways. The main effective components are wogonin and wogonoside [65]. Baicalin had a dose-dependent inhibitory effect on the expression of LasA protease, LasB elastase, pyocyanin, rhamnolipid, functional and exotoxin A caused by *Pseudomonas aeruginosa* through changing gene and protein expression [66]. Therefore, SB not only decreased the reproduction of bacteria but also stimulated TH1 induced immune response to accelerate bacterial clearance. Baicalin aluminum complexes can change the whole structure and composition of intestinal microbiome of diarrhea piglets, so as to alleviate diarrhea

75	R_1=OGluA	R_2=OCH_3	R_3=H	R_4=OCH_3	R_5=H	R_6=H	R_7=H	R_8=OCH_3	R_9=H	R_{10}=H
76	R_1=OCH_3	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=OCH_3	R_7=H	R_8=H	R_9=H	R_{10}=OGluA
77	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
78	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
79	R_1=H	R_2=OGluA	R_3=OCH_3	R_4=OH	R_5=OH	R_6=H	R_7=OH	R_8=OH	R_9=H	R_{10}=H
80	R_1=Glc	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
81	R_1=H	R_2=OH	R_3=Glc	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
82	R_1=Ara-p (α, L)	R_2=OH	R_3=Glc	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
83	R_1=Glc	R_2=OH	R_3=Ara-p (α, L)	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
84	R_1=Glc	R_2=OH	R_3=Ara-p (β, L)	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
85	R_1=Ara-p (β, L)	R_2=OH	R_3=Glc	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
86	R_1=Glc	R_2=OH	R_3=Ara-f (β)	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
87	R_1=Ara-f (β)	R_2=OH	R_3=Glc	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
88	R_1=Glc	R_2=OH	R_3=H	R_4=OH	R_5=Ara-p (α)	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
89	R_1=Glc	R_2=OH	R_3=Ara-p (α, L)	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
90	R_1=OCH_3	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=OH	R_8=H	R_9=H	R_{10}=OGlc
91	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=OH	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
										
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93	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
94	R_1=OH	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
95	R_1=H	R_2=OH	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
96	R_1=H	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
97	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
98	R_1=H	R_2=OCH_3	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
99	R_1=H	R_2=OH	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
100	R_1=H	R_2=OH	R_3=H	R_4=OCH_3	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
101	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=OH	R_8=H	R_9=H	R_{10}=OH
102	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
103	R_1=H	R_2=OH	R_3=H	R_4=OCH_3	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
104	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=OH	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OH
105	R_1=Ara-p	R_2=OH	R_3=Glc	R_4=OH	R_5=OH	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H

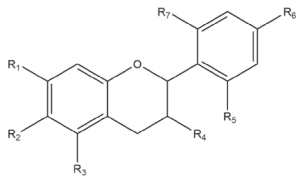
Fig. 1 continued

symptoms. However, its further antibacterial mechanism and regulation of microorganisms have not been clearly described [67]. At present, baicalein aluminum capsule has been used to treat diarrhea.

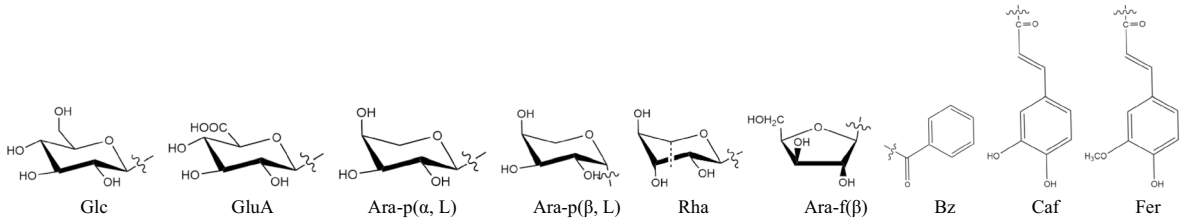
Antiviral

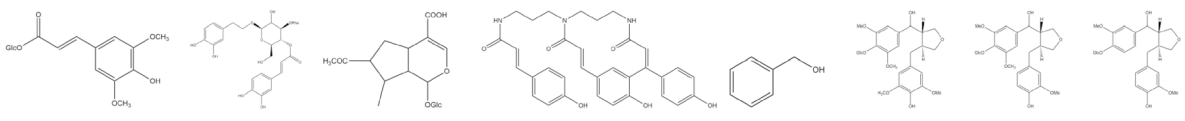
T cell infiltration and cytotoxic T-cell-mediated tissue damage have been identified as key factors in RSV disease. Baicalin can reduce T lymphocyte infiltration and pro-inflammatory factor gene expression to play the effect of antiviral [68]. IAV can cause acute lung injury, the specific manifestations were lung index and abnormal lung tissue lesions. SBE significantly improved these lesions [69] by increasing the activity of HA and NA. And the level of inflammatory factors in lung tissue were regulated to inhibit the inflammatory response. SBE can inhibit the propagation of dengue virus, and baicalein is the main active ingredient in the extract [70]. Oroxylin A significantly protects Vero cells from CVB3-induced cell death in vitro, and can improve the symptoms which reduced body weight and blood glucose levels in vivo [71]. 7 μM baicalin can

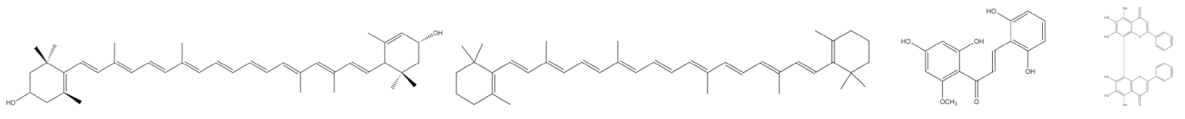
106	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
107	R_1=H	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
108	R_1=H	R_2=Glc	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=OH	R_8=H	R_9=H	R_{10}=OH
109	R_1=H	R_2=Glc	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
110	R_1=H	R_2=OGlc	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
111	R_1=H	R_2=OH	R_3=H	R_4=OH	R_5=H	R_6=OH	R_7=H	R_8=H	R_9=H	R_{10}=OGlc
112	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
113	R_1=H	R_2=OGluA	R_3=OCH_3	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=H	R_9=H	R_{10}=H
114	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H
115	R_1=OH	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
116	R_1=H	R_2=OGluA	R_3=OH	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=H	R_{10}=H
117	R_1=OH	R_2=OGluA	R_3=H	R_4=OH	R_5=H	R_6=H	R_7=H	R_8=OH	R_9=OH	R_{10}=H



118	R_1=OH	R_2=H	R_3=OH	R_4=H	R_5=OCH_3	R_6=OH	R_7=H
119	R_1=OH	R_2=H	R_3=OH	R_4=H	R_5=OH	R_6=H	R_7=OH







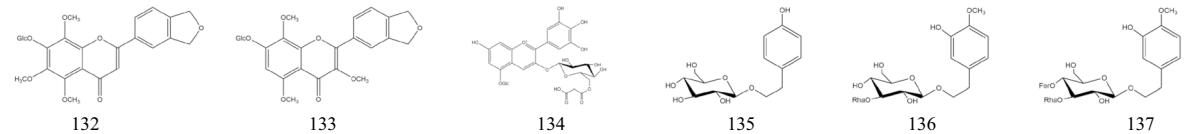


Fig. 1 continued

produce directly virus-killing activity against CHIKV in vitro [72], the levels of important protein markers for autophagy and apoptosis were reduced.

Antioxidant

Wogonin 7-O-β-D-ethylglucuronide, wogonoside and baicalein 7-O-β-D-ethylglucuronide have antioxidant

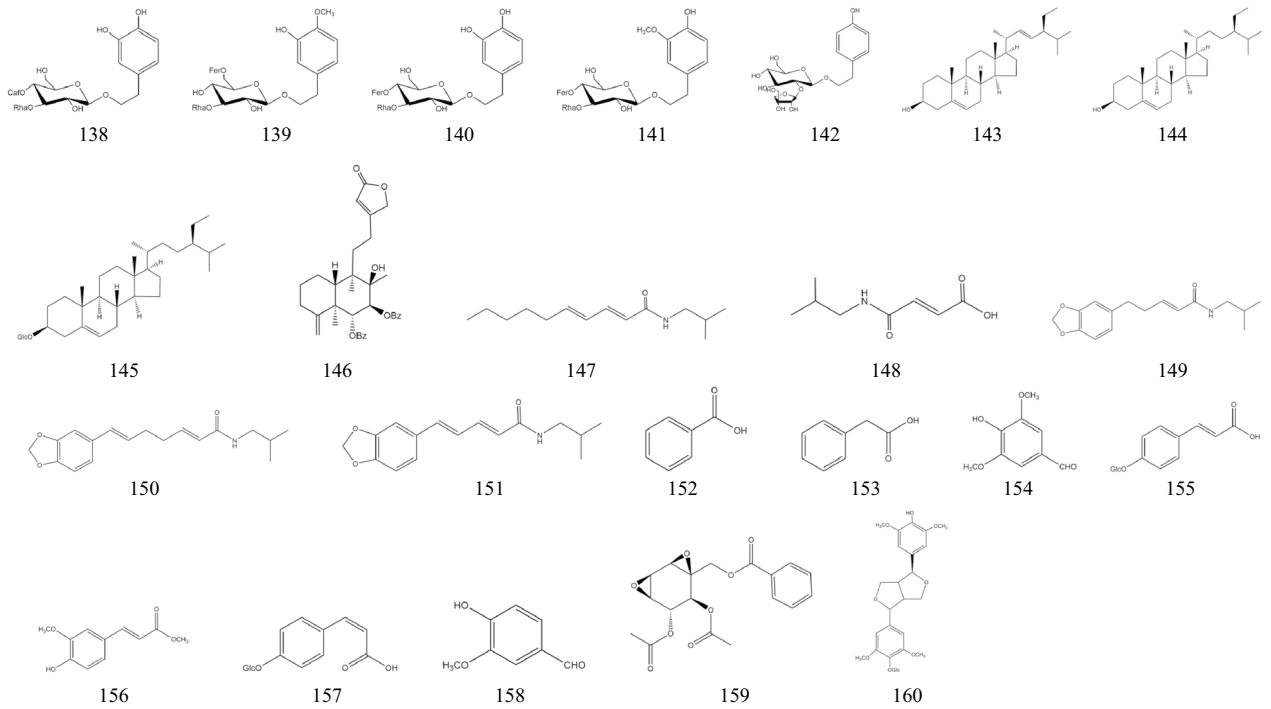


Fig. 1 continued

activity [73]. They can inhibit $FeSO_4$-Cys-induced lipid peroxidation of liver homogenate, and showed strong cytoprotective effect on H_2O_2-induced oxidative damage of human umbilical vein endothelial cells. SBE was found to effectively attenuate comet tail formation and inhibit histone γH2AX phosphorylation induced by H_2O_2 [74]. It can also restore the loss of mitochondrial membrane potential by H_2O_2 and has the activity of scavenging ROS production in cells. More importantly, SBE blocks the oxidative stress by activating Nrf2/HO-1 signaling pathway to inhibit DNA and cell damage and apoptosis induced by H_2O_2. The antioxidant activities of the mixture of polyphenols from four tissues of SB are remarkable [39]. Root has the highest antioxidant activity, followed by leaf, stem and flower. A baicalin/Pluronic F127 hydrogel has excellent cell compatibility and resistance to oxidative stress caused by reactive oxygen species, and accelerate wound healing [75]. In summary, SB has a strong antioxidant effect, and can indirectly exert a cell protective effect through the antioxidant activity.

Cardiovascular effect

Cerebral ischemia will have neuropathological abnormal symptoms such as neuron loss or swelling, Na^+-K^+-ATPase, Ca^{2+}-ATPase and the activity of SOD are significantly reduced, and the level of MDA is increased. The flavonoids in SB (35–140 mg/kg) have a significant improvement on the above abnormal conditions, indicating that the flavonoids in SB have a significant therapeutic effect on cerebral ischemia–reperfusion [76]. LysoPC is a membrane phospholipid metabolite that accumulates in ischemic myocardium and plays an important role in the occurrence of ventricular arrhythmias in myocardial dysfunction. Baicalein can protects H9c2 embryonic cardiomyocytes from hemolysin-induced cytotoxicity [77]. It prevented lysoPC-induced cardiomyocyte death, ROS production and the rise of Ca^{2+} concentration in H9c2 cardiomyocyte through the MAPK pathway. In addition, the ratio of Bcl-2/Bax was increased and the expression of cytochrome c, caspase-3, caspase-9 were decreased.

Baicalin can play an anti-hypertensive effect by improving the state of intestinal injury [78]. Intestinal barrier damage plays an important role in the pathogenesis of hypertension. Baicalin can reduce the proximal colonic lesions, intestinal permeability and release levels of related inflammatory factors to achieve anti-hypertensive effect. In addition, SCFA-producing bacteria were induced to increase. Baicalin, baicalein and wogonoside in Sanhuang decoction have vasodilating effects in vitro and anti-hypertensive effect in vivo. It is speculated that these components play roles by activating the NO/cGMP pathway, and the BKCa channel and DAG/PKC/CPI-17 pathway are also involved [79]. Furthermore, baicalin

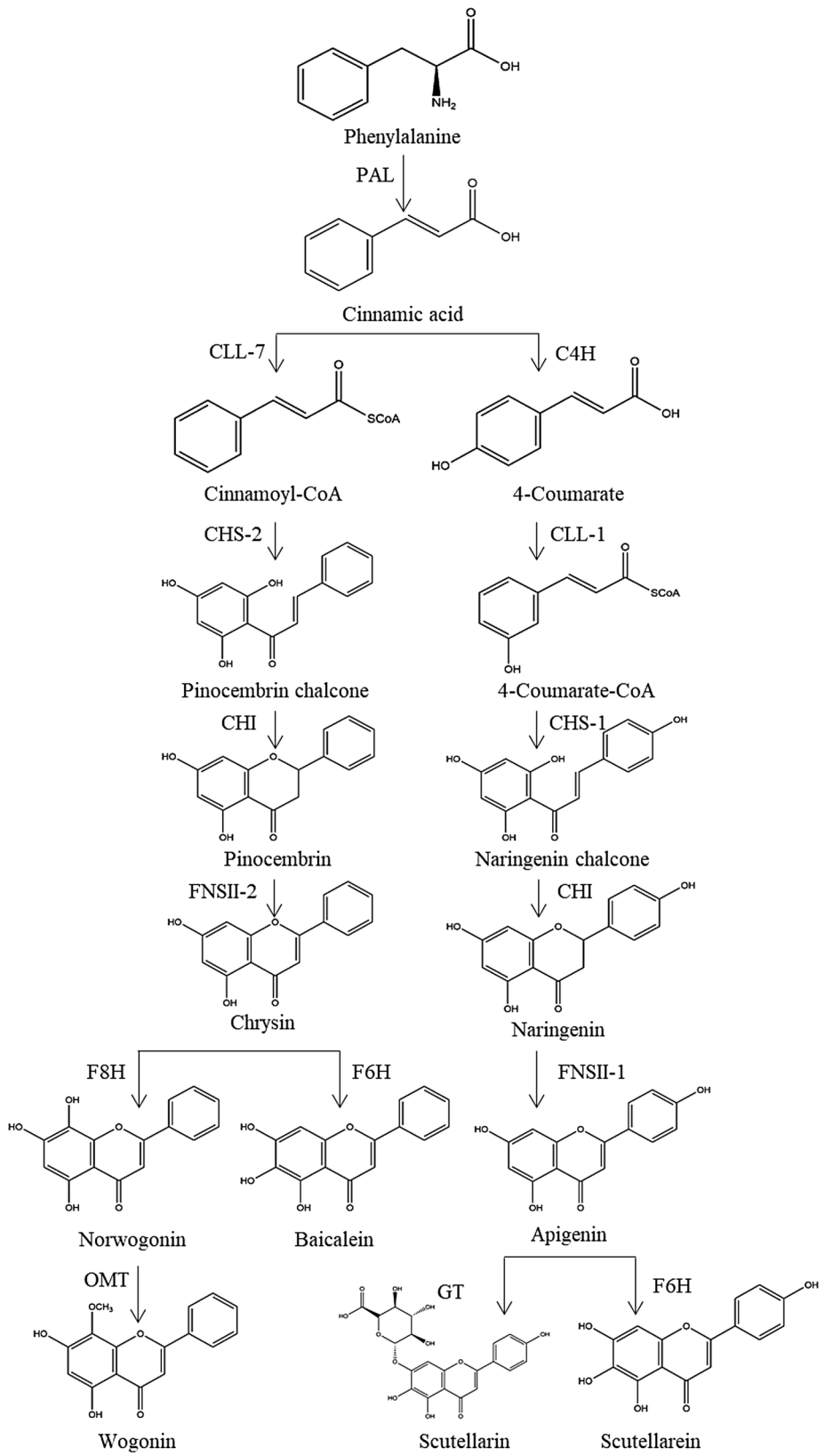


Fig. 2 Main synthetic routes of flavonoids of SB

relaxed blood vessels via regulating intracellular Ca^{2+} in vascular smooth muscle and activating ATP-sensitive potassium channel channels [80].

Anti-diabetics

SB has great therapeutic potential for T2DM, and its flavonoids are the main components that play a role [81]. α-glucosidase inhibitors are currently widely used in the treatment of T2DM. SB contains the above effective ingredients, including 5,7,3,2′,6′-pentahydroxyflavanone, baicalin, viscidulin III, 2′,3,5,6′,7-pentahydroxyflavanone, etc. [82, 83]. They mainly affected the peroxisome proliferator activated receptor signaling pathway in the development of T2DM. PPARγ, PGH2, ACACβ and NF-κB subunit 1 are key targets. Other studies had shown that SBE can play an anti diabetes effect by regulating the composition and structure of intestinal microbial. After oral administration of SBE, the composition of intestinal flora, fecal metabolites and SCFAs content changed in T2DM rats [84].

Neuroprotective effect

Wogonin has a neuroprotective effect on the rat brain after γ-irradiation [85]. It could restore the mRNA level of cells and the expression of Nrf2, HO-1 and NF-κB. And the lesions of brain tissue structure, such as focal glial degeneration and aggregated astrocytes, also could be treated. SBE can effectively reduce the spinal cord neurons/glial cells and microglial cells peroxide damage and LPS stimulation of injured spinal cord neurons [86]. In LPS-stimulated BV-2 mouse microglia, apigetrin can significantly decrease the production of TNF-α, IL-6, PGE2 and NO and inhibit the expression of COX-2, iNOS and mRNA [87]. Apgetrin, wogonin and baicalein could inhibit neuronal cell death [88, 89]. SBE could inhibit excitotoxicity induced by lactate dehydrogenase and glutamate, and it also had a stronger inhibitory effect and selectivity on NMDA receptor-mediated toxicity [90]. It suggested that SBE had NMDA receptor-mediated neuroprotective effect in excitotoxic neurons. Flavonoids in stem and leaf of SB could dramatically increase cell survival rate, the activities of SOD, glutathione peroxidase, and Na^{+}-K^{+}-ATPase, inhibit cell apoptosis and excessive production of MDA in primary cortical neurons exposed to potassium cyanide [91]. In summary, the polyhydroxy structure of flavonoids can protect the brain from hypoxia caused by potassium cyanide or cerebral ischemia and inhibit neuronal apoptosis possibly through neuroinflammation, oxidative stress and nerve injury mutual regulation. And it may have potential preventive effects on neurodegenerative diseases.

Anticancer

Baicalein showed anti-bladder tumor activity [92]. It could reduce the expression of cyclin B1 and D1 by inhibiting protein synthesis and activation via proteasome degradation and inhibit the expression and activity of MMP-2 and MMP-9 mRNA. SBE can inhibit the proliferation of MCF-7 by inhibiting mitochondrial membrane potential, down-regulating Bcl-2/Bax [93]. SBE could downregulate the expression of caspase family members (e.g. PARP), inhibit proliferation and reduce the mitochondrial membrane potential of AGS cells to induce apoptosis [94]. And it would not show obvious toxicity to normal cells. Cisplatin is an important drug for the treatment of lung cancer, but there are serious side effects (such as severe cachexia and acute kidney injury). In combination with SBE, anticancer effect was enhanced and improved the side effects caused by cisplatin therapy in vivo [95]. Baicalin which is the main component of the SBE possess antitumor activity against all leukemic cell lines especially those with MLL and PBX1 gene rearrangements. Baicalin inhibited cell proliferation, arrested the cell cycle at the G0/G1 phase, and induced cell death through caspase 3/7 activation [96]. Oroxylin A could down-regulate the expression of SHCBP1 (it is an oncogene involved in the development of various cancers) to inhibit the carcinogen-induced malignant transformation of JB6 P + skin epidermal cells and decrease the number of tumor cells [97].

Hepatoprotective effect

Liver cancer is one of the common cancers, and studies had shown that SB and its active ingredients have great potential effect in the treatment of liver cancer [98]. Baicalein could inhibit the proliferation of HepG2 cells and reduce metastasis by regulating the activity of MMP-2 [99]. In addition, it also could down-regulate the expression of mRNA and protein of CD24 (a key protein in cancer cell proliferation) to induce apoptosis of liver cancer cells [100]. SBE could down-regulate the expression of endoplasmic reticulum stress marker GRP78, and had obvious hepatoprotective effect on acute alcohol-induced liver injury [101]. It could regulate the levels of AST, ALT and TG in the serum, and the levels of GSH and MDA in liver tissues. For non-alcoholic fatty liver, Baicalin down-regulated the NLRP3–GSDMD pathway to inhibit liver cell death, but induced cytotoxicity with a doses of 32 μM [102].

Immunization effect

SBE increased the viability of far eastern catfish (*Silurus asotus*, infected with *Vibrio anguillarum* or *Streptococcus iniae*) by regulating growth and serum hormone

levels [103]. SBWE restored the level of Th2-type IgG1 and Th1-type IgG2a of ligation-induced periodontitis mice through immune response [104]. *Haemophilus parasuis* can cause a chronic disease related to inflammatory immune response. Baicalin could inhibit the production of IL-6, IL-8, IL-10 and TNF-α and the phosphorylation of ERK, JNK and p38. Thereby activating the immune response induced by Th-1 to promoting the elimination of bacteria [105]. To sum up, SB play roles of anti-inflammatory, antibacterial and anti-viral via immune response.

Other pharmacological effects

Anti-aging SBE improved aging symptoms induced by D-galactose, including the learning and memory function, the oxidative damage and histological abnormalities of the hippocampal neurons [106]. It could regulate the disorder of the metabolism of amino acid, glucose and choline. SB flower extract improved the spatial learning and memory ability, regulated the levels of D-glutamine, glutamic acid, MDA, SOD and AGEs [107]. Therefore, SB flower exerted anti-aging effect through regulating glutamate-glutamic acid metabolism pathway. In addition, 5,7,2′-Trihydroxyflavone and scutevulin inhibited senescence-associated secretory phenotype caused by bleomycin with decreasing the expression of IκBζ and C/EBPβ protein [108]. They didn't affect either BrdU uptake or the expression of senescence markers.

Anti-Osteoporosis Tectochrysin could significantly improve the loss of bone trabeculae, reduce bone in serum and decrease CTX-1, TRACP-5b and IL-6 levels to relieve the symptoms of Osteoporosis [109]. SB ether extract (Baicalein and wogonin) could promote osteogenic transformation, further bone regeneration, stromal calcification and calcified nodule formation [110]. And their activity is comparable to SIM (0.1 mg/L). Baicalin could affect bone metabolism by promoting osteoblast differentiation, inhibiting osteoclast formation, and increasing osteoclast apoptosis [111, 112].

Anti-prostatic hyperplasia SBE improved significantly prostate growth, and increase serum testosterone and 5α-reductase levels in prostatic hyperplasia rats by inhibiting the expression of AR and proliferating cell nuclear antigen, restoring the balance of Bcl-2/Bax [113]. These findings enhanced the feasibility of plant extracts to replace commercial 5α-reductase inhibitors (such as finasteride).

Anti-Alzheimer MAO-A and MAO-B are considered to treat depression and anxiety drug targets for neuropsychiatric diseases such as Alzheimer and Parkinson [114]. Wogonin and baicalein were observed as effective and selective MAO-A inhibitor [115]. They might be useful lead compound for the development of MAO inhibitors for the treatment of depression, such as Parkinson and Alzheimer. Furthermore, baicalin could promote the differentiation of neurons, which transformation into mature neurons and their survival via the Akt/FOXG1 pathway to exert antidepressant effects [116].

Anti-melanin O-methylated flavones (baicalin, wogonoside, baicalein, wogonin, and oroxylin A) have a dual-function effect on melanocytes, which are the inhibition of melanin production and intracellular melanosome transport [117]. These flavonoids had structure-specific a-ring and aglycon O-methyl. It indicated that the function of the active ingredient is related to its structure, and the structure–activity relationship is reflected.

Anti-pruritic Baicalin, baicalein and oroxylin A could improved histamine-induced scratching behavior through reducing vascular permeability and contraction [118].

Pharmacokinetics

Decoction is the main form of TCM used in clinic. Baicalein and wogonin were the major active components in Huangqin decoction [119]. After entering the body, their would be metabolized into glucuronidase and sulfatase forms. After oral administration, the $AUC_{0\text{-}t}$ of glucuronides/sulfates of wogonin and baicalein reached peak at 10 min. And in serum the content of baicalein and wogonin were ranged from 0.3 to 20 and 0.2 to 10 μg/mL, the C_{max} and $AUC_{0\text{-}t}$ of baicalein's glucuronides/sulfates at each time point were 3.3 times that of wogonin. The second peak of $AUC_{0\text{-}t}$ appeared, indicating the occurrence of enterohepatic circulation. The tissues distribution of free baicalein and wogonin were mainly lung and liver respectively. Glucuronides/sulfates of baicalein and wogonin mainly existed in live and kidney respectively. While baicalein and wogonin were mainly present in tissue, their glucuronides/sulfates mainly existed in serum. It suggested that glucuronides/sulfates were involved in circulation. The above components were not detected in brain, suggesting that the above-mentioned components taken orally cannot enter the central nervous system.

SBWE contains mainly 8 flavonoids, baicalin, wogonoside, oroxyloside, norwogonoside, baicalein, wogonin, oroxylin A, norwogonin. After incubation with intestinal bacteria, the content of the latter four components increased significantly, norwogonin had the highest content and showed the highest activity of hemolysis inhibition on sheep and rabbit erythrocytes and anti bacteria while other components didn't work [120]. Another study showed that under pathological conditions intestinal bacteria had stronger glucuronidase activity and a higher

efficiency in converting SBE to flavonoid aglycones [121]. It indicated that SB can exert pharmacological effects depending on the metabolism of intestinal bacteria to produce effective metabolites.

OG and OS were two metabolites of [122] oroxylin A. OA, OG and OS were quickly and widely distributed in tissues, especially postoperative tissues. OA is more widely distributed in tissues than its metabolites, mainly in liver and kidney. But OA was quickly eliminated in the body and the relative bioavailability was less than 2%. The $AUC_{0\text{-}t}$ values of them were proportional to dose. After oral administration, OA was mainly excreted from feces, OG was mainly excreted from bile and urine, and OS was almost not excreted.

Clinical data indicated that 100–2800 mg of baicalein in a single oral dose for healthy volunteers is well tolerated, and showed non-toxicity in liver or kidney [123]. And clinical trials had also verified the safety and tolerability it of products currently sold on the market. In summary, most of the ingredients of SB must be metabolized into active compounds by the intestinal flora, such as baicalein and wogonin. In addition, it also shows that some effective ingredients of SB have low oral absorption and availability, short biological half-life, etc. Therefore, how to improve the bioavailability of SB will be the main focus for the follow-up researchers.

Toxicity

At present, it is generally believed that Chinese herbal medicines have serious side effects, including interstitial pneumonia and liver dysfunction [124]. High dose of wogonin (40 mg/kg, intravenous injection) significantly increased weight of pregnant mice and structural chromosomal aberrations to affect fetus development [125]. Baicalin inhibited the proliferation of targeted stem cells D3 and 3T3 cells, to exert weak decomposition toxicity [126]. Shuanghuanglian injection had a sensitizing effect, and the allergen component was baicalin [127]. It could activate mast cells and increase the levels of IgE and IgG antibody to cause allergic reaction [128]. It indicated that baicalin could produce specific antibodies IgG and IgE in serum, and thus producing allergic reaction. Studies have also shown that baicalin can induce IgE-mediated pseudo-allergy via Mrgprb2 [129]. Baicalin activated TGF-β/Smad signaling pathway to increase kidney collagen synthesis and fibrosis-related protein expression to cause kidney damage and renal fibrosis [130].

SB has more applications in modern skin care industry due to its antioxidant, anti-inflammatory and melanin synthesis inhibitory effects. But the introduction of botanical preparations into cosmetics is an increasing cause of contact dermatitis in patients. There were studies reported that sunscreen containing SB could cause facial inflammation to somebody [131–133]. Therefore, whether SB can be widely used in cosmetics or skin care products still needs further study.

Probably potential therapeutic effect and mechanism of COVID-19

COVID-19 is a worldwide and severe epidemic at present, caused by SARS-CoV-2 [134]. A research team pointed out that the SARS-CoV-2 virus is similar to the SARS coronavirus [135]. It is suggested that the therapeutic target of SARS can be used as a reference for treatment strategy. Researched showed that angiotensin converting enzyme 2 (ACE2) and coronavirus 3CL Mpro on host epithelial cells affected by its S-protein are considered to be the core targets for inhibiting coronavirus proliferation [136, 137]. Simultaneously, cytokine storm induced by virus is the main cause of complications, such as inflammation, septic shock and multiple organ failure [138].

Baicalin had been confirmed to inhibit SARS-CoV in vitro [139], and scutellarin could interact with ACE2 [140]. At present, the drug research on the treatment for COVID-19 is mainly based on network pharmacology and molecular docking [141]. Baicalein and oroxylin A have a certain binding activity with ACE2 and 2019-nCoV-M^{pro}, indicating that they may directly act on the virus and host cells, thus preventing virus proliferation, preventing the body's immunity and blocking virus attack [142–144]. Naringenin and beta-sitosterol can regulate the expression of key genes (CCL2, IL-1β and IL-6) in the treatment of COVID-19, and produce anti-inflammatory and immune enhancing effects through IL-17, TNF, AGE-RAGE signaling pathways and cytokine-cytokine recepter interaction pathway [141]. It is speculated that the therapeutic effects of compounds of SB on COVID-19 mainly focus on anti-inflammatory, inhibiting pro-inflammatory cytokine production and cut of cytokine storm, regulating immune response. Mechanisms of SB in treating COVID-19 shown in Fig. 3. At present, the treatment for COVID-19 researches mainly focus on TCM prescriptions. In addition to the above mentioned, Lianhua Qingwen can regulate the imbalance of ACE-Ang-II and ACE2-Ang-(1-7), which can lead to overwhelming pro-inflammatory cytokines with cytokine storm. And regulating immune-related signal pathway (MAPK, NF-κB, PI3K-AKT, ect) to protect organ damage [145].

To sum up, TCM exhibit functions on COVID-19 via "multi-component, multi-target and multi-pathway". Some countries authorized chloroquine and hydroxychloroquine for the treatment of COVID-19 [146]. But they have adverse reactions, such as diarrhea and nausea, so it is particularly important to seek treatment

Table 2 The pharmacological effects of SB

Pharmacological effects	Model	Mechanism	Drugs or components	Doses	Efficacy	Refs.
Anti inflammatory	LPS-induced Raw 264.7 cells	Inhibiting the release of inflammatory factors	Flavonoids	10–100 μg/mL	MC = 10 μg/mL	[59]
	HCT 116 cells	Inducing apoptosis; Activating PPARγ to inhibit the activity of NF-κB	Baicalein	25–100 μM	IC_{50} = 50 μM	[60]
	AOM/DSS-induced colon cancer mices			1–10 mg/kg	MC = 1 mg/kg	
	L6 cells	Inhibiting the expression of inflammation related proteins	Flavonoids	30—150 μg/mL	MC = 150 μg/mL	[61]
	AET II cells	Inhibiting the signal pathways of NF-κB, MAPK and PI3K-AT	70% ethanol extract	3.125–200 μg/mL	MC = 50 μg/mL	[62]
	ALI rats			2–8 mg/kg	MC = 4 mg/kg	
	Human THP-1 cells	Inhibiting the production of TNF-α, IL-1β	Ploysaccharides	20–1280 μg/mL	IC_{50} = 40 μg/mL	[51]
	C57BL/6 mices			50–200 mg/kg	IC_{50} = 100 mg/kg	
Antibacterial and antimicrobial	*T. gondii* in Hela cells	Inhibiting the propagation of *T. gondii*	Water extract	10 μg/mL	Inhibiting rates > 98%	[63]
	Piglets with diarrhea	Changing the composition of intestinal flora	Baicalin-Alumium complexes	272 mg/mL	Diarrhea rates less than 50%	[108]
	Multidrug-resistant *A. baumannii*	Inhibiting the propagation of *A. baumannii*	Water extract	7.8125–1000 μg/mL	MIC = 128 μg/mL MBC = 256 μg/mL	[64]
	P. Acnes in human monocytic Th-1 cells	Inhibiting the production of IL-18, IL-6, TNF-α and IL-1β	Wogonin	5–30 μM	IC_{50} = 4.9–8.7 μM	[65]
Antibacterial and antimicrobial	*P. acnes*	Inhibiting the production of IL-8 and IL-1β via the MAPK and NF-κB signaling pathways	Wogonin Wogonoside	1.15 mg/g 8.71 mg/g	Inhibition rates > 90%	[66]
	P. aeruginosa	Decreasing the production of exotoxin A; Inhibiting inflammation	Baicalin	2–1024 μg/mL	MEC > 1024 μg/mL	[67]
	P. aeruginosa-induced peritoneal infection mouse			100 mg/kg	Bacterial counts decreased significantly	
Antivirus	RSV infect HEp-2 cells	Decreasing inflammatory cell infiltration; Significantly reducing H1N1 activity	Baicalin	3–30 μM	IC_{50} = 19.9 ± 1.8 μM CC_{50} = 370 ± 10 μM	[68]
	RSV-induced lung injury mice			50–200 mg/kg	IC_{50} = 100 mg/kg	
	IAV in MDCK cells	Inhibiting the leves of IL-6, TNF-α; Improving lung tissue abnormality	Flavonoids	2.5–40 μg/mL	Inhibiting rates > 65%	[69]
	IAV in mices			10 mg/mL		
	Dengue virus in vero cells	Inhibiting the propagation of virus	Baicalein	0.5–750 μg/mL	IC_{50} = 56.02–77.41 μg/mL	[70]
	CVB3 in male BALB/c mices	Reducing the level of inflammatory factors; Increasing phosphoric acid eIF2 α in pancreas	Oroxylin A and wogonoside	50 mg/kg	Inhibiting rates > 50%	[71]
Antivirus	CHIKV in vero, BHK-21 and HEK-293T cells	Antivirus directly; Reducing the level of important protein markers of LC3 and Bax	Baicalin	3–100 μM	EC_{50} = 14 μM	[72]

Table 2 (continued)

Pharmacological effects	Model	Mechanism	Drugs or components	Doses	Efficacy	Refs.
Antioxidant	$FeSO_4$-Cys-induced liver homogenate	Inhibiting further development of oxidation process; Producing cytoprotection	wogonin-7-O-β-D-ethylglucuronide and wogonoside	–	IC_{50} = 18.2 and 24.9 μM	[73]
	H_2O_2-induced human umbilical vein endothelial cells					
	H_2O_2-induced HaCaT cells	Decreasing comet tail formation; Inhibiting histone γH2AX phosphorylation	Ethanol extract	200–1000 μg/mL	IC_{50} = 600 μg/mL	[74]
	$DPPH^-$, $ABTS^{2+}$ scavenging activity	Inhibiting oxidation reaction	Polyphends	25–500 μg/mL	IC_{50} = 66.9 ± 0.3 μg/mL	[39]
	$DPPH^-$ scavenging activity	Inhibiting oxidation reaction; Preventing ROS from damaging cells; Accelerating wound healing	Baicalin/F 127 hydrogels	–	Wound healing rates more than 85% and cell activity more than 80%	[75]
	NIH3T3 cells					
	Wound tissues					
Cardiovascular effects	Cerebral ischemial reperfusion rats	Improving neuron loss or swelling; Enhancing memory; Reducing MDA level; Increasing Na^+–K^+–ATPase activity	Flavonoids	35–140 mg/kg	MC = 35 mg/kg	[76]
	H9c2 cardiomyoctes	Reducing LysoPC-induced cell desth and production of ROS	Baicalein	0.1–10 μM	IC_{50} = 0.69 μM	[77]
Cardiovascular effects	Age-matched male SHRs and Wistar-Kyoto rats	Improving the state of intestinal injury, Reducing intestinal permeability and the level of related inflammatory factors	Baicalin	100 mg/kg	The level of correlation factor is 2–5 times higher than that of model making	[78]
	Male SD rats, male WKY/Izm and SHRs rats	Activating the pathway of NO/cG; Paying the role of vascular relaxation	Sanhuangjiedu Decoction	1–100 μg/mL	EC_{50} = 16.2 ± 1.1 and 65.1 ± 5.5 μg/mL (baicalin and baicalein)	[79]
Hypoglycemic	α-Glucosidase	Inhibiting the activity of α-glucosidase	70% Ethanol extract	–	Six flavonoids of α-glucosidase inhibitors were screened out	[83]
	Male SD rats	Regulating the composition of intestinal flora	Water extract	6.3 g/kg	The perturbation of metabolic spectrum in T2DM rats was significantly improved	[84]
	α-Glucosidase	Regulating peroxisome proliferator receoter actiated	Flavonoids	3.34 mg/kg	Inhibiting rates > 90%	[85]
Neuroprotection	γ irradiation-induced rats	Resuming the level of cell mRNA and the expression of Nrf2, HO-1 and NF-κB	Wogonin	30 mg/kg	No lesions of the polymerized astrocytes	[85]
	Spinal cord injury rats	Reducing peroxides toxicity in nerve cells	Water extract	20 mg/kg	The pathological changes of damaged neurons were improved obviously	[86]

Table 2 (continued)

Pharmacological effects	Model	Mechanism	Drugs or components	Doses	Efficacy	Refs.
Neuroprotection	LPS -induced BV-2 and HT22 cells	Inhibiting neuroinflammatory responses	Apigetrin	20–100 μM	MC = 25 μM	[87]
	Hippocampal neuroral cells	Decreasing the production of PEG2 and NO	Wogonin, baicalein, wogonoside and baicalin	10 mg/kg	Inhibiting rates are 78.6%, 91.0%, 81.0% and 41.0%	[88, 89]
	Primary rats cortical cells	Inhibition of neurocell death	Ethanol extract	1–100 μg/mL	IC_{50} = 35.1 μg/mL	[90]
	Primary rats cortical cells exposured to potassium cyanide	NMDA receptor mediated neuroprotection; Inhibiting lactic dehydrogenase, MDA etc.; Increasing the Na+–K+–ATPase activity	Flavonoids	18.98–75.92 μg/mL	Inhibiting rates are 25.24–46.69%	[91]
Antitumor	Mouse orthotopic tumor model and femal C57BL/6 mices	Decreasing the expression of cyclin B1 and D1; Inhibit the mRNA expression of MMP-2 and MMP-9	Baicalein	25–100 μM	MC = 100 μM (G1 phase)	[92]
	MCF-7	Inhibition of mitochondrial membrane potential; Downregulating Bcl-2	Methanol extract	100–500 μg/mL	MC = 100 μg/mL	[93]
	B-ALL cell lines	Inhibiting cell proliferation, arrested the cell cycle at the G0/G1 phase	Baicalin	4–16 μg/mL	MC = 8 μg/mL	[96]
	AGS cells	Inhibition of mitochondrial membrane potential; Downregulating PARP	Flavonoids	50–400 μg/mL	IC_{50} = 100 μg/mL	[94]
Antitumor	Lewis lung cacinoma cells	Inhibiting the propagation of AGS cells and tumor growth	Extract freeze-dried powder	0.125–1 mg/mL	IC_{50} = 0.13 mg/mL	[95]
	Male C57BL/6 mices			300 mg/kg		
	Female ICR mices	Inhibiting the expression of SHCBP1	Oroxylin A	10–40 mg/kg	MC = 10 mg/kg	[97]
	JB6P + cells			5–20 μM	MC = 5 μM	
Liver protection	HCC cells	Inhibiting the metastasis of cancer cells	Flavonoids	50–400 μg/mL	MC = 100 μg/mL	[99]
	HCC cells	Downregulating the mRNA and proteins expression of CD24	Baicalein	50–100 μg/mL	MC = 50 μg/mL	[100]
	Alcohol-induced acute liver injury in mices	Inhibiting the propagation of liver cancer cells; Downregulating the GRP78 expression of endoplasmic reticulum marker	Methanol extract	40–160 mg/kg	MC = 40 mg/kg	[101]
	Non-alcoholic steatohepatitis cells	Downregulating the pathway of NLRP3-GSDMD to inhibit the liver cells death	Baicalin	1–64 μM	MC = 32 μM	[102]

Table 2 (continued)

Pharmacological effects	Model	Mechanism	Drugs or components	Doses	Efficacy	Refs.
Immunity	Far eastern catfish	Increasing viability by regulating growth and serum hormone levels	Water extract	0.25–5%	Viability more than 90%	[60]
	Srtreptococcus iniae induced periodontitis mices	Increasing the level of Th2-type IgG1	Water extract	50 mg/kg	After 4 weeks, the effect began to be obvious	[104]
Immunity	PAVECs	Anti *H. parasuis*; Inhibiting the phosphorylation of FPK, JNK, p38	Baicalin	12.5–100 μg/mL	MC = 12.5 μg/mL	[105]
Anti-aging	D-galactose induced aging rats	Regulatiing disorders of amino acid, choline and glucose metabolism	60% Ethanol extract	100–200 mg/kg	MC = 100 mg/kg	[106]
	D-galactose induced aging rats	Regulating the level of MDA, SOD, AGEs	60% Ethanol flower extract	0.4–0.8 g/kg	MC = 0.4 g/kg	[107]
	Bleomycin-induced senescence in BJ fibroblasts	Interrupting IκBζ/C/EBPβ pathway	5,7,2′-Trihydroxyflavone and scutevulin	2-4 mg/kg	Inhibitory rates > 90%	[108]
Anti-Osteoporosis	Primary bone narrow mononuclear cells	Inhibition of trabecular bone loss; Decreasing the level of CTX-1, TRAP-5b and IL-6	Tectochrysin	20–100 μmol/L	MC = 20 μmol/L	[109]
	Female C57BL/6 mices	Promoting the proliferation of bone cells and matrix calcification	Baicalein and wogonin	0.5–0.6 mg/L and 0.015–0.6 mg/L	The effect is equivalent to 0.1 mg/L simvastatin	[110]
Anti prostatic hyperplasia	Prostatic hyperplasia rats	Inhibiting prostate growth; Decreasing the level of serum testosterone and 5α-reductase	30% ethanol extract	100–200 mg/kg	MC = 100 mg/kg	[113]
Anti-alzheimer	MAO enzyme	Inhibiting MAO-A and MAO-B	Wogonin	–	IC_{50} = 6.35 and 20.8 μM (A and B)	[115]
Anti-melanin	The mouse melanoma cell line B16F10	Inhibiting the production of melanin and transport of intracellular melanosome	O-methylated flavones	7–70 μg/mL	MC = 35 μg/mL	[117]
Antipruritic	Male ICR and BALB/c mices	Inhibiting scratching behavior; Reducing vascular permeability	Baicalin, baicalein and oroxylin A	20–50 mg/kg	Oroxylin A has the strongest effect	[118]

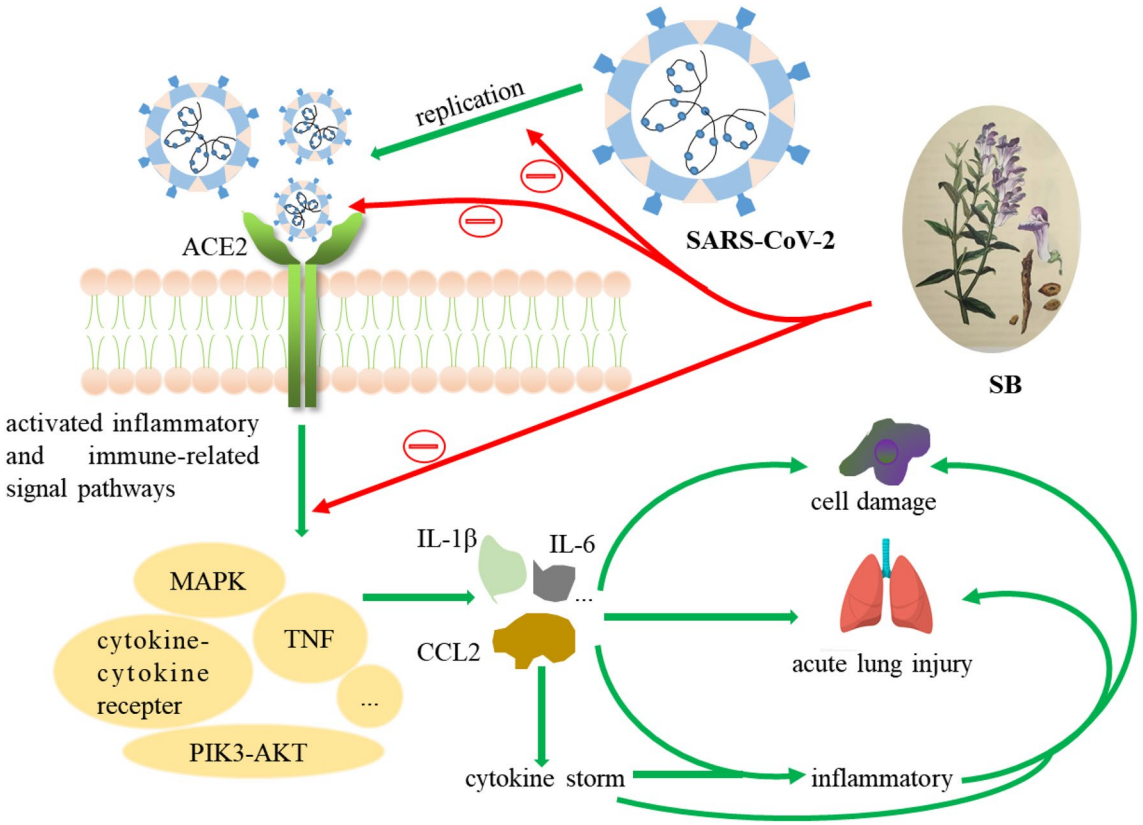


Fig. 3 Mechanisms of SB in treating COVID-19

from TCM. In China, there are three formula authorized to treat COVID-19 [147, 148], including Jinhua Qinggan granules, Lianhua Qingwen granules, and Xuebijing injection. At present, the development of accurate and effective therapeutic drugs and vaccines for COVID-19 are the research focus of various countries [149]. Although TCM has many advantages mentioned above, its exact effects still needs to be verified by clinical trials.

Conclusion and future perspectives

SB is a common TCM with a wide range of clinical effects, and usually used to treat cold, cough, dysentery, lung heat, jaundice and other diseases. According to botanical research, SB in ChP. (1st, 2020) is authentic. In addition to genuine factors, harvest time and processing technology also affect the efficacy of herbs [150]. Despite the commercial interest and increasing demand for SB, improvements through breeding have been very limited. The absence of genome information has limited the understanding of how its flavonoid bioactivities are made and have limited any improvement in productivity through genetic selection. Understanding the genes responsible for biosynthesis of the various flavonoids made in S. baicalensis and their regulation will lay a foundation for molecular breeding for improved, sustainable production.

SB contains a variety of flavonoids, which are the material basis for its strong biological activity, such as baicalin, baicalein, oroxylin A, wogonin, norwogonin and so on. But beyond that, SB also has diterpenes, polyphenols, amino acids, volatile oils, sterols, benzoic acids, etc. Therefore, it have many pharmacological functions such as antibacterial, antiviral, anti-inflammatory, anticancer, liver-protecting and neuroprotective effects. However, the effective components of SB showed low bioavailability and rapid metabolism in vivo. It's suggested that for SB oral preparation, it is necessary to study more suitable technologies to improve its bioavailability in vivo in order to achieve better curative effect. Baicalin is the allergen in SB, which can cause the allergic reaction mediated by IgG and IgE. Therefore, the injection and cream containing baicalin should be strictly controlled to ensure its safety. SB also has good application prospects in non-medical fields, such as agriculture, industry and beauty industry. Because SB can inhibit the production and transportation of melanin, it is added more in whitening skin care products. The introduction of plant preparations into cosmetics is a relatively risky measure, which may cause

adverse reactions to users, so its production needs to be strictly controlled.

Baicalin and baicalein had been proved to have inhibitory effect on SARS-CoV in vitro, and scutellarin could also bind with ACE2 receptor to prevent virus invasion. At the same time, they alleviated the complications caused by the virus, through anti-inflammatory, improve immune response and other functions. It is worth noting that the virus will affect the body through multiple pathways and cause many complications. Therefore, compared with the single component, the TCM prescriptions are still the main treatment for COVID-19, and the therapeutic characteristics of "multi-component, multi-target and multi-pathway" of TCM are brought into full play. Due to the lack of understanding of the pathogenesis of COVID-19, symptomatic treatment and alleviation of complications are the main treatment strategies before the development of effective drugs and vaccines. In conclusion, the current researches of SB are summarized, so that readers have a comprehensive understanding of the research extent of SB, and provide ideas for the follow-up study of SB, especially in how to improve the bioavailability of SB oral preparations in vivo.

Abbreviations

PAL: Phenylalanine ammonia lyase; C4H: Cinnamate 4-hydroxylase; CoA: Coenzyme A; CLL: 4-Coumarate CoA ligase; CHS: Chalcone synthase; CHI: Chalcone isomerase; FNSII: Flavone synthase II; MT: Methyltransferases; GT: Glycosyltransferases; FH: Flavone hydroxylase; OMT: O-methyltransferases; DSS: Dextran sodium sulfate; LPS: Lipopolysaccharide; iNOS: Inducible nitric oxide synthase; COX: Cyclooxygenase; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; AOM: Azoxymethane; PPARγ: Peroxisome proliferator-activated receptor gamma; NF-κB: Nuclear factor-kappa B; AET II: Alveolar epithelial type II; SBE: SB ethanol extracts; SBWE: SB water extract; MAPK: Mitogen activated protein kinase; MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration; MC: Minimal concentration; ED_{50}: Median effective dose; IC_{50}: Half maximal inhibitory concentration; HA: Hemagglutinin; NA: Neuraminidase; H2AFX: H2A histone family member X; ROS: Reactive oxygen species; Nrf2/HO-1: Nuclear factor-erythroid 2-related factor 2/Heme oxygenase 1; SOD: Superoxide dismutase; MDA: Malondialdehyde; LysoPC: Lysophosphatidylcholine; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; SCFAs: Short-chain fatty acids; NO/cGMP: Nitric oxide/cyclic Guanosine monophosphate; BKCa: Large conductance calcium-activated potassium channels; DAG/PKC/CPI-17: Diacylglycerol/Protein kinase C/Cytosolic protein of 17 kDa; T2DM: Type 2 diabetes; PGH2: Prostaglandin G/H synthase 2; ACACβ: Acetyl-CoA carboxylase beta; PGE2: Prostaglandin E2; NMDA: N-methyl D-aspartate; MMP: Matrix metalloproteinase; PARP: Poly (ADP-ribose) polymerase; FOXM1: Forkhead Box M1 activity; AST: Aspartate transaminase; ALT: Alanine transferase; TG: Triglyceride; GSH: Glutathione; GRP78: 78-kDa glucose-regulated protein; NLRP3-GSDMD: NLR pyrin domain containing 3-gasdermin D; PAVECs: Porcine aortic vascular endothelial cells; JNK: c-JUN N-terminal kinase; ERK: Extracellular signal-regulated kinase; AGEs: Advanced glycation end products; SIM: Simvastatin; CTX-1: TRACP-5b: Bone turnover markers; MAO: Monoamine oxidase; ALI: Acute lung injury; OG: Oroxylin A 7-O-glucuronic acid; OS: Oroxylin A sodium sulfonate; D3: Embryonic stem cell; 3T3: Embryonic fibroblast; TGF-β: Transforming growth factor-β; Smad: The main signal transducers for receptors of the TGF-β; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BrdU: 5-Bromo-2′-deoxy-uridine.

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Authors' contributions

J-WS wrote the manuscript. J-WS and J-YL systemically revised the manuscript for important content. LX and L-LZ completed the Figures and Tables. Q-XX, H-JC and MD collected literature and checked data and X-FL proposed the conception and designed the structure of the manuscript. All authors read and approved the final manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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