Saikosaponins: A Review of Structures and Pharmacological Activities

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Abstract

Radix Bupleuri is a traditional medicine widely used in China and other Asian countries. Phytochemistry and pharmacology study reveal that saikosaponins (SSs) are the main bioactive compounds in Radix Bupleuri. SSs are complex compounds composed of triterpene aglycone and carbohydrate part containing 1-13 monosaccharides, which can be divided into seven types based on their structural characteristics. Many different kinds of SSs have been isolated from plants of Bupleurum L. SSs show a variety of biological activities, such as central nervous system protection, liver protection, anti-virus, anti-tumor, anti-inflammation, hormone-like effects, and immune regulation functions. Due to their broad activity and favorable safety profile, SSs attract an increasing amount of attention in recent years. In this review, the structures of 86 SSs are summarized based on the different aglycones due to the diverse structures of saikosaponin (SS). The pharmacological effects and related mechanism of SSs are thoroughly reviewed, and perspectives for future research are further discussed.

Keywords

Bupleurum, Saikosaponins, structures, pharmacological effects

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Introduction

Radix Bupleuri is the root of Bupleurum chinense DC. or Bupleurum scorzonerifolium Willd., which has been used as a traditional Chinese medicine for more than 2000 years. These Bupleurum medicinal plants are widely distributed in the northern hemisphere, which are perennial herbs with compound umbels, bisexual flowers pale yellow or rarely purple, 5 stamens, fruiting, and single leaves long and slender.¹² Radix Bupleuri is widely used as herbal medicines in China, Japan, South Korea, and other Asian countries.¹⁻⁵ Radix Bupleuri was first recorded in Shennong’s herbal classic, which is the first medical skill in China. Since then, Radix Bupleuri has been widely used in traditional Chinese medicine to treat colds, fever, influenza and hepatitis in monographs such as “Jinkui Yao Lue”, “Kai Bao Ben Cao”, “Compendium of Materia Medica” and “Xin Bian Ben Cao”.¹,³ Clinically, several traditional Chinese medicine prescriptions made of Radix Bupleuri, including Xiao Yao pill, Xiao cha hu decoction, Dachaihu decoction, Cha hu Shugan powder, Cha hu Guizhi decoction and Buzhong Yiqi decoction, are all famous prescriptions with therapeutic effects.¹⁵ The different pharmacological activities should be attributed to the rich chemical components in Bupleurum species.⁷ Essential oils, triterpenoid saponins, polyacetylenes, flavonoids, lignans, fatty acids, and sterols have been previously reported from plants of genus Bupleurum.⁶ Among them, triterpenoid saikosaponins are important bioactive compounds.⁷ SSs have a variety of biological activities, such as central nervous system and liver protection, anti-virus, anti-tumor, anti-inflammation, and immune regulation functions. SSs are complex compounds composed of triterpene aglycone (the carbon-skeleton of the aglycone consists of six isoprene units), and the carbohydrate part contains 1-13 monosaccharides to form a sugar chain that can be bonded to one or more hydroxyl groups of the aglycone.⁸ In this review, SSs were classified and summarized based on the

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different aglycones (Figures 1–8 and Tables 1–8). The pharmacological activities and mechanisms of naturally occurring SSs were further reviewed.

In this paper, related literatures such as articles collected from Web of Science, Elsevier, ScienceDirect, PubMed, Scopus, and SciFinder, Springer, Google scholar and China national knowledge internet (CNKI) are searched by computer. This study was carried out from the aspects of structure and pharmacology. The key words “Bupleurum”, “saikosaponin”, “structure” and “pharmacology” were searched individually or in combination.

Structures of Naturally Occurring SSs

SSs are important bioactive compounds in plants of genus Bupleurum. So far, several techniques have been employed to identify and analyze different saikosaponins, including TLC, HPLC, HPLC-ELSD, HPLC-MS, UPLC-MS and capillary electrochromatography. Among the above methods, HPLC-ELSD is the most commonly used analytical method. At present, a variety of triterpenoid saponins can be isolated from more than 10 species of genus Bupleurum. For example, SSC can be isolated from B. chinense, SSA and SSC can be isolated from B. falcatum and B. marginatum, SSI can be isolated from B. kaoi, and 3’-O-acetylsaikosaponin a and 3’-O-acetylsaikosaponin d can be isolated from B. wenchuanense.

SSs areoleane-type pentacyclic triterpenoid saponins composed of aglycones and sugar units, and their aglycones can be divided into seven different types: epoxy ether (I); isocyclodiene (II); 12-ene (III); homocyclic diene (IV); 12-ene-28-carboxylic acid (V); isocyclodiene-30-carboxylic acid (VI); and 18-ene (VII). SSs are generally the main components of secondary metabolites of the genus Bupleurum, accounting for almost 7% of the total dry weight of roots. The aglycones of these SSs are oxygen-containing pentacyclic triterpenes, which can only be distinguished by the position and number of double bonds on the C and D rings and the oxygenation patterns at positions of C16, C23, C28, and C30. The corresponding sugar chain is composed of fucose, rhamnose, xylose, galactose, and glucose.

The structure of type I saponins contains 13β, 28-epoxy ether bond and 11-alkene bond. Type II saponins contain two double bonds in different C rings, namely 11, 13(18)-diene or 12, 16(17)-diene. While the two double bonds are in the same C ring of type IV saponins, namely 9(11), 12-diene. There is only one double bond between C12 and C13 in type III saponins, while type V saponins show a similar 12-ene structure but contain a C28 carboxylic group. Type VI saponins contain 11, 13(18)-diene structure and C30 carboxylic group. Most of the type II, III and VI saponins are substituted by α-OCH3 at the C11 position. Type VII saponins show 18-alkene structure. Generally, type I saikosaponins are the most abundant triterpenoid saponins found in plants of genus Bupleurum, and SSA, SSC and SSD are the most common saponins.

Conventionally, SSs are extract from Radix Bupleuri using traditional extraction processes such as reflux extraction, ultrasonic assisted extraction and solvent partitioning extraction. However, these methods have disadvantages such as time-consuming or waste of organic solvents. Recently, some advanced extraction methods have been employed for extraction of SSs. For example, accelerated solvent extraction (ASE)-based method was used to extract SSs from Bupleurum falcatum and it was reported that ASE method was more effective and faster under specific conditions, compared with previous traditional methods. Supercritical fluid extraction with CO2 as solvent was also employed to extract SSs from Radix Bupleuri at lower temperature and lower organic solvent pollution. Separation of SSs was principally performed by solvent partition coupled with different chromatography methods including reversed-phase and normal-phase silica gel column, macroporous resin column and preparative liquid chromatography, which are time consuming and with low recovery rate.

Epoxy Ether (I)

Figure 1.
Table 1.

Isocyclodiene (II)

11, 13(18)-Diene.

Figure 2.
Table 2.

12, 16(17)-Diene.

Figure 3.
Table 3.

12-Ene (III)

Figure 4.
Table 4.
| Plant species         | Compounds                                                | R₁        | R₂      | R₃        | R₄                        | Reference |
|-----------------------|----------------------------------------------------------|-----------|---------|-----------|----------------------------|-----------|
| B. falcatum           | Saikosaponin A                                           | β-OH      | H       | OH        | β-D-Glc-(1→3)-β-D-Fuc-     | 19        |
| B. falcatum           | Saikosaponin C                                           | β-OH      | H       | H         | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 19        |
| B. falcatum           | Saikosaponin D                                           | α-OH      | H       | OH        | β-D-Glc-(1→3)-β-D-Fuc-     | 19        |
| B. scorzonerifolium   | Saikosaponin E                                           | β-OH      | H       | H         | β-D-Glc-(1→3)-β-D-Fuc-     | 20        |
| B. chinense           | 2"-O-Acetyl-Saikosaponin A                               | β-OH      | H       | OH        | 2"-Acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 21        |
| B. falcatum           | 3"-O-Acetyl-Saikosaponin A                               | β-OH      | H       | OH        | 3"-Acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 9         |
| B. falcatum           | 4"-O-Acetyl-Saikosaponin A                               | β-OH      | H       | OH        | 4"-Acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 9         |
| B. falcatum           | 6"-O-Acetyl-Saikosaponin A                               | β-OH      | H       | OH        | 6"-Acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 22        |
| B. falcatum           | 23-O-Acetyl-Saikosaponin A                               | β-OH      | H       | OAc       | β-D-Glc-(1→3)-β-D-Fuc-     | 22        |
| B. falcatum           | 6"-O-Malonyl-Saikosaponin A                              | β-OH      | H       | OH        | 6"-Malonyl-β-D-Glc-(1→3)-β-D-Fuc- | 9         |
| B. marginatum var. stenophyllum | 6"-O-Crotonyl-saikosaponin A                           | β-OH      | H       | OH        | 6"-Crotonyl-β-D-Glc-(1→3)-β-D-Fuc- | 23        |
| B. kunmingense        | 2,3"-Diacetyl-Saikosaponin D                            | β-OH      | H       | OH        | 2,3"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 3,4"-Diacetyl-Saikosaponin A                            | β-OH      | H       | OH        | 3,4"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 3,6"-Diacetyl-Saikosaponin A                            | β-OH      | H       | OH        | 3,6"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. falcatum           | 2"-O-Acetyl-Saikosaponin D                              | α-OH      | H       | OH        | 2"-Acetyl-β-D-glu-(1→3)-β-D-Fuc- | 9         |
| B. wenchuanense B. falcatum | 3"-O-Acetyl-Saikosaponin D                            | α-OH      | H       | OH        | 3"-Acetyl-β-D-glu-(1→3)-β-D-Fuc- | 22        |
| B. falcatum           | 4"-O-Acetyl-Saikosaponin D                              | α-OH      | H       | OH        | 4"-Acetyl-β-D-glu-(1→3)-β-D-Fuc- | 9         |
| B. falcatum           | 6"-O-Acetyl-Saikosaponin D                              | α-OH      | H       | OH        | 6"-Acetyl-β-D-glu-(1→3)-β-D-Fuc- | 9         |
| B. falcatum           | 6"-O-Malonyl-Saikosaponin D                             | α-OH      | H       | OH        | 6"-Malonyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 2,3"-Diacetyl-Saikosaponin D                            | α-OH      | H       | OH        | 2,3"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 3,4"-Diacetyl-Saikosaponin D                            | α-OH      | H       | OH        | 3,4"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 3,6"-Diacetyl-Saikosaponin D                            | α-OH      | H       | OH        | 3,6"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. kunmingense        | 4,6"-Diacetyl-Saikosaponin D                            | α-OH      | H       | OH        | 4,6"-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. chinense           | Saikosaponin X                                          | = O       | α-OH    | OH        | β-D-Glc-(1→3)-β-D-Fuc-     | 23        |
| B. marginatum var. stenophyllum | 23-hydroxy-13β, 28β-epoxy-olean-11-ene-16-one-3-O- β-D-glucopyranosyl-(1→3)-β-D-fucopyranoside | = O       | H       | OH        | β-D-Glc-(1→3)-β-D-Fuc-     | 25        |
| B. scorzonerifolium   | Bupleuroside I                                          | β-OH      | H       | OH        | β-D-Glc-(1→2)-β-D-Glc-(1→3)-β-D-Fuc- | 25        |
Pharmacological Effects of SSs

Anticonvulsant and Antiepileptic Activity

SSs exert significant effects on the central nervous system and can be used to treat convulsions, epilepsy, and other nervous system diseases. Previous studies found that spontaneous limbic seizures can lead to the increase in persistent sodium current (I_{NAP}), and the decrease in I_{NAP} might be related to the anticonvulsant effect of SSA.\textsuperscript{45} SSA (0.3 μM~4 μM) effectively terminates spontaneous recurrent epileptiform discharges in the hippocampal neuron culture (HNC) model of acquired epilepsy and continuous epileptiform high-frequency bursts in HNC of the status epilepticus model in a concentration-dependent manner, SSA inhibited spontaneous recurrent epileptiform discharge (SREDs) with an IC_{50} (the half maximal inhibitory concentration) of 0.42 μM and SSA inhibited status epilepticus (SE) with an IC_{50} of 0.62 μM.\textsuperscript{46} SSA is as effective as phenytoin (50 μM) in the complete inhibition of spontaneous recurrent epileptic discharge at 1 μM. SSA may play an anticonvulsant effect by inhibiting N-methyl-D-aspartic acid receptor current and I_{NAP}.\textsuperscript{46} The anticonvulsant effects of SSA were observed at doses as low as 0.1 μM and as high as 4 μM.\textsuperscript{47} SSA exerts an anticonvulsant effect by inhibiting epileptiform discharges of hippocampal CA1 neurons induced by 4-aminopyridine (4AP).\textsuperscript{47} And in the 4AP convulsion model, SSA is similar to other anticonvulsant drugs (such as carbamazepine), which can reduce the seizure amplitude by more than 30 minutes, showing a longer lasting effect.\textsuperscript{47}

Anti-Alzheimer’s Disease

SSA can improve learning and memory impairment induced by a monoclonal antibody, which may be achieved by inhibiting the pro-inflammatory mediators in the hippocampus. Li et al\textsuperscript{41} found that the dose groups of 8 and 16 mg/kg/day of SSA can obviously improve the learning and memory impairment caused by amyloid-beta (Aβ) protein, and its mechanism might be related to the inhibition of pro-inflammatory mediators in the hippocampus. Nicotinamide adenine dinucleotide phosphate oxidase might also be involved in this effect.\textsuperscript{46} SSC has dual effects on Alzheimer’s disease by targeting two key proteins: Aβ and tau.\textsuperscript{49} SSC reduces Alzheimer’s disease by inhibiting the secretion of the Aβ peptide, inhibiting the microtubule depolymerization mediated by abnormal hyperphosphorylation of tau, and reducing synaptic destruction.\textsuperscript{49} 3 μM and 10 μM doses of SSC have a beneficial effect on cell tau function; it promotes axonal growth mediated by the nerve growth factor, increases microtubule assembly, and inhibits brain endothelial cell apoptosis induced by antipeptide.\textsuperscript{49} SSC also increases synaptic marker proteins, including synaptophysin and postsynaptic dense postsynaptic density-95.\textsuperscript{49}

Oxidative stress (OS) injury is an important factor in the development and progression of senile neurodegenerative diseases (including Alzheimer’s disease and Parkinson’s disease).\textsuperscript{50} SSD significantly improved the H_{2}O_{2}-induced decrease in the antioxidative ability of PC12 cell at concentrations of 200, 300, and 400 μg/mL.\textsuperscript{51} SSD reduces the activation of the mitogen-activated protein kinase (MAPK) signaling pathway in a dose-dependent manner by scavenging reactive oxygen species (ROS), thereby alleviating H_{2}O_{2}-induced apoptosis and oxidative damage of PC12.\textsuperscript{51} SSD may be a potential antioxidant for neurooxidative diseases and may relieve Alzheimer’s disease-like symptoms.

Previous studies reported that early postmenopausal use of estrogen can delay or prevent the progression of Alzheimer’s disease.\textsuperscript{52,53} SSD is similar to estradiol in structure and has an estrogenic effect.\textsuperscript{44} Zeng et al verified the protective effect of SSs on the Aβ-induced neuronal death AKT (protein kinase B) signaling pathway by using network pharmacology.\textsuperscript{55} Du et al\textsuperscript{56} elucidated the possible protective effects of SSD on glutamate-induced neurotoxicity in SH-SYSY cells and the underlying mechanism. They found that SSD(0.5, 1, 5,
| Plant species       | Compounds                          | R₁  | R₂    | R₃    | R₄    | R₅    | R₆              | Reference |
|----------------------|------------------------------------|------|-------|-------|-------|-------|----------------|-----------|
| B. falcatum          | Saikosaponin B₁                    | β-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 19        |
| B. falcatum          | Saikosaponin B₂                    | α-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 19        |
| B. polyanum          | 2º-O-Acetyl-Saikosaponin B₂        | α-OH | CH₃   | CH₃   | H     | OH    | 2º-acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 27        |
| B. polyanum          | 3º-O-Acetyl-Saikosaponin B₂        | α-OH | CH₃   | CH₃   | H     | OH    | 3º-acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 27        |
| B. wenchuanense       | 6º-O-Acetyl-Saikosaponin B₂        | α-OH | CH₃   | CH₃   | H     | OH    | 6º-acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 28        |
| B. wenchuanense       | 3º,6º-Diacetyl-Saikosaponin B₂      | α-OH | CH₃   | CH₃   | H     | OH    | 3º,6º-Diacetyl-β-D-glu-(1→3)-β-D-Fuc- | 25        |
| B. chinense           | 23-O-acetyl-saikosaponin B₂         | α-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 20        |
| B. longiradiatum      | Saikosaponin H                     | β-OH | CH₃   | CH₃   | H     | H     | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 29        |
| B. sorryantherium     | Bupleuride V                       | α-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 20        |
| B. sorryantherium     | Bupleuride X                       | α-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 20        |
| B. sorryantherium     | Bupleuride XII                     | α-OH | CH₃   | CH₂OH | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 30        |
| B. smithii            | Saikosaponin M                     | H    | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 30        |
| B. smithii            | Saikosaponin N                     | β-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 31        |
| B. smithii            | Saikosaponin S                     | α-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 32        |
| B. smithii            | Saikosaponin O                     | β-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 33        |
| B. smithii            | Saikosaponin P                     | β-OH | CH₃   | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 34        |
| B. chinense           | Saikosaponin Q                     | β-OH | CH₂OH | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 35        |
| B. chinense           | Saikosaponin Q₂                    | α-OH | CH₂OH | CH₃   | H     | OH    | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 36        |
| B. marginatum var.    | Sibericaikosaponin II              | =O   | CH₃   | CH₃   | α-OH  | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 23        |
| B. marginatum var.    | Sibericaikosaponin IV              | β-OH | CH₃   | CH₂OH | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 23        |
| B. marginatum var.    | Sibericaikosaponin IV              | =O   | CH    | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 23,26     |
| B. spinosum           | 3β,23,28-trihydroxy-11,13(18)-diene-16-one-3-O-β-D-glucopyranosyl-(1→3)-β-D-fucopyranoside | =O   | CH    | CH₃   | H     | OH    | β-D-Glc-(1→3)-β-D-Fuc- | 37        |
| B. spinosum           | 3β,16α,23,28-tetrahydroxyoleana-11,13(18)-dien-30-oic acid 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-fucopyranoside | α-OH | COOH  | CH₃   | H     | OH    | β-D-Glc-(1→2)-β-D-Glc-(1→3)-β-D-Fuc- | 37        |
| B. spinosum           | 3β,16α,23,28,30-pentahydroxyoleana-11,13(18)-dien-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→3)-β-D-fucopyranoside | α-OH | CH₂OH | CH₃   | H     | OH    | β-D-Glc-(1→2)-β-D-Glc-(1→3)-β-D-Fuc- | 37        |
10 μM) enhanced cellular antioxidant capacity through not only intrinsic free radical-scavenging activity but also induction of endogenous antioxidant enzyme activities and heme oxygenase-1 (HO-1) expression mediated, at least in part, by activating phosphatidylinositol 3-kinase (PI3K) and subsequently Nrf2 nuclear translocation, thereby protecting the SH-SY5Y cells from glutamate-induced oxidative cytotoxicity. In concert, these data raise the possibility that SSD may be an attractive candidate for prevention and treatment of Alzheimer’s disease and other diseases related to oxidation in the future.

**Antidepressant Activity**

SSA has obvious anti-inflammatory activity; it can improve cytokines and regulate inflammation-related pathways. Moreover, SSA has potential antidepressant activity. In accordance with the inflammation hypothesis of depression, stress stimulation can trigger the inflammatory process, leading to abnormal changes in the normal physiological function of 5-hydroxytryptamine and hypothalamus-pituitary-adrenal (HPA) axis. In addition, high levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been found in injured brain tissue, and SSA decreases the levels of interleukin-1 beta (IL-1β), IL-6, and TNF-α in the chronic unpredictable mild stress (CUMS) depression model of peri-menopausal female rats. In addition, SSA improves desperate-like depressive behavior during peri-menopause, which may be achieved by improving neuroendocrine, neuroinflammatory, and neurotrophic systems. The level of brain-derived neurotrophic factor (BDNF) is low in serum of depressed patients. Animals that exhibit symptoms similar to depression also express less BDNF in the serum or brain. In addition, treatment associated with depression increases BDNF levels. Chen et al. administered SSA to rats by intragastric administration of 25, 50, 100 mg/kg/day SSA, with fluoxetine of 10 mg/kg/day as control. And SSA decreases the expression of BDNF induced by CUMS at 4 weeks after administration of SSA. In addition, SSA can restore the deranged regulation of the HPA axis and neuroinflammatory response induced by CUMS, promote the signal transduction of BDNF–tyrosine kinase receptor B (BDNF-TrkB) in the hippocampus, and inhibit the activation of microglia and the release of pro-inflammatory cytokines in the brain. SSA reverses depression-like behavior by maintaining the normal regulation of the HPA axis and activating the BDNF signal.

![Figure 3. Structure of type II (2).](image)

**Table 3. Type II (2) Saikosaponins.**

| Plant species                     | Compounds               | R                          | Reference |
|----------------------------------|-------------------------|----------------------------|-----------|
| B. marginatum var. stenophyllum  | Tibesaikosaponin I      | β-D-Glc-(1→3)-β-D-Fuc-     | 23        |
Targeted lysophosphatidic acid receptor 1 (LPA1) may be a potential treatment for depression, which is related to the regulation of neuronal apoptosis. SSD was dissolved in normal saline and given by intragastric administration of 0.5 and 1 mg/kg/d for 2 weeks, and the two doses of SSD preconditioning could significantly block the prolongation of immobility time induced by LPS stimulation. SSD targeting LPA1 attenuates the activation of the Ras homolog gene family member A/MAPK/NF-κB signaling pathway induced by LPS. Chao et al. administered SSD to rats by intragastric administration of 0.75 mg/kg/day and 1.50 mg/kg/day with fluoxetine as positive control (10 mg/kg/day), and SSD significantly improved the depression-like behavior induced by CUMS in rats. SSD can down-regulate the expression of fibroblast growth factor-2 mRNA by negatively regulating NF-κB and positively targeting microRNA-155, thereby attenuating CUMS-induced depression-like behavior in rats. SSD can down-regulate the expression of fibroblast growth factor-2 mRNA by negatively regulating NF-κB and positively targeting microRNA-155, thereby attenuating CUMS-induced depression-like behavior in rats.

Total SS (TSS, 25 μg/mL) purified from B. jindoense, which mainly contains SSA, SSC, SSD, SSC and SSF, can partially reverse the neuropathy in corticosterone-induced PC12 cells. The mechanism may be related to stabilize Ca²⁺ homeostasis and regulate the B-cell lymphoma-2 (Bcl-2) family. Furthermore, TSS stabilizes the endoplasmic reticulum and inhibits the mitochondrial apoptosis pathway. Therefore, the protective effect of TSS on cells may contribute to its antidepressant drug-like effect. Guo et al. aimed to explore the anti-depression effect of SSA and screen the target proteins regulated by SSA in a rat model of CUMS-induced depression. Results showed that 8-week CUMS combined with separation could successfully produce depression-like behaviours and cause a decrease of dopamine (DA) in rat hippocampus, and 4-week administration of SSA (50 mg/kg) could relieve CUMS rats’ depressive symptoms and up-regulated DA content. There were 15 kinds of significant differentially expressed proteins that were detected not only between the control and CUMS groups, but also between the CUMS and SSA treatment groups. PRRT2 was down-regulated by CUMS while up-regulated by SSA. These findings reveal that SSA may exert antidepressant effects by up-regulating the expression level of PRRT2 and increasing DA content in hippocampus.

**Hepatoprotective Activity**

The liver protective effects against D-galactosamine hydrochlorate (D-GalN) induced liver injury were investigated after treatment of rats with each kind of SSs (SSA, SSD, SSB1, SSB2 and SSC) (5 mg/kg /day, i.p.) for 4 days. The results showed that SSA and SSD have significant inhibitory effects on liver injury induced by D-galactosamine hydrochlorate (D-GalN). They can reduce the activity of drug metabolism in the whole body of rats, resulting in a significant decrease in microsomal enzyme activity and P450 content, and SSD shows much stronger effect than SSA. However, SSB1, SSB2 and SSC did not cause any change in enzyme activities. And long-term intraperitoneal injection of different doses (1.0, 1.5 and 2.0 mg/kg/d) of SSD has a certain therapeutic effect on hepatic fibrosis and down-regulates the expression of TNF-α, IL-6, and NF-κB in rat liver tissue. In the study of Lin et al, different doses of SSD (0.5, 1 or 2 μM) could attenuate acute hepatocyte injury induced by CCl₄ in HL-7702 cells. The results showed that SSD played an antioxidant role by inhibiting the production of malondialdehyde (MDA) and increasing the level of total superoxide dismutase to alleviate the acute hepatocyte injury of HL-7702 cells induced by CCl₄. And SSA (5 μM) can regulate the level of bone morphogenetic protein-4 (BMP4) growth factor BMP4 by inhibiting the expression of alpha-smooth muscle actin (α-SMA) and preventing the activation of hepatic stellate cells (LX-2 cells). Therefore, SSA and SSD can be used to treat liver diseases with increased expression of BMP4 in a dose-dependent manner. In addition SSA(5,10 and 20 mg/kg, i.p) could attenuate liver injury induced by LPS (60 mg/kg) and D-GalN (800 mg/kg) in mice. SSA might inhibit the NF-κB signaling pathway and inflammation by increasing the expression of liver X receptor alpha (LxRα) and then prevents LPS/D-GalN-induced liver injury in a dose-dependent manner.

Only estrogen receptor beta (ERβ) is expressed in primary cultured rat stellate cells but not estrogen receptor alpha (ERα). SSD (5 μM) prevents the activation of hepatic stellate cells induced by OS depend on ERβ activity, and may be at partially attributed to inhibition of the ROS/MAPK signaling pathway. Li et al. found that both SSA(5,10, and 20 mg/kg) and SSD (5,10, and 20 mg/kg) improved diet-induced Nonalcoholic Fatty Liver Disease (NAFLD). Integrative lipidomic and transcriptomic analysis revealed that SSA and SSD modulated glycerolipid metabolism by regulating related genes, like Lipe and Lipg. SSD profoundly suppressed the fatty acid biosynthesis by downregulating Fasn and Acaca expression and promoted fatty acid degradation by inducing Acox1 and Cpt1a expression. Bioinformatic
| Plant species         | Compounds                        | R₁     | R₂     | R₃     | R₄     | R₅                        | Reference |
|----------------------|----------------------------------|--------|--------|--------|--------|---------------------------|-----------|
| B. scorzonerifolium  | Saikosaponin B3                  | β-OH   | CH₂OH  | OCH₂   | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 19        |
| B. chinense          | Saikosaponin B4                  | α-OH   | CH₂OH  | OCH₂   | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 19        |
| B. falcatum          | 6"-O-Acetyl-Saikosaponin B4      | α-OH   | CH₂OH  | OCH₂   | OH     | 6"-acetyl-β-D-Glc-(1→3)-β-D-Fuc- | 22        |
| B. kunmingense       | 3",4"-Diacetyl-Saikosaponin B4   | α-OH   | CH₂OH  | OCH₂   | OH     | 3",4"-Diacyl-β-D-glu-(1→3)-β-D-Fuc- | 24        |
| B. falcatum          | Saikosaponin F                   | β-OH   | CH₂OH  | H      | H      | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 22        |
| B. marginatum var. stenophyllum | 11-α-methoxy-saikosaponin F      | β-OH   | CH₂OH  | α-OCH₃ | H      | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 23        |
| B. marginatum var. stenophyllum | Nepasaikosaponin K              | β-OH   | CH₂OH  | H      | OH     | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 23        |
| B. chinense          | Saikosaponin W                   | β-OH   | CH₂OH  | NHCONH₂| OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 38        |
| B. chinense          | Saikosaponin T                   | β-OH   | CH₂OH  | OCH₁   | H      | β-D-Glc-(1→3)-β-D-Fuc-    | 39        |
| B. falcatum          | Hydroxy Saikosaponin C           | β-OH   | CH₂OH  | OH     | H      | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 9         |
| B. falcatum          | Hydroxy Saikosaponin D           | α-OH   | CH₂OH  | OH     | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 9         |
| B. scorzonerifolium  | Bupleuroside II                  | α-OH   | CH₂OH  | OCH₂   | OH     | β-D-Glc-(1→2)-β-D-Glu-(1→3)-β-D-Fuc- | 20        |
| B. scorzonerifolium  | Bupleuroside III                 | β-OH   | CH₂OH  | OH     | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 20        |
| B. scorzonerifolium  | Bupleuroside IV                  | α-OH   | CH₂OH  | OH     | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 20        |
| B. scorzonerifolium  | Bupleuroside VI                  | β-OH   | CH₂OH  | =O     | OH     | β-D-Glc-(1→3)-β-D-Fuc-    | 20        |
| B. scorzonerifolium  | Bupleuroside VII                 | β-OH   | CH₂OH  | =O     | H      | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 20        |
| B. scorzonerifolium  | Bupleuroside VIII                | H      | COOH   | H      | H      | β-D-Glc-(1→2)-β-D-Ara-(1→3)-β-D-GluA- | 20        |
| B. scorzonerifolium  | Bupleuroside IX                  | α-OH   | CH₂OH  | OCH₂   | OH     | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 20        |
| B. scorzonerifolium  | Bupleuroside XI                  | H      | CH₂OH  | H      | H      | β-D-Glc-(1→6)-[α-L-rha-(1→4)]-β-D-Glc- | 20        |
analysis further predicted the implication of master transcription factors, including peroxisome proliferator-activated receptor alpha (PPARα), in the protective effects of SSA and SSD.

Chang et al. also showed that SSD has a hepatoprotective effect in liver injury by suppressing inflammatory responses and acting as an antioxidant. The SSD (2 mg/kg) group showed significantly higher food intake, body weight, and hepatic antioxidative enzymes such as catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD), lower hepatic cyclooxygenase-2 (COX-2), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), IL-1β, TNF-α, and fibroblast growth factor-21 (FGF21) compared with controls. SSD also reduced the mRNA expression of initiation factor 2α (eIF2α), activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP).

**Antivirus Activity**

SSA, SSB2, SSC, and SSD have activities against human immunodeficiency virus (HIV), measles, influenza virus, herpes simplex virus, and *Streptococcus hydrophila* virus.

The results of Cheng et al. showed that SSs have antiviral activity in the range of 0.25–25 μM, among which SSB2 has the strongest antiviral activity (IC50 = 1.7 ± 0.1 μM). SSB2 is the most selective SS for inhibiting hepatitis C virus (HCV) infection. SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication. SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication. SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication. SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication. SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication. SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 has been found to inhibit the infection of several other viruses (measles virus, dengue virus, herpes simplex virus type I, and unenveloped reovirus). In addition, SSB2 can neutralize virus particles, inhibit virus attachment, and prevent virus invasion. SSB2(10, 100 μM) can inhibit the infectivity of HCV, and SSB2 did not affect cell viability up to 100 μM in Huh-7.5.1 cells. The results show that SSB2 can neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious, and SSB2 can effectively prevent the entry of HCV virus into cells and RNA replication.

**Antitumor Activity**

SSs can inhibit the adhesion of some solid tumor cells, interfere with tumor cell proliferation cycle, interfere with protein metabolism, inhibit cell proliferation, and induce cell apoptosis and other anti-tumor effects. SSA, SSD, and SSE can significantly inhibit tumors by reducing the adhesion of solid tumor cells. SSA can activate caspase-2 and caspase-8 to trigger apoptosis of hepatoma cells.

**Table 5.** Structures of type IV.

| Plant species | Compounds       | R1  | R2  | R3             | Reference |
|---------------|-----------------|-----|-----|----------------|-----------|
| *B. chinense* | Saikosaponin G  | β-OH| OH  | β-D-Glc-(1→3)-β-D-Fuc- | 29        |
| *B. kaoi*     | Saikosaponin I  | β-OH| H   | β-D-Glc-(1→6)-α-L-rha-(1→4)-β-D-Glc- | 29        |
| *B. chinense* | Saikosaponin Z  | α-OH| OH  | β-D-Glc-(1→3)-β-D-Fuc- | 25        |
SSD has a glucocorticoid-like steroid structure that can inhibit Na⁺-K⁺-ATP enzyme activity; it also has a potential anti-tumor effect. And SSD inhibits the activation of NF-κB induced by TNF-α and participates in the expression of target genes involved in cancer cell proliferation, invasion, angiogenesis, and survival. SSD could apparently inhibit the TNF-α induced invasive ability of H1299 human lung cancer cells at nontoxic concentrations (10 μM), suggesting that SSD-mediated inhibitory effect on cancer cell invasion is specific, and it has no direct cytotoxicity of the drug. SSD (10, 20 μM) has been reported to show effective anti-tumor activity through inhibited the cell growth of human lung cancer cell line A549 in a dose-and time-dependent manner. And the activity of SSD-induced p53 and Fas (TNF receptor superfamily member 6)/Fas ligand (FasL) apoptosis system may be involved in the inhibitory effect of SSD on the proliferation of A549 cells. P53 can regulate various downstream target genes related to apoptosis and cell cycle arrest, such as Bax, Bcl-2, and p21. As an inhibitor of cell cycle progression, the upregulation of p21 protein will lead to cell cycle arrest in the G1 phase. In addition, cyclin-dependent kinase 2 (CDK2) is a member of the silk cyclin-dependent kinase family, which plays an important regulatory role in the G1/S phase. The treatment with SSD (3 μg/mL) can significantly induce apoptosis of SMMC7721 cells under hypoxia and hypoxia conditions, and SSD increases radiosensitivity and induces the apoptosis of SMMC7721 hepatoma cells. In another study, SSD(0, 1, 2.5, 5, 10, 20 or 50 μM) inhibited the proliferation of DU145 cells in a concentration-dependent manner, and mitochondrial dysfunction induced by SSD is the main reason for the apoptosis of human prostate cancer cell DU145 induced by SSD. According to Wang et al., SSD (10, 15 or 20 μM) could lead to tumor cell apoptosis through inhibit Wnt (Wingless/Integrated)/β-catenin signal transduction and the expression of β-catenin and its downstream target genes but does not act on epidermal growth factor receptor and neutrosensin receptor 1. SSD nanoparticles induce apoptosis through the mitochondrial pathway. Their anti-melanoma activity is mediated by the phosphorylation of c-Jun N-terminal kinase, the phosphorylation of p38 and p53, the increase in cytochrome c level, and the activation of caspase 9.

SSB2 (64 μM, 128 μM) enhances the efficacy of liver-targeted anticancer drugs by inhibiting multidrug resistance-related drug transporters (Pgp, MRPl/Mrp1 and MRPl/Mrp2). Therefore, SSB2 improves the efficiency of chemotherapeutic drugs and prevents the development of multidrug resistance in hepatocellular carcinoma. However, the combination of platinum-containing anticancer drugs with SSB2 should be avoided. Cancer chemotherapy induced neutropenia (CCIN) is one of the most common toxicity caused by cytotoxic anticancer agents. A study exploring the function of SSD in CCIN therapy found that SSD (6,12 mg/kg) contributed to generate functional mature neutrophils which capable of fighting infection both in vitro and in vivo. Network pharmacology was employed to explore the mechanism, 61 signal pathways might play an important role in CCIN treatment. Western Blot was employed to further confirm the potential pathway involved. They found CBL-ERK1/2 pathway was activated by SSD, followed by upregulating PU.1 and CEBPβ expression and leading to neutrophil differentiation. Their findings suggest a natural regimen SSD which could regenerate microbicidal neutrophils to effectively...
reduce CCIN-associated infection via activating CBL-ERK1/2, providing a rationale for future therapeutic approaches. In addition, as a highly efficient anticancer agent, Doxorubicin (DOX) is used for various cancers’ treatment, but DOX-induced oxidative damages contribute to a degenerative irreversible cardiac toxicity. Recent study has shown that 1 μM SSD could enhance the proliferation of H9c2 cells, and inhibit DOX-induced apoptosis, and SSD(10 mg/kg) efficiently protected the cardiomyocytes from DOX-induced cardiotoxicity by inhibiting the excessive OS via p38 MAPK signaling pathway. Although SS has the effects of anti-tumor, yet we still do not know the mechanism by total Saponin extracts (TBSE) produces this effect on colon cancer. Zhang et al firstly confirmed that TBSE(50ug/ml) significantly up-regulated the expression of pro-apoptotic proteins Bax, Caspase3, Caspase9, cleaved Caspase3 and cleaved Caspase9, and down-regulated the expression of anti-apoptotic protein Bcl-2, significantly down-regulate (P < 0.01) the expressions of PI3 K, Akt, mTOR and phosphorylated proteins P-PI3 K, P-Akt, P-MTOR. Chemosensitivity is also one of the key factors affecting the therapeutic effect on cancer, but the clinical application of corresponding drugs is rare. Zhang et al110 showed that SSD (6 μM) inhibits the malignant phenotype of HCC cells while increasing their sensitivity to the herpes simplex virus thymidine kinase/ganciclovir (HSVtk/GCV) drug system under transcriptional activator 3 (STAT3)/retinoid-related orphan nuclear receptor γt (ROR-γt), and the NF-κB pathway by regulating T helper cell 2/T helper cell 17 (Th2/Th17) cytokines. In the study of Ali et al SS (1,5,10 mg / kg / day) was administered one hour before 5-fluorouracil (5-FU) injection for 7 days. The results shown that SSA significantly inhibits pro-inflammatory mediators such as TNF-α, COX-2, IL-1β, and IL-6, and SSA significantly inhibits apoptosis markers such as phosphorylated c-Jun N-terminal kinase (p-JNK) and caspase-3. SSD can also significantly decrease the level of ROS, inactivate P38 and JNK, and inhibit the NF-κB signaling pathway. SSD was intragastrically perfused with 8 mg/kg/day to improve

**Anti-Inflammatory Activity**

SSs exhibit anti-inflammatory activity, and SSD has the strongest anti-inflammatory effect among all SSs. SSD can inhibit a variety of inflammatory processes, including inflammatory exudation, increased capillary permeability, release of inflammatory mediators, leukocyte migration, and connective tissue proliferation. The production of inflammatory cytokines is regulated by the NF-κB signaling pathway. The results of Lu et al showed that both SSA (3.125 μM~12.5 μM) and SSD (3.125 μM~50 μM) can inhibit the activation of NF-κB, thereby inhibiting the production of inducible nitric oxide synthase, COX-2, and proinflammatory cytokines in LPS-induced RAW264.7 macrophages.67

LPS can also induce the activation of the NF-κB signaling pathway. SSA (12.5~100 μM) could significantly reduce the survival rate of RAW264.7 cells. SSA can inhibit pro-inflammatory cytokines in LPS-stimulated macrophages and promote the production of anti-inflammatory cytokines, and its mechanism is related to the regulation of MAPK and NF-κB signals. And SSA (50 μM) can inhibit the signal transduction of PI3 K/AKT/NF-κB/NOD (nucleotide-binding oligomerization domain)-like receptor family 3 and the expression of inflammatory cytokines in human acute monocytic leukaemia cell line THP-1 cell. In addition SSA5(20 mg/kg /day, i.p) can significantly inhibit the production of nitric oxide (NO), TNF-α, and IL-1β induced by cigarette smoke (CS). SSA inhibits the contents of myeloperoxidase (MPO) and MDA in lung tissue induced by CS and significantly inhibits NF-κB induced by CS. A study in which the mice received SSA (5, 10, and 20 mg/kg) intraperitoneally 1 h before LPS treatment revealed that SSA up-regulates the expression of nuclear factor E2-related factor 2 (Nrf2) (Nrf2 can regulate the inflammatory response) and HO-1 in a dose-dependent manner. SSA may inhibit NF-κBp65 and IκBα phosphorylation induced by LPS and inhibit the NF-κB signaling pathway by activating Nrf2, thereby producing anti-inflammatory effect. LxRα is involved in the regulation of inflammation. Activation of LxRα attenuates the activation of NF-κB.

According to report of Zhou et al, the mice were received SSA (5, 10, 20 mg/kg /d, i.g) for 14 days and the results shown that SSA can dose-dependently inhibit TNF-α and NF-κB activation induced by dextran sulfate sodium (DSS), up-regulate the expression of LxRα, and significantly reduce the level of IL-1β. SSA(2 mg/kg /day and 10 mg/kg/day) inhibits IL-6 signal transduction, signal transducer and transcriptional activator 3 (STAT3)/retinoid-related orphan nuclear receptor γt (ROR-γt), and the NF-κB pathway by regulating T helper cell 2/T helper cell 17 (Th2/Th17) cytokines.
intestinal inflammation induced by DSS.\textsuperscript{127} And SSD can increase the expression of anti-inflammatory cytokine interleukin-10 mRNA.\textsuperscript{127} Thus, SSD decreases the release of pro-inflammatory cytokines (TNF-\(\alpha\), IL-1\(\beta\), and IL-6). Total SS purified from \textit{Radix Bupleuri}, which mainly contains SSA, SSB2, SSC and SSD, shows obvious anti-inflammatory effect on formalin-induced mice.\textsuperscript{128} In terms of plasma metabolomics, SS plays an anti-inflammatory role by regulating the metabolism of nicotinic acid, nicotinamide, and arachidonic acid. The study indicating that the development of inflammation was inhibited in all dose groups with SS-treated mice, especially in HD-SS-treated (4.68 g/kg) mice.\textsuperscript{128} And the inhibited effect of SS on paw edema was similar to that of aspirin.\textsuperscript{128}

Wu et al\textsuperscript{129} evaluated the potential therapeutic properties of SSD in LPS-induced inflammatory bone loss mouse model and found that SSD suppressed LPS-induced inflammatory bone loss \textit{in vivo}. Further mechanism study revealed that SSD (2 \(\mu\)M) inhibited the formation and bone resorption of osteoclasts induced by Receptor Activator of Nuclear Factor-\(\kappa\) B Ligand (RANKL) \textit{in vitro}.

**Hormone-Like Activity**

\textit{Radix Bupleuri} is believed to be able to treat some gynecological diseases, such as menopausal symptoms.\textsuperscript{130} The chemical structure of SSD is similar to that of estradiol. It plays an estrogenic role by binding to the estrogen receptor and is a weak phytoestrogen.\textsuperscript{54} SSD (0.01 \(\mu\)M~10 \(\mu\)M) stimulated the growth of MCF-7 cells and significantly affected the cell cycle changes of MCF-7 cells.\textsuperscript{54} The proliferation-promoting effect of SSD can be reversed by the combination of anti-estrogen ICI-182780.\textsuperscript{54} Therefore, SSD has potential estrogenic activity in MCF-7 cells.\textsuperscript{54} As an agonist of estrogen receptor, SSD could activate estrogen response element (ERE)-luciferase activity via the ER\(\alpha\)-mediated pathway in a dose-dependent manner (10 nM to 10 \(\mu\)M); and the activation of ER\(\beta\)-mediated ERE-luciferase activity by SSD only occurred at a high concentration (10 \(\mu\)M).\textsuperscript{54} SSD can increase the expression of ER\(\alpha\) protein and mRNA and activate ER\(\alpha\) preferentially.\textsuperscript{54}

SSA can increase the levels of plasma adrenocorticotropin (ACTH) and corticosterone \textit{in vivo}.\textsuperscript{131} In addition, SSD (0.2, 2.0 and 20 \(\mu\)g/kg, i.e.v.) has a special effect on corticotropin-releasing factor (CRF) neurons.\textsuperscript{132} SSD may stimulate the expression of the CRF gene and the release of CRF, which in turn stimulates the ACTH secretion of anterior pituitary and the expression of the proopiomelanocortin gene in a dose-dependent manner.\textsuperscript{132}

**Immunomodulatory Activity**

Previous studies have shown that SSA, SSF, and 23-O-acetylsaikosaponin a have moderate immunomodulatory activity, whereas SSD has the strongest immunomodulatory activity among all SSs.\textsuperscript{133}
SSA (2, 10 mg/kg/day, i.g.) can reduce the level of ovalbumin-specific immunoglobulin IgE/IgG1 in BALB/c male mice. Sun et al. indicated that SSA (5 and 10 µM) selectively promotes the apoptosis of activated T lymphocytes, thereby avoiding non-specific immunosuppression. SSA destroys the mitochondrial membrane potential in a dose-dependent manner, resulting in the release of cytochrome c from the mitochondria to the cytoplasm. SSA can also block the G0/G1 phase and induce T lymphocyte apoptosis through the mitochondrial pathway.

SSD (10 and 20 µM) can significantly inhibit the expression of early (CD69) and late (CD71) T lymphocytes stimulated by concanavalin A or phorbol 12-myristate 13-acetate (PMA). CD69 may be involved in the pathogenesis of some autoimmune and inflammatory diseases. SSD interferes with the transport of protein kinase Cθ (PKCθ) from the cytoplasm to membrane and inhibits the phosphorylation of IkBα and JNK in PMA-activated mouse T lymphocytes, but it does not inhibit the phosphorylation of extracellular signal-regulated kinase. SSD regulates protein kinase C pathway through PKCθ, JNK, and NFκB.

**Anti-Asthmatic Activity**

In the study of Park et al, SSA (1 mg/kg~10 mg/kg, i.v.) has anti-asthmatic effects in rats. SSA exerts partial anti-allergic or anti-asthmatic effects and significantly inhibits bronchoconstriction by directly antagonizing the histamine effect and reducing the release of histamine from mast cells. SSB is a direct TAS2R14 (TAS2R14, as a bitter receptor, has the function of bronchiectasis and anti-inflammation) agonist, which can inhibit IgE-induced mast cell degranulation. Further studies are needed to verify their anti-asthmatic activity. Chloroquine, as a positive control, significantly inhibited IgE-induced hexosidase release from mast cells at 1000, 500, and 250 µM. In addition, SSB at 10.0 µM and 5.0 µM inhibited IgE-induced mast cell degranulation.

**Anti-Adipogenic Effects**

Obesity is a lipid metabolism disorder caused by genetic, medical, nutritional, and other environmental factors. It is characterized by a complex condition of excess lipid accumulation in adipocytes. Adipogenesis is a differentiation process that converts preadipocytes into mature adipocytes and contributes to excessive fat deposition. Lim et al. investigated the anti-obesity effects of SSA and SSD in mouse 3T3-L1 adipocytes. They showed that SSA and SSD significantly inhibited lipid accumulation without affecting cell viability within the range of the tested concentrations (0.938-15 µM). SSA and SSD also dose-dependently suppressed the expression of peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT/enhancer binding protein alpha (C/EBPα), sterol regulatory element binding protein-1c (SREBP-1c), and adiponectin. Furthermore, the decrease of these transcriptional factors resulted in the repressed expression of several lipogenic genes including fatty acid binding protein (FABP4), fatty acid synthase (FAS), and lipoprotein lipase (LPL). In addition, SSA and SSD enhanced the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and its substrate, acetyl-CoA carboxylase (ACC), and inhibited the phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) and p38, but not c-Jun-N-terminal kinase (JNK). These results suggest that SSA and SSD inhibit adipogenesis through the AMPK or MAPK pathways in the early stages of adipocyte differentiation. This is the first study on the anti-adipogenic effects of SSA and SSD, and further research in animals and humans is necessary to confirm the potential of SSs as therapeutic agents for obesity.

**Structure-Activity Relationship**

As mentioned above, SSA and SSD have obvious protective effect on liver injury caused by D-galactosamine hydrochloride (D-GalN), which can significantly reduce microsomal enzyme activity and P450 content, and the effect of SSD is obvious stronger than SSA. However, SSB1, SSB2 and SSC did not alter microsomal enzymatic activity. In addition, SSA and

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**Table 8. Type VII Saikosaponin.**

| Plant specie         | Compounds   | R                      | Reference |
|----------------------|-------------|------------------------|-----------|
| *B. scorzonerifolium*| Bupleurososide XIII | β-D-Glc-(1→3)-β-D-Fuc- | 20        |
SSD can induce apoptosis of tumor cells and are cytotoxic to tumor cells, but SSC has no anti-proliferative activity at high concentration, which may be due to the different types of sugar chains on C-3. And the anti-proliferative activity of SSD is stronger than that of SSA. SSA can increase ACTH levels in plasma. The role of SSA in the stimulation...
| Compound | Animal/Cell (organ) | Model/stimulation | Dosage | Effects | Reference |
|----------|--------------------|-------------------|--------|---------|-----------|
| SSA      | Hippocampal neuronal culture | Epilepsy and status epilepticus | 0.3 μM-4 μM | Terminates SREDs in the HNC model of AE, reduced the peak amplitude of NMDA-evoked current and the peak current amplitude of INAP | 46 |
| SSA      | CA1 neurons of rat hippocampal | 4AP seizure | 1 μM | Epileptiform discharges frequency and duration | 47 |
| SSA      | B57BL/6 mice Aβ | Aβ | 8-16 mg/kg | improve the learning and memory impairment | 48 |
| SSC      | SH-SY5Y cell, SK-N-SH cell, H4 cell and PC12 cell Aβ | Aβ | 3-10 μM | promote axonal growth mediated by the nerve growth factor, increases microtubule assembly, and inhibits brain endothelial cell apoptosis induced by antipeptide | 49 |
| SSD      | PC12 cell H2O2 | | 200-400μg/ml | reduces the activation of the MAPK signaling pathway by scavenging ROS | 51 |
| SSD      | SH-SY5Y cell | Glutamate-induced neurotoxicity | 0.5-10 μM | intrinsic free radical-scavenging activity, induction of endogenous antioxidant enzyme activities and HO-1 expression mediated | 52 |
| SSA, SSD | SD rats | Carrageenan-induced paw edema | SSA 5-20 mg/kg; SSD 5-20 mg/kg | Acute inflammation ↓, paw thickness ↓ | 57 |
| SSA      | Wistar rats | Chronic unpredictable mild stress | 25, 50 or 100 mg/kg | Perimenopausal depression-like symptoms ↓, sucrose preference↑, latency to feed in the novelty-suppress ed feeding test, immobility time in the forced swimming test↓ | 60 |
| SSD      | SD rats | Chronic unpredictable mild stress | 0.75-1.5 mg/kg | Serum corticosterone levels ↓, BDNF, generation of neurons, GR expression and nuclear translocation↑ | 67 |
| SSD      | ICR mice | LPS | 1 mg/kg | HMGB1↑, NF-κB↑, IL-1β↑, IL-6↑, TNF-α↑ inhibits the translocation of HMGB1 from the nucleus to cytoplasm in primary microglia | 72 |
| SSD      | ICR mice | LPS | 0.5 mg/kg | attenuates the activation of the Ras homolog gene family member A/MAPK/NF-κB signaling pathway | 74 |
| SSD      | SD rats | Chronic unpredictable mild stress | 0.75-1.5 mg/kg | down-regulate the expression of fibroblast growth factor-2 mRNA by negatively regulating NF-κB and positively targeting microRNA-155, reducing OS in hepatocytes and inhibiting hepatic inflammation during liver injury, hepatoprotective effects by regulating the activity of glucose-6-phosphatase, NADPH-cytochrome C reductase and 5′-nucleotidase | 75 |
| SS       | Wistar rats | D-galactosamine | 5 mg/kg | | 78 |
| SSD      | SD rats | CCl4 | 1.0-2.0 mg/kg | TNF-α1, IL-61, NF-κBp65↑ | 79 |
| SSD      | HL7702 cells (liver) | CCl4 | 0.5-2 μM | MDA, TSOD, OS, inflammation ↓ | 80 |
| SSA      | LX-2 cells | / | 5 μM | BMP-4 expression, hepatic stellate cell activation↓ | 81 |
| SSA      | C57BL/6 mice | LPS | 5-20 mg/kg | inhibit the NF-κB signaling pathway and inflammation by increasing the expression of LxRα | 82 |
| SSD      | HSC-T6 cell | OS | 5 μM | ECM deposition, TGF-β1, hydroxyproline, collagen-1 and tissue inhibitor of metalloproteinases-1↓, matrix metalloproteinase-1↑ | 84 |
| SSA, SSD | C57BL/6 mice, MPH | | | SSA and SSD modulated glycerolipid | 81 |

(Continued)
| Compound | Animal/Cell (organ) | Model/stimulation | Dosage | Effects | Reference |
|----------|--------------------|------------------|--------|---------|-----------|
| SSD      | C57BL/6j mice      | Thioacetamide    | 2 mg/kg| food intake↑, body weight↑, CAT↑, GPx↑, SOD↑, COX-2↓, ALT↓, AST↓, ALP↓, IL-1β↓, TNF-α↓, FGF21↓, NFκB and iNOS mRNA↓ | 82       |
| SSA, SSB2| Human fetal lung fibroblasts | Human coronavirus 229E infection | 0.25-25 μM | Viral attachment and penetration↓, SSB2 IC₅₀ 1.7 μM | 87       |
| SSB2     | Human hepatoma HuH7 cells, HuH7.5 and S29 cells | HCV | 50 μM | Neutralization of virus particles, viral attachment, viral entry/fusion, binding of serum-derived HCV onto hepatoma cells↓ | 88       |
| SSB2     | HuH7.5 cell | HCV | 10-100 μM | neutralize the virus or induce conformational changes in the glycoprotein so that the virion is not contagious | 89       |
| SSC      | Human hepatoma cells | HBV | 2.5-40 μg/ml | HBV DNA replication↓ | 90       |
| SSC      | HepG2.2.15 cells | HBV | 2-40 mg/ml | stimulates the expression of IL-6, down-regulates the host transcription factors hepatocyte nuclear factor 1α and hepatocyte nuclear factor 4α, and inhibits the synthesis of HBV pgRNA | 91       |
| SSD      | Vero cells | Measles and herpes simplex virus | 5 mM | direct inactivating effects on both measles and herpes simplex virus | 92       |
| SSD      | HeLa and HEK293 T cells | EV-A71 | 15-30 μM | inhibited EV-A71 RNA replication and subsequent viral protein synthesis, thereby preventing EV-A71-induced cell death | 89       |
| SSD      | HeLa and MCF-7 cells | TNF-α | 10 μM | cytosolic calcium level, autophagy induction, disruption of calcium homeostasis↑ | 97       |
| SSD      | A549 cells | / | 10,20 μM | p53, p21, cell cycle arrest, FasL pathway↑ | 98       |
| SSD      | SMMC-7721 cells | Radiation | 3 μg/ml | Potentiates the effects of radiation on SMMC-7721 cells to induce G0/G1 arrest | 102      |
| SSD      | DU145 cells | / | 1-50 μM | Proliferation of DU145 cells↓, caspase-3, p53 and p21↑, mitochondrial membrane potential↓, release of cytochrome c, apoptosis and cell cycle arrest at G0/G1 phase↑ | 103      |
| SSD      | HCC1937, MDA-MB-468, MDA-MB-231, MCF-7 and HT-29 cells | / | 10-20 μM | lead to tumor cell apoptosis through inhibit Wnt /β-catenin signal transduction and the expression of β-catenin and its downstream target genes | 104      |
| SSD      | MCF-7 cells | Adriamycin(ADR) | 1-5 μg/ml | Sensitivity to ADR↑, p-gp-mediated efflux↓ | 105      |
| SSA, SSC, SSD | A375.S2 cells | / | 20 μM | | 106      |
| SSB2     | HEK293 and BRL3A cells | Cisplatin and colchicine | 64, 128 μM | Pgp↑, MRP1/Mrp1↑, MRP2/Mrp2↑ | 107      |
| SSD      | NB4,HEK 293 cells | psPAX2, pMD2.G | 6.12 mg/kg | contributed to generate functional mature neutrophils which capable of fighting infection both in vitro and in vivo. | 104      |
| SSD      | Rat H9c2 cells | DOX | 1 μM,1 μg/kg | enhance the proliferation of H9c2 cells, and inhibit DOX-induced apoptosis, downregulate the DOX-induced p38 phosphorylation | 105      |
| TBSE     | Human colon cancer cell SW480 and SW620 cells | / | 50 μg/ml | pro-apoptotic proteins Bax↑, Caspase3↑, Caspase9↑, Cleaved Caspase3 and Cleaved Caspase9↑, Bel2↓, PI3K↓, Akt↓, mTOR | 106      |

(Continued)
of CRF neurons appears to be small. The specific effect of SSD on CRF neurons can stimulate the expression of CRF gene and the release of CRF, thereby promoting the secretion of ACTH in the anterior pituitary, and SSD has the strongest anti-inflammatory activity. In addition, the 13,28-epoxy group, as the unique structure of type I saponins, show good anti-influenza activity and strong cytotoxicity. SSs with different ethylenic structures show different anti-influenza activities, which indicates that different ethylenic structures may affect the pharmacological activity of SSs. However, some SSs with same aglycone structure have different anti-influenza activities, which may also be due to the effect of different types of sugar chains on C-3 on the activity. In addition, SSN and SSH showed similar EC50 (50% effective concentration) values, indicating that the hydroxyl groups on C-23 show almost no effect on antiviral activity. And the direction of 16-OH had a slight effect on the antiviral activity. Nepasaikosaponin K showed more effective antiviral activity than 11-α-methoxy-saikosaponin F, which indicated that the methoxy group of C-11 might weaken the antiviral activity. It can be seen from the above that 13,28-epoxy group, as a unique structure of type I saponins, can enhance the protective effect of liver injury, enhance the anti-tumor effect, increase the level of ACTH by stimulating the expression of CRF gene and the release of CRF, enhance anti-influenza parade and have greater cytotoxicity. The hepatoprotective activity,

| Compound | Animal/Cell (organ) | Model/stimulation | Dosage | Effects |
|----------|---------------------|------------------|--------|---------|
| SSA      | RAW 264.7 cells     | LPS              | 3.125-12.5 μM | and phosphorylated proteins P-PI3K↓, P-Akt↓, P-MTOR↓, COX-2, iNOS, TNF-α, IL-1β, IL-6, NF-κBα, MAPK↓, IL-10↑ |
| SSA      | C57BL/6 mice        | CS               | 5, 10, and 20 mg/kg | NO↓, TNF-α↓, IL-1β↓ |
| SSA      | C57BL/6 mice        | LPS              | 5, 10, and 20 mg/kg | MPO↓, MDA↓, TNF-α↓, IL-1β↓, IL-6↓, Nrf2↑ |
| SSA      | C57BL/6 mice        | DSS              | 5, 10, and 20 mg/kg | MPO↓, TNF-α↓, IL-1β↓, LXRα↑ |
| SSA      | BALB/c mice         | Ovalbumin        | 2, 10 mg/kg | IL-4↓, IL-5↓, IL-6↓, IL-13↓, IL-17↑, TNF-α↓ |
| SSA      | BALB/c mice         | 5-FU             | 1-10 mg/kg | TNF-α↓, COX-2↓, IL-1β↓, IL-6↓ |
| SSD      | HK-2 cells          | Cisplatin        | 20-150 μM | Viability rate↓, attenuated the caspase-3 activation and programmed apoptosis, TNF-α↓, IL-1β↓, IL-6↓, iNOS↓, DDP-induced activation of NF-κBα, JNK↓, and MAPKs↓ |
| SSD      | BALB/c mice         | DSS              | 8 mg/kg | TNF-α↓, IL-1β↓, IL-6↓ |
| SS       | Kunming mice        | Formalin-induced paw edema | 0.52-4.68 g/kg | AA↑ and PGE2 production ↓ |
| SSD      | Bone marrow-derived macrophages | LPS | 2 μM | SSD inhibited the formation and bone resorption of osteoclasts induced by RANKL in vitro. SSD suppressed LPS-induced inflammatory bone loss in vivo. |
| SSA      | Mouse lymph node cell isolated | ConA | 1-10 μM | Con A-stimulated IL-2, IFN-γ and TNF-α production↓, G0/G1 arrest |
| SSD      | Mouse lymphocytes from lymph nodes | ConA, and PMA | 5, 10 and 20 μM | IL-2 production, CD69 and CD71 expressions of mouse T cells, phosphorylations of IkBα and JNK↓, interfered with PKCθ translocation |
| SSA      | Guinea pig trachea  | Histamine, leukotriene D4 | 100-500 μg/ml | Trachea contraction ↓, cutaneous dyeexudation ↓ |
| SSA      | Peritoneal mast cells | Compound 48/80, A23187 | 100-500 μg/ml | Histamine releases ↓ |
| SSA      | Male mice           | 0.1-0.5 mg/kg | Histamine releases ↓ |
| SSB      | HEK293 cell/ Mast cells | IgE | 2.5-10 μM | SSB activates TASSR14 with EC50 4.9 μM, mast cells degranulation ↓ inhibit adipogenesis through the AMPK or mitogen-activated protein kinase (MAPK) pathways in the early stages of adipocyte differentiation |
| SSA, SSD | 3T3-L1 Preadipocytes | / | 0.938-15μM | |

Table 9. Continued.
anti-tumor activity, anti-inflammatory activity and immuno-modulatory ability of SSD were stronger than those of SSA. It is suggested that 16α-OH has stronger pharmacological activity than 16β-OH. And the methoxy group of C-11 and the different alkene bonds on different types of saponins also affect the anti-influenza virus activity.

Conclusion

Studies in vivo and in vitro have shown that SSs are a group of widely distributed triterpenoids. SSs play an important role in anticonvulsant, antiepileptic, anti-Alzheimer disease, antidepressant, liver protection, antiviral, anti-tumor, anti-inflammatory, hormone-like activity and immunomodulatory function. The structures of SSs are closely related to their pharmacological activity. At present, research on the structure-activity relationship of SSs is still lacking. Future work is necessary to better understand the structure-activity relationship of SSs for clinical application.

By reviewing pharmacological activities of SSs, this work provides a basis for further studying the mechanism of action of SSs and developing better therapeutic drugs with SSs in the future. However, the detailed mechanism of action and the metabolism process of SSs in vivo was still insufficient, and it needs to be strengthened in the future. There are many different kinds of SSs, and the contents of SSs in several of Bupleurum species are also different. Among them, SSA, SSC and SSD are the most common saponins, which have many related studies. But studies on other saponins with low content are still lacking.

Taken together, this review summarizes the structure and pharmacological action of SSs as the main active component of Bupleurum L. plants, which reflects the importance of SSs and provides a necessary direction for future research. In addition, this review also provides a reference for the research and development of new drugs with SSs.

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Author Contributions

Y.Y. and J.L. conceived and designed the manuscript. A.J. and X.Y. wrote, revised the manuscript, and prepared Figure 1–9 and Table 1–9. A.J., X.Y., B.Z., J.L., Y.W. and R.M. collected and analyzed the literatures.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

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| Abbreviation | Full Form | Details |
|--------------|-----------|---------|
| SSs | Saikosaponins |  |
| SS | Saikosaponin |  |
| I$_{\text{NAP}}$ | Persistent sodium current |  |
| HNC | Hippocampal neuron culture |  |
| SREDs | Spontaneous recurrent epileptiform discharge |  |
| SE | Status epilepticus (SE) |  |
| 4AP | 4-aminopyridine |  |
| Aβ | Amyloid-beta |  |
| MAPK | Mitogen-activated protein kinase |  |
| OS | Oxidative stress |  |
| ROS | Reactive oxygen species |  |
| HO-1 | Heme oxygenase-1 |  |
| PI3K | Phosphatidylinositol 3-kinase |  |
| 5-HT | 5-Hydroxytryptamine |  |
| HPA | Hypothalamus-pituitary-adrenal |  |
| TNF | Tumor necrosis factor |  |
| IL | Interleukin |  |
| CUMS | Chronic unpredictable mild stress |  |
| BDNF | Brain-derived neurotrophic factor; brain-derived neurotrophic factor–tyrosine kinase receptor B | BDNF-TrkB |
| PRRT2 | Proline-rich transmembrane protein-2 |  |
| DA | Dopamine |  |
| GR | Glucocorticoid receptor |  |
| HMGB1 | High mobility group box-1 |  |
| NF-κB | Nuclear factor kappa-B |  |
| LPS | Lipopolysaccharide |  |
| TLR4 | Toll-like receptor 4 |  |
| LPA1 | Lyosphosphaticid acid receptor 1 |  |
| mRNA | Messenger RNA |  |
| Bel-2 | B-cell lymphoma-2 |  |
| i.p. | Intraperitoneal |  |
| D-GalN | D-galactosamine |  |
| MDA | Malondialdehyde |  |
| BMP4 | Bone morphogenetic protein-4 |  |
| α-SMA | Alpha-smooth muscle actin |  |
| LxRα | Liver X receptor alpha |  |
| ERβ | Estrogen receptor beta |  |
| Erα | Estrogen receptor alpha |  |
| NAFLD | Nonalcoholic Fatty Liver Disease |  |
| PPARα | Peroxisome proliferator-activated receptor alpha |  |
| CAT | Catalase |  |
| GPx | Glutathione peroxidase |  |
| SOD | Superoxide dismutase |  |
| COX-2 | Cyclooxygenase-2 |  |
| ALT | Alanine aminotransferase |  |
| AST | Aspartate aminotransferase |  |
| ALP | Alkaline phosphatase |  |
| FGF21 | Fibroblast growth factor-21 |  |
| NFκB | Nuclear factor kappa B |  |
| iNOS | Inducible nitric oxide synthase |  |
| SREBP1 | Sterol regulatory element–binding protein 1 |  |
| p-eIF2α | Phosphorylated eukaryotic initiation factor 20 subunit |  |
| ATF4 | Activating transcription factor 4 |  |
| CHOP | C/EBP homologous protein |  |
| HIV | Human immunodeficiency virus |  |
| HCV | Hepatitis C virus |  |
| HBV | Hepatitis B virus |  |
| CoV | Novel coronavirus |  |
| 2019-nCoV | 2019 novel coronavirus |  |
| CDK2 | Cyclin-dependent kinase 2 |  |
| P-gp | P-glycoprotein |  |
| CCIN | Cancer chemotherapy induced neutropenia |  |
| DOX | Doxorubicin |  |
| TBSE | Bupleurum saponin extracts |  |
| HSVtk/GCV | Herpes simplex virus thymidine kinase/ganciclovir |  |
| SUMO | Sentinel/small ubiquitin-like modifier |  |
| SENP5 | Specific protease 5 |  |
| NO | Nitric oxide |  |
| CS | Cigarette smoke |  |
| MPO | Myeloperoxidase |  |
| Nrf2 | Nuclear factor E2-related factor 2, i.e.: Gavage |  |
| STAT3 | Signal transducer and transcriptional activator 3 |  |
| ROR-γ | Retinoid-related orphan nuclear receptor γ |  |
| Th2/Th17 | T helper cell 2/T helper cell 17 |  |
| 5-FU | 5-Fluourouracil |  |
| p-JNK | Phosphorylated c-Jun N-terminal kinase |  |
| ERE | Estrogen response element |  |
| icv | Intra-cerebroventricular injection |  |
| RANKL | Nuclear Factor-κ B Ligand |  |
| ACTH | Adrenocorticotropic |  |
| CRF | Corticotropin-releasing factor |  |
| PMA | Phorbol 12-myristate 13-acetate |  |
| PKCθ | Protein kinase Cθ |  |
| PPARγ | Peroxisome proliferator-activated receptor gamma |  |
| C/EBPα | CCAAT/enhancer binding protein alpha |  |
| SREBP-1c | Sterol regulatory element binding protein-1c |  |
| FABP4 | Fatty acid binding protein |  |
| FAS | Fatty acid synthase |  |
| LPL | Lipoprotein lipase |  |
| AMPK | Adenosine monophosphate-activated protein kinase |  |
| ACC | Acetyl-CoA carboxylase |  |
| ERK1/2 | Extracellular-regulated kinase 1/2 |  |
| JNK | c-Jun-N-terminal kinase |  |
| ADR | Adriamycin |  |