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Review

Saposhnikovia divaricata—An Ethnopharmacological, Phytochemical and Pharmacological Review*

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ABSTRACT ***Saposhnikovia divaricata*** **(Turcz.) Schischk., a perennial herb belonging to the family *Umbelliferae*, is widely distributed in Northeast Asia. Its dried root (*Radix Saposhnikoviae*) is used as a Chinese herbal medicine for the treatment of immune system, nervous system, and respiratory diseases. Phytochemical and pharmacological studies have shown that the main constituents of *S. divaricata* are chromones, coumarins, acid esters, and polyacetylenes, and these compounds exhibited significant anti-inflammatory, analgesic, antioxidant, antiproliferative, antitumor, and immunoregulatory activities. The purpose of this review is to provide comprehensive information on the botanical characterization and distribution, traditional use and ethnopharmacology, phytochemistry, and pharmacology of *S. divaricata* for further study concerning its mechanism of action and development of better therapeutic agents and health products from *S. divaricata*.**

KEYWORDS ***Saposhnikovia divaricata*****, Chinese medicine, ethnopharmacology, phytochemistry, pharmacology**

Saposhnikovia divaricata, the sole species in the genus *Saposhnikovia* Schischk. (*Umbelliferae*), is widely distributed in China, Japan and Korea.[1] Previous literature showed that its dried roots (*Radix Saposhnikoviae*) is commonly used to treat cold and gout diseases,[2] which has been used in Chinese medicine (CM) practices for over 2000 years.[1,3] So far, a lot of the phytochemical and pharmacological studies on *S. divaricata* have been carried out, but the mechanism of action of most of its active constituents remains largely unknown.[4] And the reports on the herbal composition and traditional use of *S. divaricata* are scattered. This review summarizes previously and currently known information regarding the botanical characterization, habitats, distribution, ethnopharmacology, phytochemistry, and pharmacology of *S. divaricata*. This review can guide future studies in their investigation of the mechanism of action of *S. divaricata* and develop novel therapeutic drugs and health products from this plant.

Botanical Characterization and Distribution

S. divaricata is a perennial herb, which grows to a height of 30–80 cm. The root is cylindrical, branched, and annular; while the crown is surrounded by fibrous remnant sheaths. The stem is branched from the base, and the branches are as long as the stem. The leaves are ovate or oblong, 14–35 cm in length, 6–18 cm in width, and contain 2–3 pinnatisect. Its flowers are white, glabrous, and obovate with an incurved tip. The cremocarp is oblong or ellipsoid and its dorsal ribs are slightly prominent while the lateral ribs are narrowly winged. The plant blossoms from July to August and fruits in September.[5,6] The roots of *S. divaricata* are generally harvested during August due to their important folk medical properties and as food resource (Appendix 1).

As a cold- and drought-resistant plant, *S. divaricata* is ecologically adaptable;[7-9] giving it the ability to grow on grasslands, hills, and gravel slopes. It was mainly produced in Henan, Jiangsu, Shaanxi, Hebei, and Shandong provinces in ancient China.[3] A

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comprehensive analysis of ancient herbal books showed northward movement of *S. divaricata*-producing areas in China with changes in dynasties, for which natural resources have been destroyed by the expansion of cultivated land with a growth in population.[10] At present, *S. divaricata* is mainly produced in Northeastern China, Inner Mongolia, Shanxi, Hebei, Shandong, and Shaanxi provinces. *S. divaricata* cultivation has regained momentum as its high medicinal and dietary value and became more apparent in recent years. Heilongjiang Province, China is the major producing region of cultivated *S. divaricate* and has the largest output.[11] *S. divaricata* is classified according to its quality in different regions. *S. divaricata* produced in Heilongjiang, Jilin, Liaoning, and Inner Mongolia (East) is of the best quality and is known as Guanfangfeng or Dongfangfeng. By contrast, *S. divaricata* produced in Inner Mongolia (West), Hebei (Chengde, Zhangjiakou), and Shanxi, known as Xifangfeng, and that produced in Hebei (Baoding, Tangshan) and Shandong, known as Shanfangfeng, Huangfangfeng, and Qingfangfeng, are of inferior quality.[12]

Traditional Uses and Ethnopharmacology

S. divaricata was first recorded in *Shen Nong's Materia Medica* (Shen Nong Ben Cao Jing) written in 300 A.D. China with significant therapeutic properties against common cold, headache, rheumatic diseases, arthralgia, rubella, pruritus, and tetanus. It was ranked as a premium-grade herb in this ancient pharmaceutical monograph.[3] Its dried roots possess the property of pungent, sweet and slight warm, which are widely used clinically for treating exterior syndromes including migraines and headaches caused by common cold and internal diseases including Bi syndrome and rosacea in CM.[13] Various traditional preparations containing the roots of *S. divaricata* are listed in Appendix 2.

Phytochemistry

Phytochemical studies have revealed that there are approximately 100 compounds with different structural patterns isolated from *S. divaricata*, including chromones, coumarins, acid esters, polyacetylenes, volatile oils, polysaccharides, and inorganic elements[1,4,13-28] as shown in Appendixes 3–9.

Chromones

Chromones, a subclass of flavonoids, are a class of oxygen-containing heterocyclic compounds having a benzo-cyclized γ-pyrone ring. They are the primary active components of *S. divaricata*, and research on these compounds has been well studied than that on other components. To date, 17 chromones have been identified (Appendix 3), which are ledebouriellol (1), hamaudol (2), *sec*-*O*-glucosylhamaudol (3), 3'-*O*-acetylhamaudol (4), 3'-*O*-angleoylhamaudol (5), divaricatol (6), cimifugin (7), *prim*-*O*-glucosylcimifugin (8), 5-*O*-methylvisamminol (9), 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol (10), norcimifugin (11), (3'S)-3'-*O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosylhamaudol (12), (2'S)-4'-*O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosylvisamminol (13) (14), 4'-*O*-β-D-glucopyranosylvisamminol (14), 4'-*O*-β-D-glucopyranosyl-5-*O*-methylvisamminol (15), undulatoside A (16), and wogonin (17).[15] Despite their simple structure, they have good anti-inflammatory, free radical-scavenging, and immunostimulatory effects.[16-18] Among them, compounds 3, 7–10 are the primary chromones, which are abundant in *S. divaricata*, in particular, compounds 7 and 8.[19,20]

Coumarins

Coumarins, a type of benzopyrones containing a benzene ring fused to a pyrone ring, are the most abundant chemical constituents of *S. divaricata*. They have extremely diverse structures, which are divided into simple coumarins, pyranocoumarins, furanocoumarins, and other coumarins.[1,21,22] At present, a total of 35 coumarins, primarily furanocoumarins and pyranocoumarins, have been identified from *S. divaricata* (Appendixes 4 and 5). Among them, the 17 furanocoumarins isolated include bergapten (18), byakangelicin (19), deltoin (20), imperatorin (21), isoimperatorin (22), isobergapten (23), marmesin (24), methoxy-8-(3-hydroxymethyl-but-2-enyloxy)-psoralen (25), nodakenetin (26), oxypeucedanin hydrate (27), phellopterin (28), psoralen (29), sapodivarin (30), xanthotoxin (31), 5-hydroxy-8-methoxypsoralen (32), nodakenin (33), and xanthoarnol (34).[23] Five simple coumarins isolated from the herb, including fraxidin (35), isofraxidin (36), scopoletin (37), umbelliferone (38) and 5-methoxy-7-(3, 3-dimethylallyloxy)-coumarin (39), have simple structures but show a variety of biological activities such as dispelling phlegm and antitumor activity. Lastly, 13 pyranocoumarins have also been identified from *S. divaricata*, including anomalin (40), decursinol (41), decursinol angelate

(42), divaricoumarin A (43), divaricourmarin B (44), divaricourmarin C (45), praeruptorin B (46), praeruptorin F (47), cis-3', 4'-disenecioylkhellactone (48), cis-3'-isovaleryl-4'-acetylkhellactone (49), cis-3'-isovaleryl-4'-senecioylkhellactone (50), (–)-cis-khellactone (51), and (3'S)-hydroxydeltoin (52).[24-27]

Recently, compounds 43, 44 and 45, with the molecular formulas $C_{25}H_{32}O_{12}$, $C_{25}H_{30}O_{12}$, and $C_{25}H_{30}O_{12}$, respectively (Appendix 6), were found to be effective against the porcine epidemic diarrhea virus (PEDV).[28] Compound 44 has the strongest inhibitory effect on PEDV in Vero cells. *In vitro* studies showed that compound 44 inhibits viral replication during the protein synthesis stage, thus, demonstrating its antiviral properties for potential application in intractable human diseases caused by coronavirus.[28]

Acid Esters

Nineteen fatty acids, 2 organic acids, and 9 methyl ester derivatives of organic acids have been isolated from supercritical CO_2 extract, fatty acid extract, and ethanol extracts of *S. divaricata* roots, respectively. Among them, a phenylpropanoid fatty acid ester, identified as (±)-2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-3-methoxypropyl nervonic acid ester (53), significantly suppressed nitric oxide (NO) in lipopolysaccharide (LPS)-induced RAW 264.7 mouse macrophages.[16] Another acid ester, lindiol (54), has also been isolated from *S. divaricata* roots (Appendix 7).

Polyacetylenes

Five polyacetylene compounds, including panaxynol (55), falcarindiol (56), (8*E*)-heptadeca-1,8-dien-4,6-diyn-3,10-diol (57), (9*Z*)-1-methoxy-9-heptadecene-4,6-diyn-3-ol (58), and (8*E*)-10-hydroperoxy-1,8-heptadecadiene-4,6-diyn-3-ol (59) have been isolated from the fibrous roots of *S. divaricata* (Appendix 8).[29]

Others

There are a series of other compounds isolated from *S. divaricata*, such as adenosine (60), daucosterol (61), β-sitosterol (62), marmesinin (63), fangfengalpyrimidine (64), clemiscosin A (65), bitter glycoside (66), melanochrome (67), tectochrysin (68), glycerol monolinoleate (69), glycerol monooleate (70), stigmasterol (71), and 8'-epicleomiscosin A (72), shown in Appendix 9.[23] To date, 45 inorganic elements have been detected in *S. divaricata* by inductively coupled plasma atomic emission spectroscopy. High levels of Zn, Sr, Cr, and Ni are found in the root of *S. divaricata*, especially those of Zn and Sr, with average values being 29.4 and 25.8 μg/g, respectively.[4]

Essential oils, which are relatively complex, have also been isolated from *S. divaricata*. In recent years, nearly 70 volatile compounds have been identified by gas chromatography-mass spectrometry from the roots and fruits of the plant, including panaxynol, α-pinene, β-eudesmol, β-bisabolene, hexanal, pentanol, hexanol, octanal, octanol, nonanal, α-muurolene, acetophenone, 7-octen-4-ol, naphthalene, octadecadienoic acid, falcarinol, cyclohexene, calacorene, decenal, and decadienal, which have been isolated from the roots. Essential oils isolated from the fruit of *S. divaricata* primarily include *n*-heptane, *n*-octane, *n*-caproaldehyde, 2-heptanone, 2-octanone, benzaldehyde, *n*-nonane, myrcene caprylic aldehyde, heptanal, α-thujene, α-pinene, β-pinene, and camphene.[30,31] The compositions and quantities of essential oils in *S. divaricata* vary greatly depending on the extraction method, production area, and mineral elements in the rhizosphere soil.

Polysaccharides are another class of compounds in *S. divaricata*. Three homogenous polysaccharides, saponikovan A, B, and C (relative molecular masses, 5.4×10^4, 2.8×10^5, and 1.32×10^5, respectively), have been isolated from *S. divaricata*. Furthermore, two other acidic *Saposhnikovia* polysaccharides (SPSs), SPSa and SPSb, have been isolated from the dried root and rhizome of *S. divaricata* by DEAE-sepharose fast flow column chromatography. SPSa is primarily composed of galactose, arabinose, rhamnose, and galacturonic acid in the molar ratio of 1:2.3:0.15:4.8. While SPSb is primarily comprised of galactose, arabinose, rhamnose, xylose, and galacturonic acid in the molar ratio of 1:1.5:0.8:0.2:10.2, respectively.[32] SPSa and SPSb are novel acidic polysaccharides isolated from *S. divaricata*.

Pharmacology

Previous studies have demonstrated that *S. divaricate* exhibits a broad range of pharmacological activities, including anti-inflammatory, analgesic, antioxidant, antiproliferative, antitumor, immunoregulatory, antiallergic, antipyretic, anticoagulant, blood circulation-promoting, anticonvulsive, antileukemia, anti-atherosclerosis, and hepatoprotective effects (Appendix 10).[18,33-49]

Anti-inflammatory and Analgesic Activities

Many reports have demonstrated that the extract of *S. divaricata* (SDE) and several of its constituents, including *sec-O*-glucosylhamaudol, cimifugin, *prim-O*-glucosylcimifugin, 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol, 5-*O*-methylvisamminol and anomalin, exhibit significant anti-inflammatory and analgesic activities.[33-39]

Chun, et al[42] reported that SDE extracted with 70% ethanol demonstrated an anti-inflammatory and anti-osteoarthritis activities through *in vitro* and *in vivo* studies. They examined the levels of 4 proinflammatory cytokines in LPS-stimulated RAW 264.7 cells to evaluate the anti-inflammatory activity of SDE *in vitro*, and found that it significantly inhibited the production of NO, prostaglandin E_2 (PGE_2), tumor necrosis factor (TNF), and interleukin-6 (IL-6) at a concentration of 200 or 400 μg/mL. A monosodium iodoacetate (MIA)-induced osteoarthritis model was used to investigate the anti-osteoarthritic activity of SDE *in vivo*. The results of the hind paw weight-bearing assay in rats showed that the weight-bearing distribution reduced rapidly in the group with MIA injection while it decreased only slightly in the group treated orally with SDE (200 mg/kg) and indomethacin (IM, 2 mg/kg). The serum levels of IL-1β, IL-6, TNF-α, and PGE_2 increased in the MIA group but decreased in the SDE- and IM-treated groups. Following MIA injection, the expression of cytokine and inflammatory mediator mRNAs increased while the expression of the cytokine decreased in the SDE- and IM-treated groups. The results showed that SDE maintained normal weight-bearing in MIA-induced osteoarthritis rats, suggesting that SDE could be used to treat osteoarthritis. All of above results indicated that the SDE attenuated stiffness, inhibited the production of proinflammatory cytokines and mediators, and protected cartilage and subchondral bone tissue in the rat model.[50,51]

Chromones isolated from *S. divaricata*, including *prim-O*-glucosylcimifugin, 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol, 5-*O*-methylvisamminol, and cimifugin also have anti-inflammatory properties, which can significantly reduce pain and swelling in arthritic rats.[33] *Prim-O*-glucosylcimifugin was found to inhibit the pathways of mitogen activated protein kinase (MAPK) phosphorylated-extracellular signal-regulated kinase, c-Jun Nterminal kinase (JNK), p38, and p-JNK which was the most effectively suppressed among the MAPK subtypes.[37] Compared with *prim-O*-glucosylcimifugin, cimifugin and 5-*O*-methylvisamminol had a stronger inhibitory effect on NO and inducible NO synthase (iNOS) production.[35] A study showed that *prim-O*-glucosylcimifugin, 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol, cimifugin, and *sec-O*-glucosylhamaudol were all matrix metalloprotease (MMP) inhibitors, which had concentration-dependent inhibitory effects *in vitro* with the 50% inhibitory concentration (IC_{50}) values being 15.6, 108.87, 313.25, and 344.4 μmol/L, respectively, and 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol was the strongest inhibitor of MMP-2.[34]

Anomalin, a coumarin compound isolated from *S. divaricata*, is an active compound against hyperalgesia-associated inflammation.[52] Khan, et al[38] investigated the effect of anomalin on the production of inflammatory molecules in LPS-stimulated murine macrophages to clarify the cellular signaling mechanisms underlying the anti-inflammatory action of anomalin. Cells were treated with various concentrations of anomalin (1, 10, and 50 μmol/L). The results suggested that anomalin can block the protein synthesis and phosphorylation of inhibitor of nuclear factor kappa-B (NF-κB) α (IκBα) and deactivate the transcription of NF-κB by inhibiting iNOS, cyclooxygenase-2, TNF-α and IL-6 in RAW 264.7 cells.

The analgesic and antinociceptive activities of *S. divaricata* are the results of synergistic actions of its various chemical components, including chromones, coumarins and polyacetylenes, although the content and potency of these compounds differ. Oral administration of the *sec-O*-glucosylhamaudol and cimifugin at 40 and 80 mg/kg, respectively, induced significant analgesia.[33] Another study showed that the aglycone part of *sec-O*-glucosylhamaudol and cimifugin significantly increased the potency at doses of 1, 5 and 10 mg/kg.[33] Interestingly, the non-glycosylated dihydropyran C-ring may play an important role in the analgesic effect of chromones.[33] The pain threshold tail writhing test also showed that spasmodic pain was effectively reduced when intramuscular injections of *prim-O*-glucosylcimifugin and 4'-*O*-β-D-glucosyl-5-*O*-methylvisamminol at doses of 100 mg/kg were administered in murine models. The study also demonstrated that chromones including divaricatol, ledeouriellol, and hamaudol exhibited the strongest analgesic effect when administered orally at a dose of 1 mg/kg in rats.[33]

Antioxidant Activities

Oxidative stress is implicated in the pathogenesis of numerous diseases.[53] Polysaccharides and various individual compounds such as cimifugin, 5-*O*-methylvisamminol, imperatorin, and deltoin isolated from *S. divaricata* possess significant antioxidant activities.[54,55] SPS scavenged free radicals and inhibited lipid peroxidation, and the effects on scavenging 1,1-diphenyl-2-trinitrobenzene hydrazine (DPPH) and hydroxyl radical (OH) were especially significant.[18] Acid SPS, the potential primary active ingredient in SPS, was isolated from *S. divaricata* by hot water extraction and ethanol precipitation method; this compound had strong antioxidant activity. The total reducing power, scavenging effect on superoxide anion (O^{2-}), OH, and DPPH, and inhibitory effect on lipid peroxidation induced by Fe^{2+} of different SPS was measured *in vitro* in chemical-simulated systems to evaluate the antioxidant activity. The scavenging rate of acid SPS for DPPH and OH approached 70% with the concentration of 8 mg/mL, which is considered to have a better effect among different SPS.[43] Li, et al[56] prepared different extracts using ultrasound-assisted extraction for different times, temperatures, and solvents, and determined the antioxidant activity of the different extracts by the DPPH assay. Their study results showed that the 80% ethanol extract (prepared after 120 min extraction time) exhibited strong antioxidant activity in the DPPH assay. Furanocoumarins including imperatorins and deltoin isolated from *S. divaricata* also showed antioxidant potential.[39] The inhibitory mechanism involved weakening the activation of IκB kinase and janus kinase, blocking the nuclear translocation of NF-κB and Stat-1 and eliminating the induction of iNOS. The undiluted ethanolic SDE had substantial antioxidant activity determined by the 2,2'-azinobis [3-ethylbenzothiazoline-6-sulfonic acid] (ABTS) hydroxyl radical-scavenging assay; the antioxidant activity values of two batches in different dried roots from *S. divaricata* were equivalent to 6.9 and 7.6 μmol/L trolox, respectively.[18]

Antiproliferative and Antitumor Activities

Animal studies on transplanted S180 tumor strains *in vivo* have shown that polysaccharides from *S. divaricata* possess antineoplastic function. Li, et al[44] combined the S180 oncocyte with celiac macrophagocyte (Mφ) of immunized mice to vaccinate the mice, and at the same time, blocked the function of Mφ by silica gel to observe the effect on the antineoplastic function of *S. divaricata in vivo*. The results showed that *S. divaricata in vivo* could inhibit S180 tumor growth by 52.92%. The antineoplastic activity increased upon vaccination with the combination of S180 oncocyte and celiac Mφ of immunized mice ($P<0.01$). However, the antineoplastic function of *S. divaricata* greatly decreased after Mφ function was blocked by silica gel, and the tumor inhibitory rate decreased from 52.92% to 11.82%. The study indicated that the antineoplastic effect of *S. divaricata* was closely related to Mφ, and the enhancement of the antitumor activity of Mφ could be related to the promotion of the secretion of lysosomal enzymes or cytotoxic cytokines.

In vitro studies have found differential antiproliferative activities of the 70% ethanol SDE (10 mL/g) in leukemia and breast cancer. The combination of *S. divaricata* with camptothecin (CAM) and paclitaxel (PTX) inhibited the proliferation of K562, HL60, MCF7, and MDA-MB-468 cells with reduced IC_{50} values at the dilutions of 1/300, 1/400, 1/250, and 1/600, respectively. The results indicated that the combination of SDE with a lower concentration of CAM or PTX could achieve the same antiproliferative activity as shown by a high concentration of CAM or PTX.[18]

Panaxynol, another active component of the root of *S. divaricata*, was found to suppress the proliferation of K562, Raji, Wish, HeLa, Calu-1, and Vero cells by 30.0%±4.1%, 34.0%±5.6%, 19.4%±3.2%, 32.0%±8.5%, 14.5%±16.8%, and 8.9%±3.2%, respectively, at 25 μmol/L.[41] It induced G0/G1 to S and G2/M phase cell cycle arrest at a concentration of 100 μmol/L *in vitro*. Therefore, its effect may be related to the blocking of cyclin E mRNA expression. Kuo, et al[41] also showed that the ethanol SDE potently inhibited the proliferation of various tumor cells; while a study reported that coumarins showed antitumor activities at concentrations >100 μg/mL.[57]

Immunoregulatory Activities

Besides the antioxidant and antitumor activities, polysaccharides from the roots of *S. divaricata* also show immunostimulatory activity. Liu, et al[58] used a marked test to observe spleen cell proliferation and spleen index as well as the macrophage and phagocytic rate in mice to study the immunoregulatory effects of these polysaccharides. The lymphocyte subset ratio for $CD3^+CD4$ increased from 27.28%±2.30% to 45.82%±1.54% at doses of 250–1000 mg/kg, while the ratio for $CD3^+CD8^+$ was significantly higher

at 17.44%±1.78% (250 mg/kg), but decreased by 13.22%±1.34% (1,000 mg/kg). Polysaccharides increase the release of IL-1 and IL-8 from macrophages *in vivo* and improve the proliferation and lethality of immune cells.[49] Another study showed that SDNP-2 (a purified native polysaccharide) from the water extract of *S. divaricata* exhibited significant antagonistic effect against immunosuppression as shown by the cell viability of the culture supernatants of melanoma cells on RAW 264.7 macrophages.[49]

The percentage of mouse peritoneal macrophage phagocytosis was 20.8%±2.2% in the control group and 30.7%±3.1% in the experimental group treated daily for 4 days with 20 g/kg polysaccharide, and the phagocytosis index of the experimental group was 1.7 times higher than that of the control group.[46]

Others

S. divaricata also showed an antiallergic effect. Controlled trials for the antiallergic effect showed that *S. divaricata* group (2.90±0.45 mg) was significantly lower than the control group (4.88±0.78 mg, $P<0.05$) in body temperature in mice, indicating that *S. divaricata* could inhibit the delayed hypersensitivity induced by 2,4-dinitrochlorobenzene (DNCB).[46] Yang, et al[59] studied the antipyretic effect of SDE prepared by CO_2 supercritical extraction depending on 2,4-dinitrophenol (DNP). The results showed that the antipyretic effect in the low- and middle-dose groups was lower than that in the aspirin control group, while the effect in the high-dose group was similar to that in the control group. *S. divaricata* also has anticoagulant, blood circulation-promoting, and blood stasis-removing effects. Its n-butanol extract can prolong bleeding and coagulation times in mice, which may play a role in activating blood circulation and removing blood stasis by affecting the quantity and function of erythrocytes and fibrinogen.[59] Volatile oils isolated from *S. divaricata* can significantly prolong the coagulation time in Kunming mice and have a good anticoagulant effect.[60] A previous study demonstrated that an intragastric dose of *S. divaricata* extract exhibited a 60% reduction in albino mice experiencing electroshock convulsions. Chen, et al[61] reported that the water SDE showed significant anticonvulsant effects. Additional effects such as antileukemia, anti-atherosclerosis, and hepatoprotective have been observed *in vivo*.[45,62-64]

Toxicity

To evaluate the influence of *S. divaricata* extract in rats, Shang, et al[65] conducted a study on the acute toxicity of the water extract and water extracting-alcohol precipitating extract of the root of *S. divaricata*. After 20–30 min of administration, the mice suffered from lassitude, shortness of breath accompanied by sound, urinary incontinence, other phenomena indicative of poisoning, and death due to generalized convulsions. The test results showed that the water extract and water extracting-alcohol precipitating extract of *S. divaricata*, which had a long history of clinical use, could induce a toxic reaction in mice. The median lethal dose of the water extract of the root of *S. divaricata* was 184.03 g/kg, while that of the water extracting-alcohol precipitating extract was 118.14 g/kg. The acute toxicity of the water extract is less than that of the water extracting-alcohol precipitating extract.[65]

The viability assay based on neutral red incorporation showed that *S. divaricata* had a significant protective effect on LPS-activated RAW 264.7 cells, with no cytotoxicity observed in cells at 1/10,000, 1/5,000 and 1/2,000 dilutions ($P<0.05$). The extract still had no cytotoxic effect, although it reduced viability of the LPS-activated cells at a dilution of 1/1,000 ($P<0.05$).[1]

Conclusions

Although this review makes a systematic and detailed summary of this species, there are some knowledge gaps that require elucidation. Potential future research should address the following. (1) The wild variety of *S. divaricata* cannot fulfill the increasing market demand due to the limitations associated with reduction in plant growth. Overexploitation of wild varieties is a direct consequence of a decline in their wild populations. At the local level, there is no effective managing strategy for *S. divaricata* loss, which may lead to a decline in seed germination in the following year before the seeds maturation. (2) Not only the root but also the leaves, flowers and fruits of *S. divaricata* were used to cure diseases in ancient times.[57] It is imperative to study the medicinal value of the aboveground parts of *S. divaricata* in order to make full use of the resource. (3) There are limited clinical studies on pharmacokinetics for this plant, and the scientific evidence is insufficient to explain the specific mechanism underlying the plant's biological activity. Pharmacokinetic and clinical studies should be conducted to assess the possible therapeutic effect on target organs and the active ingredients responsible for it. (4) The toxicity of *S. divaricata* has not been thoroughly analyzed and

described. Systemic evaluation of toxicity for this plant has not been conducted; similarly, it remains known whether this herb causes serious side effects. Therefore, physiological data are needed to study its toxicity. And the toxicity of *S. divaricata* should be studied in line with its pharmacological potential.

Overall, *S. divaricata* is a valuable herb, which deserves further attention due to its wide applicability and biological activities. Although research on *S. divaricate* is far from being flawless, we have reviewed the latest research results. This article highlights the ethnopharmacological potential of *S. divaricata* and provides a foundation for its utilization.

Conflict of Interest

There are no conflicts of interest.

Author Contributions

Wang WL, Zhang CH and Li MH conceived the structure of article. Yang M, Wang CC, Xu JP, and Wang J searched literature. Yang M and Wang CC wrote the paper. Wang WL, Xu JP and Wang J reviewed and edited the manuscript. All authors read and approved the manuscript.

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