Phytochemical and Biological Progress of *Ixeris sonchifolia* (Bge.) Hance

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Abstract *Ixeris sonchifolia* (Bge.) Hance is a famous traditional Chinese herb (TCH) for medicinal treatment and diet with wide distribution and rich resources. Flavonoids, triterpenoids and sesquiterpene lactones are the characteristic constituents of this TCH. Biological investigation on *I. sonchifolia* revealed the remarkable pharmacological activities of this herb for the treatment of cardiovascular and cerebrovascular diseases. This review summarized the phytochemical and biological progress of *I. sonchifolia* to provide a reference for further research and development of this TCH.

Keywords *Ixeris sonchifolia*, chemical composition, pharmacological activities, flavonoids, sesquiterpene lactones, anti-tumor

Introduction

Ixeris sonchifolia (Bge.) Hance is a plant of the Compositae family, which is also known as “Kudiezi”, “Mantianxing”, etc. *I. sonchifolia* is a biennial herb mainly distributed in northeast China, north China and Inner mongolian.^[1] *I. sonchifolia* is listed as the top species with the effects of clearing away heat-evil, alleviating pain eliminating swelling, and for the treatment of appendicitis, enteritis, dysentery and various purulent inflammation according to *Shennong Herbal Classic* and *Inner Mongolian Chinese Herbal Medicine*.^[1] Modern phytochemical and pharmacological investigation revealed the anti-tumor, anti-inflammatory, analgesic, sedative and cardiovascular diseases activities of this TCH. Recent studies have shown that it can also inhibit platelet aggregation, increase fibrinolytic enzyme activity, increase coronary flow, improve myocardial circulation, and have inhibitory effects on ascites, liver cancer and cervical cancer. *I. sonchifolia* showed valuable medicinal value with many advantages such as abundant source, low price, wide and exact curative effect, no toxic side effect, etc. This review summarized the phytochemical and pharmacological progress on *I. sonchifolia* to provide a reference for better understanding its effective substances.

Chemical Constituents

Since the 1980s, researchers have conducted a series of studies on the chemical constituents of *I. sonchifolia*. More than 100 compounds involving flavonoids, triterpenoids, sesquiterpene lactones and other compounds have been isolated from this plant.^[3-6]

Flavonoids

The content of flavonoids in *I. sonchifolia* is high, and 15 species have been found with flavonoids (Figure 1). According to the structures of the flavonoid aglycones, the flavonoids in *I. sonchifolia* can be classified into two types: luteolin-7-O- β -D-glucopyranoside (1) type and apigenin (2) type.^[7] Eight luteolin glycosides, luteolin-7-O- β -D-glucuronopyranoside (3), luteolin-7-O- β -D-glucuronopyranoside

ethyl ester (4), luteolin-7-O- β -D-glucuronopyranoside ethyl ester (5),^[2,8,9] lutein-7-O-gentibioside (6) and lutein-7-O- β -D-glucuronopyranoside (7) and luteolin-7-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside (8)^[10] and four apigenin-glycosides, apigenin-7-O- β -D-glucopyranoside (9), apigenin-7-O- β -D-glucuronopyranoside methyl ester (10) and apigenin-7-O- β -D-glucuronopyranoside (11).^[11] Among them, luteolin-7-O- β -D-glucuronopyranoside is the main active ingredient and content is the highest in *I. sonchifolia*.

Figure 1 Flavonoids isolated from *I. sonchifolia*.

Besides the above mentioned constituents, four other flavonoids constituents were also isolated, namely 5,7-dihydroxy-4'-methoxy-flavone-7-O-rutinoside (12),^[3] quercetin (13), rutin (14) and isorhamnetin-3-O- β -D-glucoside (15).^[11,12]

Triterpenoids

In addition to flavonoids, triterpenoids are another type of characteristic constituents in *I. sonchifolia*. 16 triterpenoids in-

cluding skeleton of oleanane, ursane, dandelion and lupin^[6] were found in *I. sonchifolia* (Figure 2).

Figure 2 Triterpenoids isolated from *I. sonchifolia*.

These triterpenoids were identified as oleanolic acid (16),^[13] ixeris saponins A–F (17–22),^[14] α -amyrin (23), β -amyrin (24), oleanane (25),^[15] 3 β -hydroxyurs-12-en-11-one acetate (26), 3 β -hydroxyolean-12-en-11-oneacetate (27), 3 β -acetoxytaraxastane-20-en-30-al (28), taraxaster-20-en-3 β , 16 α -diol-3-acetate (29), lupeol (30)^[2,14] and bauereny lactate (31).^[13]

Sesquiterpenes lactones

Sesquiterpenes are the characteristic constituents in *I. sonchifolia*, and there are 17 compounds with defined structures (Figure 3). According to their skeletons, the sesquiterpenes lactones in *I. sonchifolia* can be classified into two types: guaianolide-type and germacranolide-type. Sonchifolactones A–D (32–35) were isolated from the chloroform extraction layer.^[2] 8-Desoxyartelin (36), ixerin X (37), ixerin Z (38), 9 α -hydroxyzaluzlin (39),^[14] 8-desoxyartelin- β -D-glucopyranoside (40), ixirinoside A (41),^[16] and sonchifoliasolides A–H (42–49)^[17,18] were also isolated from *I. sonchifolia*.

Phenylpropanoids

Lignans

Lignans is a type of natural products of oxidative polymerization of phenylpropanoids, mostly in the form of dimers, and a few are trimers and tetramers. There are six lignans isolated from the *I. sonchifolia* (Figure 4), named as dihydroconiferol (50),^[19] sonchifolignan A (51), sonchifolignan B (52),^[2,14] sonchifolinin (53),^[20] (+)-syringarensinol (54)^[6] and glochidiboside (55),^[21] respectively.

Coumarins

Lu *et al.* isolated esculetin (56)^[15] from this plant for the first time (Figure 4).

Adenosine

In 1981, Meng *et al.* isolated and identified adenine nucleosides (57)^[5] in the whole grass of *I. sonchifolia*, which showed an effect of expanding coronary artery.

Figure 3 Sesquiterpenes lactones isolated from *I. sonchifolia*.

Figure 4 Phenylpropanoids and adenosine isolated from *I. sonchifolia*.

Sterols

Three types of compounds including β -sitosterol (58),^[2] daucosterol (59)^[13] and stigmasterol (60)^[22] were isolated from *I. sonchifolia* (Figure 5).

Figure 5 Sterols and alkaloids isolated from *I. sonchifolia*.

Alkaloids

Ma *et al.* isolated scopolamine (61)^[8] from *I. sonchifolia* (Figure 5).

Organic acids and fatty acids

(E)-2,5-Dihydroxycinnamic acid (62),^[8] vanillic acid (63)^[24] and ferulic acid (64)^[14] were isolated from *I. sonchifolia* (Figure 6). Moreover, others were found in this plant, named as palmitic

acid, succinic acid, linoleic acid,^[3, 15] chicoric acid, (-)-3,4-dihydroxycaffeoyl tartaric acid,^[10] 1-furancarboxylic acid,^[20] dandelion-B,^[25] hydroxybenzoic acid,^[24] caffeic acid, original acid and 3,4-dihydroxybenzoic acid.^[7]

Figure 6 Organic acids and fatty acids isolated from *I. sonchifolia*.

Amino acids

A variety of amino acids such as glutamic acid, aspartic acid, serine, proline, citric acid and arginine were isolated and identified from *I. sonchifolia* by Young *et al.*^[26]

Other compounds

Other types of compounds were isolated from *I. sonchifolia*, named as dehydrovomifolol (**65**), lolilide (**66**),^[19] 1,3-dihydropyrimidine (**67**),^[20] 3,4,5-trimethoxyphenyl-1-O- β -D-glucopyranoside (**68**),^[21] (Figure 7) 3 β -acetoxy-11-oxo- Δ -12-ene, 3 β -acetoxy-20-tamxastan-22-one,^[13] 3 β -hydroxy-olean-12-en-11-one acetate, 3,4-dihydroxybenzalacetone,^[3] 8-deoxyartemisactone,^[13] protocathechuic acid ethyl ester, vanillin, protocathechuic aldehyde, 3-(4'-hydroxy-3'-methoxy-phenyl)-1-propanol, liriorelinol-A,^[19] wax alcohol, tryptamine, 11 β ,13-dihydrosantamarine, 3 β -hydroxy-11 β ,13-dihydrocostunolide, ixeriside E, 8-epidesacylcinaropicrin glucoside,^[15] bis-(2-ethylhexyl)phthalate, *p*-hydroxybenzaldehyde, 1,4-benzene dimethanol, and echinocystic acid-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)- α -L-arabinopyranoside.

Figure 7 Other compounds isolated from *I. sonchifolia*.

In addition, Qi *et al.* identified 37 compounds from the volatile oil components of *I. sonchifolia*, including fatty alkanes, ketones, aldehydes, alkenes, enols, alkenes and esters. The main component of the volatile oil is 6,10,14-trimethyl-2-pentadecanone.^[26]

Biological activities and clinical applications

Pharmacological study on *I. sonchifolia* revealed that the crude extracts and pure compounds showed a wide range of biological activities, including the treatment of cardiovascular and cerebrovascular diseases, and anti-tumor, analgesic and sedative activities. "Kudiezi injection" made by its active ingredient is clinically used for treating diseases such as coronary heart disease.

Activity for cardiovascular and cerebrovascular diseases

The adenosine and flavonoids are potent ingredients to treat cardiovascular disease.^[27-31] Hu *et al.* reported *I. sonchifolia* has a preventive effect on atherosclerosis ($P < 0.01$).^[31] Jia *et al.* found 16 and 8 mg/kg group of flavonoids of Kudiezi could reduce the mortality of mice, prolonged death time ($P < 0.05$, $P < 0.01$); 16, 8, 4 mg/kg group could improve behavioral disorder and reduce behavioral score ($P < 0.05$, $P < 0.01$); 10, 5 mg/kg group could reduce the extent of cerebral infarction in rats with focal cerebral ischemia, reduce the water

content of brain tissue and the content of nitric oxide synthase and inducible nitric oxide synthase ($P < 0.05$). It indicated the flavonoids of *I. sonchifolia* could protect ischemic brain injury.^[28] Wang *et al.* found Kudiezi injection showed a significant protective effect on ischemic myocardium.^[32] Feng *et al.* proved the extract of Kudiezi could treat coronary heart disease.^[33] Tao *et al.* reported Kudiezi injection showed a lipid-lowering effect on patients with unstable angina pectoris and further relieved clinical symptoms, improved myocardial ischemia and reduced the incidence of angina pectoris.^[34] Zhao *et al.* reported *I. sonchifolia* could effectively relieve the symptoms of coronary heart disease and angina pectoris.^[35]

Anti-tumor activity

Sesquiterpene lactones and triterpenoids from *I. sonchifolia* are active components for anti-tumor. Liu *et al.* found *I. sonchifolia* could inhibit the growth of transplanted tumors in animals. The inhibition rate of transplanted sarcoma 180 (S180) in high, medium and low dose groups were 39.86%, 38.14%, 35.73%, respectively. It is also found *I. sonchifolia* could prolong the survival time of mice with Heric's ascites tumor. The prolongation rate of mice in high, medium and low dose groups were 41.27%, 29.78%, 17.88%, respectively.^[36] Feng *et al.* reported saponin B and C showed obvious cytotoxicity effects on cancer cell lines A375 (human melanoma cells), L929 (mouse lung epithelial cells) and HeLa (human cervical cancer cells) with IC₅₀ values ranging from 8.83 to 15.83 μ M.^[14] Wang *et al.* observed that *I. sonchifolia* inhibited the growth of melanoma cells in a concentration-dependent manner.^[37] Zhou *et al.* found Kudiezi injection (5, 10, 20 mg/kg) showed a significant inhibitory effect on tumor growth in three tumor-bearing mice ($P < 0.05$, $P < 0.01$, $P < 0.001$). At the same time, it increased significantly the number of peripheral blood leukocytes in liver cancer H22 mice ($P < 0.05$). It could also inhibit the proliferation of human cervical cancer Hela cells or liver cancer HepG-2 cells *in vitro*.^[38]

Analgesic and sedative activity

Feng *et al.* found that Kudiezi injection showed an analgesic and sedative effect.^[33,39]

Activity of regulating blood lipids

Zhao *et al.* proved that saponin (400 mg/kg) showed an anti-atherosclerosis effect by regulating blood lipid metabolism and correcting free radical metabolism disorders.^[40] Li *et al.* found that Kudiezi injection could significantly regulate the blood lipid metabolism in experimental hyperlipidemia rats.^[29] Sohn *et al.* reported *I. sonchifolia* could reduce the increase of serum total cholesterol, triglyceride, low-density lipoprotein cholesterol and glutamate oxaloacetate transaminase in rats, which was caused by ethanol.^[41]

Anti-oxidation activity

Zhao *et al.* reported that the flavonoids and lignans showed strong activity of scavenging free radical and the potential to become natural antioxidant.^[21]

Antiviral effect activity

Liu *et al.* reported that Kudiezi showed a good inhibitory effect on respiratory influenza virus H₃N₂, syncytial virus (RSV) and adenovirus (ADV-3).^[36]

Liver protection activity

Zhang *et al.* reported that Kudiezi injection showed a certain anti-fibrosis effect.^[42] Zhao *et al.* found Kudiezi injection showed a significant therapeutic effect for the liver fibrosis.^[43] Guo *et al.* confirmed Kudiezi injection had a good therapeutic effect for rats with acute alcoholic liver injury.^[44]

Activity of improving blood system

Wei *et al.* found that Kudiezi injection showed an effect of improving blood circulation and microcirculation.^[45] Wei *et al.* have proved *I. sonchifoia* could prevent and treat diabetic vascular lesions by lowering blood fat and blood viscosity.^[46] Feng *et al.* found that *I. sonchifoia* could inhibit platelet aggregation significantly in the blood system and increase the activity of plasmin significantly, which can treat thromboembolic disease.^[47] Zhang *et al.* found Kudiezi could dilate blood vessels, improve microcirculation, reduce vascular resistance, increase blood flow, reduce platelet aggregation, inhibit thrombosis and reduce plasma viscosity. Thereby, it could reduce the occurrence, development and improvement of ischemia and hypoxia.^[48]

Other activities

Bae *et al.* found that the extract of *I. sonchifoia* showed an effect of increasing the stability and fluidity of phospholipid liposomes.^[49] Tong *et al.* reported Kudiezi had a protective effect on rat kidney caused by anti-oxidative stress.^[50] Wu *et al.* found *I. sonchifoia* could increase the expression of vascular endothelial growth factor, promote capillary angiogenesis, reduce inflammatory infiltration of the flap, and improve the survival rate of rat random flaps significantly.^[51] Peng *et al.* proved *I. sonchifoia* could promote the proliferation of HUVEC cells ($P < 0.05$).^[52]

Conclusion and Perspective

I. sonchifoia is a famous Chinese traditional herb with wide distribution, rich resources and variously clinical use. Kudiezi injection is widely used for treating cardiovascular and cerebrovascular diseases. Compared with its chemical compositions and clinical applications, the pharmacological research is not systematic and comprehensive enough, and it needs further investigation. Therefore, comprehensive research on pharmacological effects should be strengthened to provide more direct guidance for clinical applications, especially in pharmacological mechanisms, target research, and medical combination.

Acknowledgement

This work was supported by the Science and Technology Tackling Project of Henan Science and Technology Department (No. 182102310063).

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Received March 19, 2019

Accepted May 8, 2019