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Review Article

Progress on research and development of *Paederia scandens* as a natural medicine

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Abstract: *Paederia scandens (Lour.)* (*P. scandens*) has been used in folk medicines as an important crude drug. It has mainly been used for treatment of toothaches, chest pain, piles, hemorrhoids, and emesis. It has also been used as a diuretic. Research has shown that *P. scandens* delivers anti-nociceptive, anti-inflammatory, and anti-tumor activity. Phytochemical screening has revealed the presence of iridoid glucosides, volatile oils, flavonoids, glucosides, and other metabolites. This review provides a comprehensive report on traditional medicinal uses, chemical constituents, and pharmacological profiles of *P. scandens* as a natural medicine.

Keywords: *P. scandens*, phytochemistry, pharmacology

Introduction

Paederia scandens (Lour.) (*P. scandens*) is a perennial herb belonging to the Paederia L. genus of Rubiaceae. It is popularly known as "JiShiTeng" due to the strong and sulfurous odor exuded while its leaves or stems are crushed or bruised. *P. scandens* is a deciduous climbing plant that grows to 5.5 m with a hard lignified stem [1]. The herb is native to temperate and tropical Asia and it is widely distributed in most parts of India throughout the Malayan Archipelago, extending over Mauritius northward to China, Japan, and the Philippines. Recent studies have also shown that it can be found in North America [1]. The plant is listed as a local medicinal material in Sichuan (1987 supplement), Shanghai (1994 edition), Henan (1993 edition), Guizhou (2003 edition), and Guangxi (2008 edition) [2-4].

The whole plant can be utilized for various purposes. In China, *P. scandens* is traditionally used as a vegetable and it can be mixed into noodles, baba, or cakes. *P. scandens* is used in Chinese Traditional Herbal Medicine. It is in the generally recognized as safe (GRAS) category of plants [5]. In China, for thousands of years, *P. scandens* has been widely used to treat toothaches, chest pain, piles, hemorrhoids, and emesis, in addition to being used as a diuretic. Research has shown that *P. scandens* has antibacterial effects [6]. Recently, the anti-nociceptive, antiviral, antitumor, and anti-inflammatory properties of *P. scandens* have been reported [7-9]. In this review, the beneficial properties of *P. scandens* and its active components were examined, readdressing the potential use of this plant as a pharmaceutic or an agricultural resource.

Materials and methods

Relevant studies were collected by searching major scientific databases, including PubMed, Google Scholar, Baidu scholar, CNKI, and Wikipedia. Studies examining the phytochemical, phytopharmacological, and medicinal importance of *P scandens* were included. Some articles were found through tracking citations from other publications or by directly accessing a journal's website. They were considered according to the geographical region of the study's origin.

Table 1. Chemical constituents of *Phyllanthus urinaria*

Type	Compounds	Tissue	Extract Method	Reference
Idoid glucosides	6β-O-β-D-glucosylpaederosidic acid	Stems	Ethanol	[18]
	Asperuloside, deacetyl asperulosidic acid methyl ester, dimer of paederosidic acid, paederoscandoside, paederoside, paederoside B, paederosidic acid, saprosmoside D, saprosmodide E, saprosmoside F, Scandosid	Leaves and stems	n-BuOH	[20]
	6-β-O-synapoyl scandoside methyl ester, dimer of paederoside, scandoside methyl ester	Aerial	Unknown	[13]
	Asperulosidic acid, geniposide	Roots	Methanol	[12]
	Paederia lactone	Fruits	Unknown	[15]
	Caffeic acid 4-O-β-D-glucopyranoside paederoside B, taraxerol	Whole plan	Ethyl Acetate	[35]
	Deacetylasperulosidic acid, Decatylasperuloside acid methyl ester, Geniposidic acid	Stems	Ethanol	[18]
	10-O-E-feruloylmonotropein, 6'-O-E-feruloylmonotropein, 6α -hydroxygeniposide, deacetylasperuloside ester, paederosidic acid methyl, phyllosid	Aerial	Methanol	[21]
	Methyl paederosidate	Whole plant	Ethanol	[35]
	Dimer of methyl paederosidate, ethyl paederosidate	Aerial	Ethanol	[19]
Volatile oil	(E)-3-hexen-1-ol, (Z)-3-hexen-1-ol, 2-camphanol, 3-(Z)-hexen-1-(ol)acetate, n-hexanol, β-linalool	Whole	Steam Distillation	[27]
	1-Octen-3-ol, 1-Terpinen-4-ol, 1-Undecene, 2-Hexen-1-ol, 2-Hexenal, 3-Hexen-1-ol, 3-Thujene, 4-vinylphenol, 6,10,14-trimethyl, 9, 12, 15-Octadecatrienoic acid, ethylester, 9,12-Linoleic acid, Alloaromadendrene, Aromadendrene, Benzeneacetaldehyde, Bisabolene, Borneol, Bornyl acetate, Bulnesol, Camphene, Camphor, Caryophyllene, Citronellal, Decanal, Dimethyl trisulfide, Ethyl salicylate, Eucalyptol, Geranial, Geraniol, GermacreneD, Globulol, Guaiol, Ionene, Isopulegol, Limonene, Methyl salicylate, Neral, Nerolidol, oxide, p-Cymene, Pentadecanal, Sabinene, Sabinol, Spathulenol, Terpinolen, Tetradecanoic acid, Valencene, α-Citronellol, α-Cubebene, α-Eudesmol, α-Gurjunene, α-Phellandrene, α-Pinene, α-Terpinene, β-Cadinene, β-Damascenone, β-Elemene, β-Eudesmol, β-Myrcene, β-Pinene, Γ-Elemene, γ-Eudesmol, γ-Muurolol, δ-Cadinene, τ-Terpinene	Leaves and stems	Steam Distillation	[28]
	Butyl isohexyl ester, Octadec-9-enoic acid, Octadecanoic acid, Oleic acid	Stems	Cyclohexane	[29]
	2,4,6-cycloheptatrien-1-one 2,3-dimethyl, 3-buten-2-one, 4-butanediol monoacrylate, acetoin, analgin, dimethyl sulphone, N-methanesulfonylimidazole., Phthalic acid, Phthalic acid isobutyl nonyl ester, Propyl-Hydrazine, trans-1,2:4,5-diepoxy-p-menthane, β-propiolactone	Leaves and stems	Ether	[30]
	1-ethoxyl pentane, 2-phenylethyl acetate, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-2(4H)-benzofuranone, acetate, benzaldehyde, ethyl hexanoate, hexadecanoic acid, isopentyl acetate, isopentyl decanoate, pentadecanoic acid ethyl ester, phenylmethyl, phenylmethyl formate	Leaves and stems	Ether	[23]
	4-Di-tert-butylphenol, Benzoic acid, Lauric acid, Myristic acid, Nonanoic acid, Palmitic acid, Pentadecylic acid, Stearic acid	Whole	Ether	[31]
	dotriacotane	Whole	Ethanol	[37]
	(E)-β-Ocimene, (Z)-β-Farnesene, 1,8-Cineol, 2,4,5-Trimethyl benzaldehyde, 4-Acetyl-3-methylphenol, 4-Terpineol, 4-Vinylguaiacol, Bornylene, Caryophyllene oxide, Chavibetol, cis-Citral, cis-Muurola-4(14), 5-diene, cis-ρ-Menth-2-en-1-ol, Citronellyl acetate, Dihydroactindiolide, Geranyl acetone, Isoelemicin, Methyl eugenol, Methyl isoeugenol, Phenylethyl alcohol, trans-Nerolidol, trans-β-Damascenone, α-Cadinol, α-Calacorene, α-Copaene, α-Farnesene, α-Terpineol, β-Geranyl acetate, β-Selinene, β-Terpinene, γ-Cadinene, γ-Terpinene, δ-Terpinene, ρ-Cymene-8-ol	Aerial	Steam Distillation	[32]
	11,14-Eicosadienoic acid methyl ester, linolenic acid, N-hexadecanoic acid, phytol, squalene, stigmastero	Leaves	Sfe-co2	[25]
	2- Methyl-2-buten- 1-ol, 3-Furanmethanol, 3-(Methylthio)propionaldehyde, 5-Methyl-6,7-dihydro-(5H)- cyclopentapyrazine, Acetic acid, beta.Fenchyl alcohol, Epoxylinalol, Furfural, Isoborneol, Isophorone, Linalool, Linalool oxide, trans- Linalool oxide	Aerial	Ether	[24]
	Diisobutyl phthalate, dibutyl phthalate, dimethyl disulfide, dimethyl phthalate, nonanal, quinoline, thymol	Whole	Spme	[26]
Flavonoids	Astragalin, isoquercitrin, kaempferol3-0-rutinoside-7-0-glucoside, kaempferol3-0-rutinoside, paederinin, populnin, quercetin3-0-rutinoside-7-O-glucoside, quercimeritrin, rutin	Leaves and stems	Methanol	[33]
	Diadzein, linarin	Whole plant	Ethanol	[34]

Glucosides	Butane-1,2,3,4-tetraol 1-O-β-(6-O-(E)-feruloyl) glucopyranoside, paederol A	Aerial	Methanol	[36]
	Deacetyl-daphylloside, daphylloside	Aerial	Ethanol	[19]
	Caffic acid, daucosterol, caffeic acid 4-O-b-D-glucopyranoside	Whole plant	Ethanol	[16]
Quinones	1,3,4-trimethoxyl-2-hydroxyanthraquinone, 1,4-dimethoxyl-2-hydroxyanthraquinone, 2,3-dihydroxy-1-methoxylanthraquinone	Whole plant	Ethyl acetate	[38]
	1,3-Dihydroxy-2,4-dimethoxy-9,10-anthraquinone, 2-Hydroxy-1,4-dimethoxy-9,10-anthraquinone, 1-Methoxy-2-methoxymethyl-3-hydroxy-9, 10-anthraquinone, 1-Hydroxy-2-hydroxymethyl-9, 10-anthraquinone	Roots	Ethyl acetate	[6]
	Rubiadin-1-methylether	whole plant	Ethanol	[16]

Results and discussion

Phytochemistry

More than 250 compounds have been obtained from *P. scandens*, including iridoid glucosides (IGS), volatile oils, flavonoids, glucosides, and so forth [10]. Of the isolated compounds, IGS is the major constituent. It has many biological activities [2]. In 1969, Inouye et al. isolated IGS from this plant, for the first time, including asperuloside, paederoside, scandoside, paederosidic acid (PA), and deacetylasperuloside [11]. A series of novel IGS, including dimeric IGS, acylated IGS, and sulfur-containing IGS, were then isolated from the plant, such as 6-β-O-synapoyl scandoside methyl ester, a dimer of paederoside, 6'-O-E-feruloylmonotropein and 10-O-E-feruloylmonotropein, as well as paederoside B [12-20]. More recently, a total of 13 IGS dimers, containing three groups of isomers in *P. scandens* extract, were identified or tentatively characterized using HPLC-ESI-QTOF based on the tandem mass spectra from previous studies [21]. Furthermore, a total of 24 IGS, including 14 new species, were identified or tentatively characterized based on exact mass, RIA values, tandem mass spectra, and D-labeling experiments [22]. Thus far, more than 30 iridoid glycosides have been identified from *P. scandens*. These are presented in **Table 1**.

Volatile oils are one of the major constituents of *P. scandens.* More than 180 volatile oils compounds have been obtained from the herb [22-32]. In 2000, Ma, Y., et al. isolated 31 volatile oils compounds. Principal chemical constituents of the essential oils were isopentyl acetate (20.2%), phenylmethyl acetate (8.0%), pentadecanoic acid ethyl ester (6.8%), hexadecanoic acid (6.8%), and isopentyl decanoate (5.7%) [23]. Yu A et al. identified 27 compounds from fresh *P. scandens* through general steam distillation [24]. Contents of the 7 components were higher than 5%, including acetic acid (31.14%), furfural (7.49%), 3-furanmethanol (6.10%), linalool oxide (8.54%), trans-linalool oxide (10.37%), isoborneol (6.35%), and β-fenchyl alcohol (7.30%) [24]. Next, 15 volatile constituents were separated from the leaves of the herb by supercritical CO_2 extraction. The main chemical components were phytol (31.9%), squalene (26.4%), linolenic acid (17.6%), 11,14-Eicosadienoic acid methyl ester (8.96%), N-hexadecanoic acid (7.41%), and stigmasterol (5.42%) [25]. Zhang W. and Z. H. Yin identified 18 kinds of volatile constituents by head-space solid micro-extraction coupled with GC/MS and the Kovats index. Major compounds were thymol (30.97%), dimethyl disulfide (9.78%), quinoline (5.74%), n-hexadecanoic acid (5.53%), and dibutyl phthalate (5.07%) [26]. More than 160 volatile constituents have been identified from *P. scandens*. These are presented in **Table 1**. Results suggest that the volatile oils of *P. scandens* are significantly different from plant tissues, other extraction methods, and fresh or dried plants.

Flavonoids are one of the major constituents of *P. scandens*. In 1990, nine flavonol compounds were isolated from a methanolic extract of *P scandens* leaves and stems, including four kaempferol glucosides and five quercetin glucosides [33]. Next, linarin and diadzein were isolated from the plant and identified as a flavonoid composition [34, 35]. Thus far, more than 10 Flavonoids have been identified from *P. scandens*. These are presented in **Table 1**.

Several other compounds have been isolated from the herb, including glucosides, quinones, phenols, terpenes, and sterols. Eight glucoside compounds have been obtained from the herb, listed in **Table 1** [17, 19, 34-37]. Eight quinone compounds were recently isolated from *P. scandens* (**Table 1**) [6, 34, 38]. Five phenol compounds have also been isolated from this plant, including cleomiscosin D, cleomiscosin B, coumaric acid, isolariciresinol, isoscopoletin, scopoletin, and trans-ferulic acid [19, 34, 38]. Four terpene compounds have also been reported: 3-O-acetyloleanolic acid, 3-oxours-12-en-28-oic acid, oleanolic acid, and ursolic acid [34, 37, 38]. Also, two sterol compounds have been obtained from the herb, including stigmast-5-ene-3,7-diol and β-sitosterol [7, 34, 37, 38].

In vivo absorbed constituents and metabolites of a *P. scandens* decoction in rats have been investigated [39, 40]. A total of seven compounds (3 IGS and 4 IGS metabolites) and 6 compounds (including 4 IGS and 2 IGS metabolites) were identified in rat urine and serum samples after treatment, respectively [39]. Wang DM et al. identified 4 compounds in rat serum from rats treated orally with P. scandens

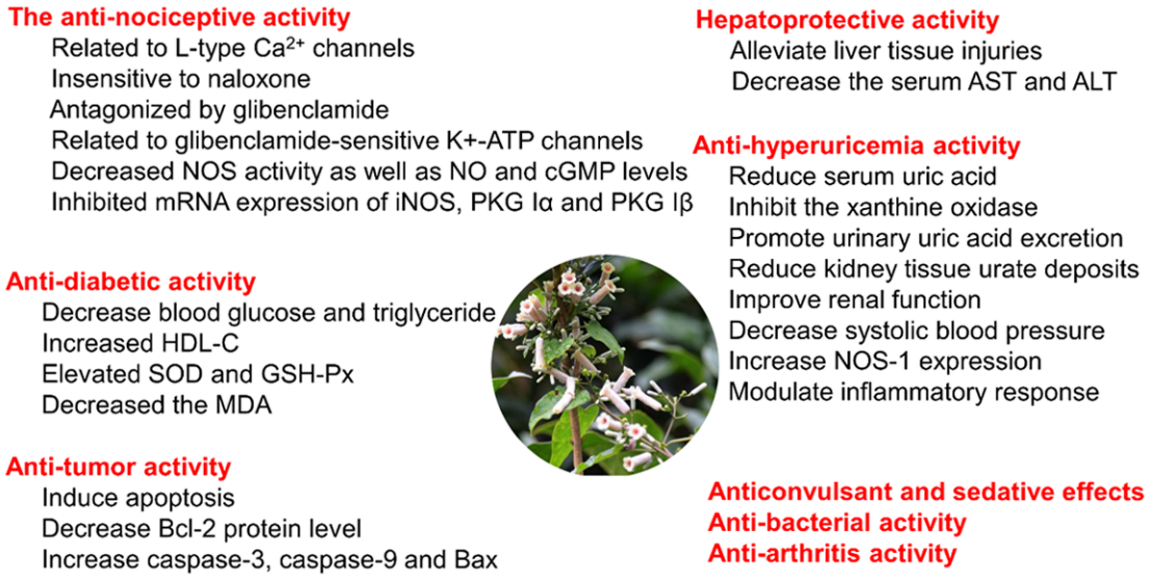

Figure 1. Schematic effects of *P. scandens* and its active constituents in metabolic syndrome, together with some relevant mechanisms.

extract by comparing their retention times and mass spectrometry data or by conducting mass spectrometry analysis and retrieving reference values from the literature [40]. Results suggest that glucuronidation after deglycosylation is the primary metabolic pathway for IGS in *P. scandens* [40].

Pharmacological properties

P. scandens has been shown to have a broad spectrum of biological properties, including anti-nociceptive, anti-inflammatory, antioxidant, antimicrobial, and anti-tumor activity (**Figure 1**). The following is an overview of modern pharmacological evaluations conducted with this herb.

Anti-nociceptive activity

Studies have shown that n-butanol fraction, aqueous fraction (AF), and the petroleum ether fraction (PEF) of *P. scandens* have dominant anti-nociceptive activity in mice, in both chemical and thermal models of nociception [41-43]. The n-butanol fraction had significant inhibition of nociception [41]. This anti-nociceptive activity might be related to the involvement of L-type Ca^{2+} channels [41]. Given orally, PEF at doses of 20, 40, and 80 mg/kg produced significant inhibition of nociception [7]. PEF-induced anti-nociception in both capsaicin and formalin tests was insensitive to naloxone but was significantly antagonized by glibenclamide, suggesting that the PEF produced anti-nociception is possibly related to glibenclamide-sensitive K^+-ATP channels [7]. Furthermore, oral administration of AF at doses of 200, 400, and 800 mg/kg produced significant inhibition of nociception [44]. The AF of *P. scandens* had the same anti-nociceptive activity as central analgesic morphine [44].

P. scandens produced anti-nociception that is possibly related to the IGS. An IGRS compound called Paederosidic Acid Methyl Ester (PAME) was intraperitoneally injected at doses of 20, 40, and 60 mg/kg, producing significant inhibition of both chemical and thermal nociception. PAME-induced anti-nociception effects were insensitive to naloxone or nimodipine but were significantly antagonized by L-NAME (N (G)-nitro-L-arginine methyl ester), methylene blue, and glibenclamide [5]. Another separate experiment showed that treatment with total IGS from *P. scandens* (70, 140, 280 mg/kg) significantly alleviated neuropathic pain and markedly decreased NOS activity, as well as NO and cGMP levels [45]. Furthermore, total IGS markedly inhibited mRNA expression of iNOS, PKG Iα, and PKG Iβ in the spinal cord [45]. Results suggest that IGS possesses antinociceptive effects, which may be partially related

to the inhibition of NO/cGMP/PKG signaling pathways.

PEF is a complex mixture of sterols and fatty acids. Chen YF et al. showed that the antinociceptive activity of PEF is related to a combination of three major chemical compounds, cis-9, cis-12-octadecadienoic acid, stigmasterol, and β-sitosterol [7]. Additionally, previous studies have reported that stigmasterol and β-sitosterol could significantly reduce formalin-induced pain and increase reaction times in the hot-plate test [46, 47].

Anti-hyperuricemia activity

Uric acid nephropathy (UAN) is caused by excessive uric acid, leading to kidney tissue damage via urate crystal deposits in the kidneys [48]. Studies have demonstrated the protective effects of IGS isolated from *P. scandens* on UAN induced by adenine and potassium oxonate in rats [49-51]. IGS (4.5, 2.25 and 1.125 g/kg/day), given orally for 14 days, could significantly reduce levels of serum uric acid and inhibit liver xanthine oxidase substantially in hyperuricemia mice [8]. IGS could dramatically improve the UAN in rats with general symptoms by significantly inhibiting serum xanthine oxidase activity, lowering blood uric acid content, promoting urinary uric acid excretion, reducing kidney tissue urate deposits, improving renal function, and lowering the renal index [49]. IGS exerts protective effects by modulating pro-inflammatory mediator production in nephropathy tissue to improve renal fibrosis in UAN rats [50]. A recent study showed that treatment with IGS significantly decreased systolic blood pressure through upregulation of NOS-1 expression in UAN rats [51]. Therefore, *P. scandens* has good preventive and therapeutic effects on UAN rats.

Anti-diabetic activity

Studies have demonstrated that *P. scandens* produces hypoglycemic effects. After 30 days of treatment, *P. scandens* extracts made with EtOH (PSE-EtOH) lowered levels of blood glucose and triglycerides and increased levels of HDL-C [52]. Also, serum and liver tissue levels of SOD and GSH-Px were elevated. The MDA content was decreased after PSE-EtOH administration [53]. Furthermore, Wang SJ et al. suggest that the hypoglycemic mechanisms of *P. scandens* were likely due to improvements in anti-oxidative activity [53].

Anti-tumor activity

P. scandens shows significant anti-tumor activity. Kapadia GJ et al. evaluated the anti-tumor activity of 15 iridoids, with paederoside displaying the highest amount of anti-tumor promoting activity [54]. PA isolated from *P. scandens* exerted significant inhibitory effects on MGC-803, BGC-823, and SGC-7901 cells. PA may induce apoptosis by upregulating caspase-3, caspase-9, and Bax proteins, as well as down-regulating Bcl-2 in SGC-7901 cells [55].

Hepatoprotective activity

Previous research has indicated that the total IGS in Paederia possesses notable hepatoprotective potential [56]. IGS significantly alleviated liver tissue injuries and decreased serum AST and ALT levels in carbon tetrachloride (CCl4)-induced hepatotoxicity in rats. Furthermore, IGS significantly increased the activities of GSH, GAT, and SOD, whereas levels of MDA decreased [56].

Anti-arthritis activity

PSE has remarkable efficacy in improving symptoms of acute gouty arthritis induced by monosodium urate crystals. PSE significantly inhibits joint swelling, reduces inflammatory cell infiltration of articular tissues, and improves the pathological changes of synovial membranes [57]. Furthermore, PSE may reduce levels of TNF-α and IL-1β in synovial tissue [9, 57].

Anticonvulsant and sedative effects

PA isolated from *P. scandens* has shown significant anticonvulsant and sedative effects in a dose-dependent manner. PA increased brain γ-aminobutyric acid and reduced glutamic acid in the brain [42]. Additionally, PA increased expression of GAD 65 [42].

Anti-bacterial activity

P. scandens has been shown to have strong antibacterial activity. PSE-EtOH showed anti-Helicobacter pylori activity [58]. Additionally, minimum inhibitory concentration (MIC) tests revealed that the ethanol extract for the herb possessed low MIC values, ranging from 0.64

to 5.12 mg/mL against five *H. pylori* strains [58]. PSE-EtOH also showed anti-bacterial effects against *Escherichia coli*, but there were no effects on *Bacterium proteus* and *Bacillus subtilis* [59]. The volatile oil (eugenol, camphor, borneol, methyl salicylate) of *P. scandens* may reduce the intestine crypt depth from *Salmonella enteritidis* infection in broilers [60, 61]. Quang ĐN showed that anthraquinones from *P. scandens* had antimicrobial activity [6]. Polysaccharides from *P. scandens* PSP2a could protect mice infected with *P. aeruginosa* [62].

Anti-inflammatory activity

In recent years, studies of the anti-inflammatory effects of *P. scandens* have been reported [57, 63, 64]. PSE-EtOH reduced inflammatory cell infiltration of articular tissues. Radioimmunoassay revealed that PSE-EtOH could reduce levels of TNF-α and IL-1β in the synovial membranes of rats [57]. In addition, administration of PSE-EtOH remarkedly inhibited RNA levels of TNF-α and IL-1β, as well as the biological activity of NF-kappaB in rates with monosodium urate crystals [9]. IGS may inactivate NF-κBp65 pathway transmembrane signal transduction and downregulate expression of MCP-1 and alpha-SMA to modulate pro-inflammatory mediator production in rats with uric acid nephropathy (UAN) [50]. IGS also inhibited the biological activity of TNF-alpha and TGF-beta1 and suppressed mRNA expression levels of TNF-alpha and TGF-beta1 in renal tissue in UAN rats [51].

Anti-oxidative activity

PSE-EtOH remarkedly inhibits the rate of elimination of hydroxyl free radicals [65]. PSE-EtOH elevated serum and liver tissue levels of SOD and GSH-Px as well as decreased the MDA content in streptozotocin (STZ)-induced diabetic mice [53]. Peng W et al. evaluated anti-oxidant enzyme activity in liver tissues in rats with acute liver injuries that were treated with IGRS. It was found that IGRS significantly increased the activity of GSH, GAT, and SOD [56].

Long-term toxicity testing

Pang M et al. investigated the long-term toxicity of iridoid glycosides from *P. Scandens* (IGPS) [66]. Rats were treated with 280, 700, and 1,750 mg/kg/d of IGPS for three months, equal to approximately 40, 100, and 250 times the amount of the clinical dosage. General states of the animals, weights, hematological indicators, routine blood biochemistry, and pathological changes in tissues and organs were observed. There were no evident differences between the IGPS-treated group and control group [66]. Moreover, the number of red blood cells had a transient increase in the high dose group [66].

Conclusion

In summary, through in-depth investigations in recent years, the effects of *P. scandens*, including anti-nociceptive, anti-inflammatory, anti-hyperuricemia, anti-oxidant, antimicrobial, and anti-tumor activity, have been developed and discovered. Injections and oral solutions based on *P. scandens* have appeared on the market. They have good curative effects, treating nociceptive disorders, inflammatory disease, and tumors. Therefore, further investigation of *P. scandens* is urgently needed due to its crucial clinical significance and high potential for medical treatments. It is believed that additional applications and better treatment effects can be achieved in the future.

Disclosure of conflict of interest

None.

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