Review

Chemical composition and pharmacological activities of the *Phellodendron chinense* Schneid

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Abstract

***Phellodendron chinense* Schneid (*P. chinense*), as a traditional Chinese medicine, is commonly used in clinical practice. It has the effects of drying dampness, clearing heat, detoxifying, purging fire, and reducing swelling. Its main chemical components are flavonoids and alkaloids, which have various pharmacological effects such as lowering blood sugar, lowering blood pressure and immunosuppression. With the continuous development of modern science and technology, the research on *P. chinense* Schneid has increased. This study reviews the chemical components and pharmacological effects of *P. chinense* Schneid, and provides reference for its further research and development.**

Keywords: *Phellodendron chinense* Schneid; chemical composition; pharmacological activity

1 Introduction

Phellodendron chinense Schneid (*P. chinense*) is a traditional Chinese medicine commonly found in mixed forests above 900 m, primarily in Sichuan, Guizhou, and other regions [1,2]. The dried bark, used medicinally, comes from *P. chinense*, a plant in the genus Phellodendron of the Rutaceae family. It is also known as a traditional natural dye, capable of producing yellow or brown colors [3,4].

P. chinense is bitter and cold in nature, and enters the kidney and bladder meridians. It can clear heat and dry dampness, purge fire and remove steam, detoxify and heal sores [5]. *P. chinense* was first recorded in the "Shennong's Materia Medica", originally named "bo wood", and was a superior medicine. It "treats heat accumulation in the five viscera and intestines, jaundice, intestinal hemorrhoids, stops diarrhea and dysentery, treats women's leukorrhea, red and white, and yin injury and ulceration" [5]. Clinically, *P. chinense* is mainly used to treat patients with yang syndrome such as damp-heat diarrhea, jaundice, leukorrhea, heat

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stranguria, hemorrhoids, night sweats, seminal emission, bone steaming and fever, rubella and pruritus, and wound infection after sores [6-8].

P. chinense, commonly known as Huáng bǎi, is recognized as one of the fifty fundamental herbs in traditional Chinese medicine. This species has been propagated globally, not only for its decorative appeal but also for its therapeutic properties. A comprehensive review of the Sciencedirect and Web of Science databases yielded 68 pertinent articles, 27 of which focused on the chemical constituents and pharmacological activities of *P. chinense*. Modern research has revealed that *P. chinense* has various pharmacological activities, such as antibacterial, antifungal, antitussive, antihypertensive, antitrichomonas, antihepatitis, antiulcer and immunosuppressive effects. Moreover, *P. chinense* also has antioxidant, antigout, anticancer, diuretic, stomachic and subcutaneous hemorrhage absorption-promoting effects, demonstrating a broad market development potential.

In recent years, other pharmacological effects of *P. chinense* have also been widely used in clinical practice [9-11]. This article reviews the chemical constituents, pharmacological effects and clinical applications of *P. chinense*, aiming to provide a reference for the further development and utilization of *P. chinense* resources.

2 Chemical composition

P. chinense contains a variety of medicinal active components, the main chemical constituents of it are flavonoids and alkaloids. Among them, alkaloids are the most important active ingredients of *P. chinense*, and their content is especially rich. In addition to alkaloids and flavonoids, *P. chinense* also contains terpenoids, lactones, sterols and other compounds [12-14]. The chemical compositions are shown in Fig. 1. These compounds together contribute to the unique pharmacological effects and medicinal value of *P. chinense* [15,16].

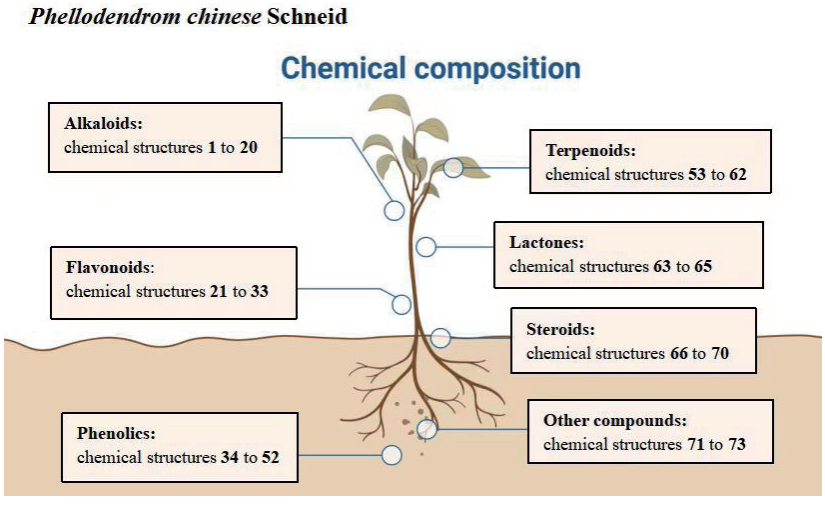

Fig. 1 Chemical composition of *P. chinense*

2.1 Alkaloids

Studies have shown that alkaloids in *P. chinense* mainly include *N*-methylflindersine (**1**), (*S*)-canadine (**2**), rutaecarpine (**3**), xanthoplanine (**4**), tetrahydropalmatine (**5**), palmatine (**6**), menisperine (**7**), magnoflorine (**8**), lotusine (**9**), jatrorrhizine (**10**), *P.* chinenseine (**11**), berberine

(**12**), berberrubine (**13**), candicine (**14**), palmidin A (**15**), phellodendrine (**16**), tetrahydroberberine (**17**), tetrahydrojatrorrhizine (**18**), *N-trans*-cinnamoyltyramine (**19**) and epiberberine (**20**) [12-16]. The structural formulas of these alkaloids are shown in Fig. 2.

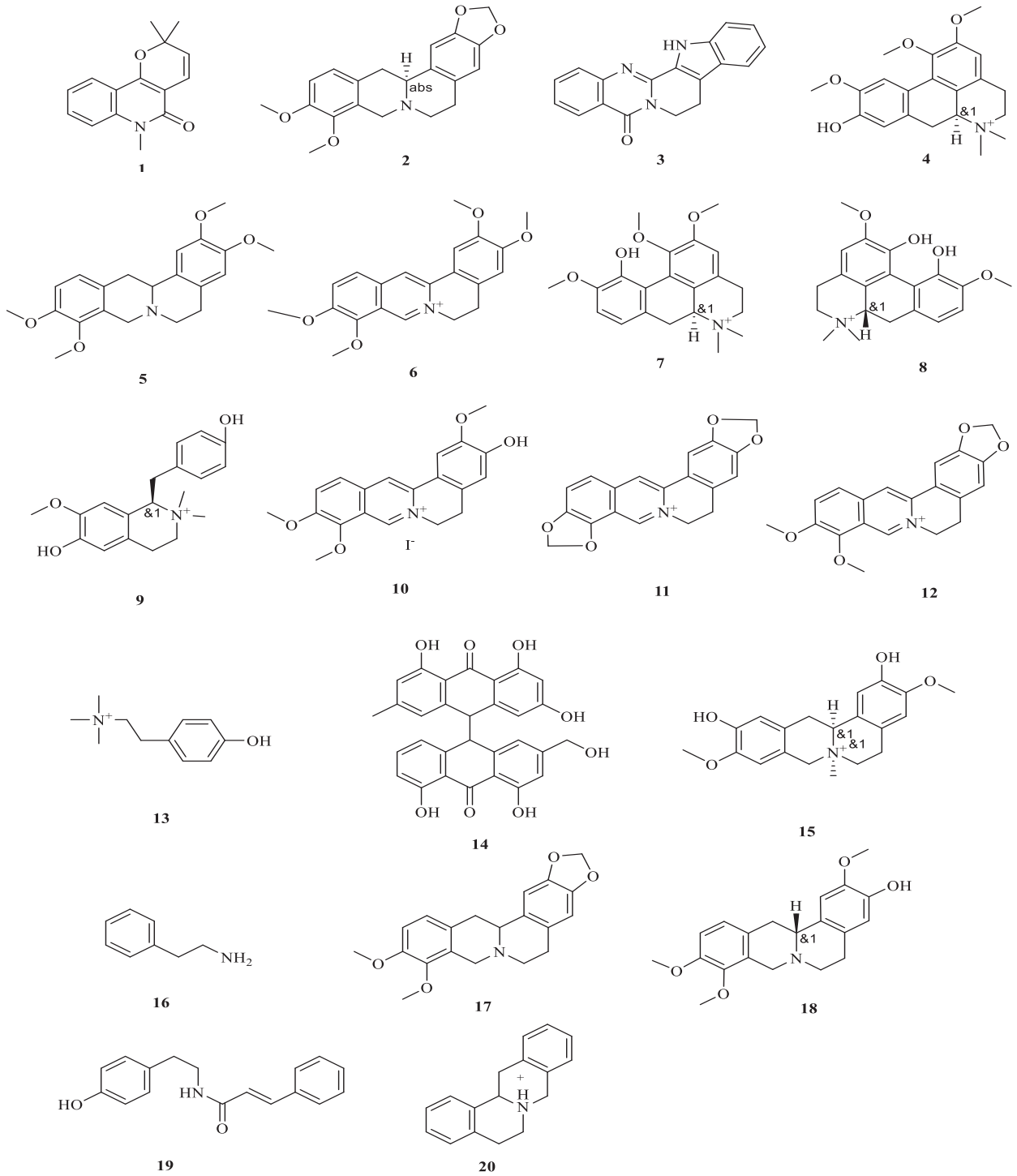

Fig. 2 Structures of alkaloids isolated from *P. chinense*

2.2 Flavonoids

Studies have shown that flavonoids in *P. chinense* mainly include hyperin (**21**), amurensine (**22**), amurensin (**23**), schkuhrin I (**24**), quercetin (**25**), wogonin (**26**), niloticin (**27**), dihydroniloticin (**28**), chrysin (**29**), baicalein (**30**), javanicin (**31**), kihadanin B (**32**) and columbianetin (**33**) [12-16]. The structural formulas of these flavonoids are shown in Fig. 3.

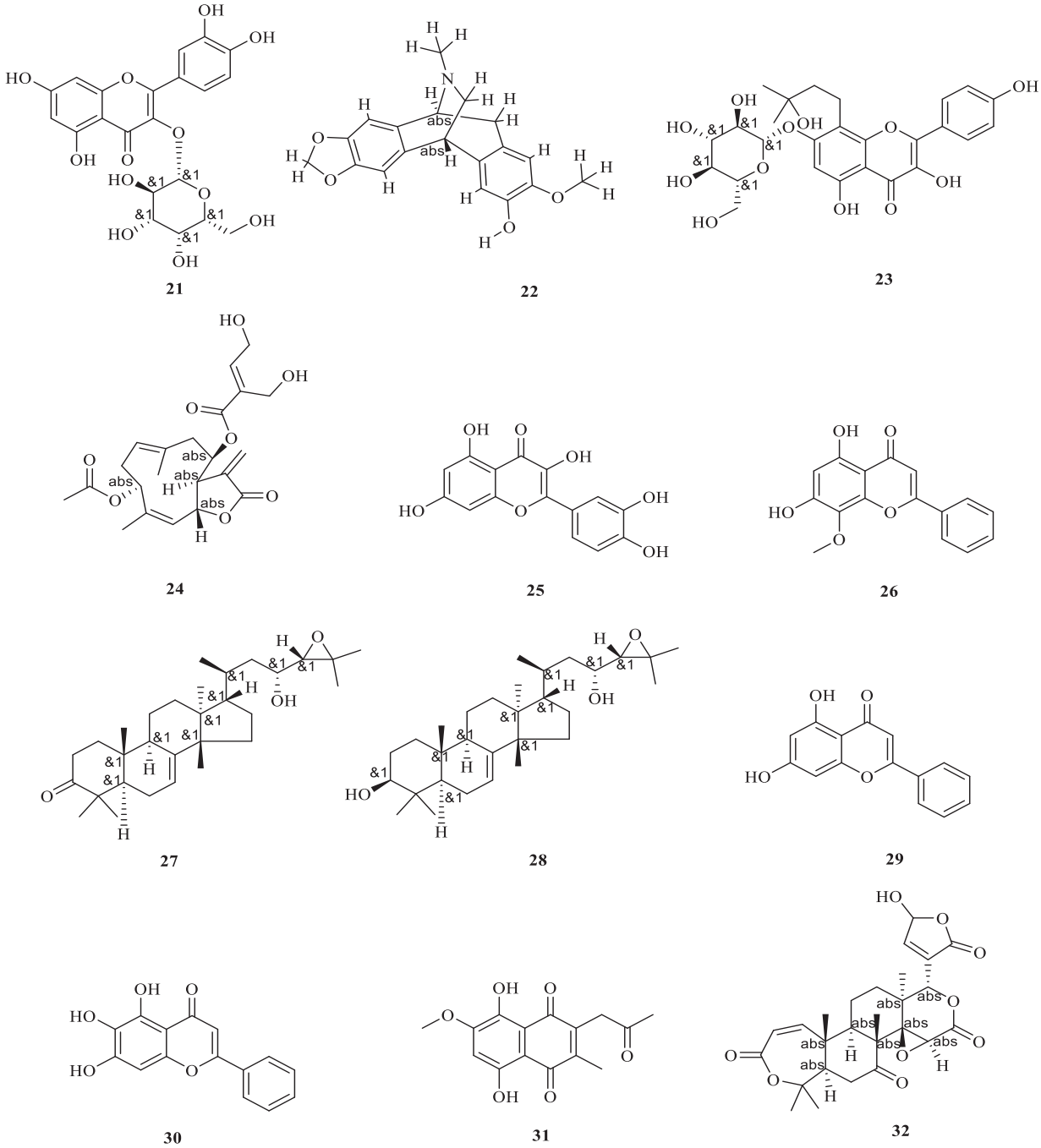

Fig. 3 Structures of flavonoids isolated from *P. chinense*

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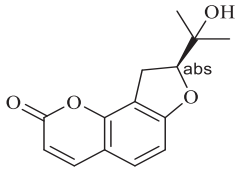
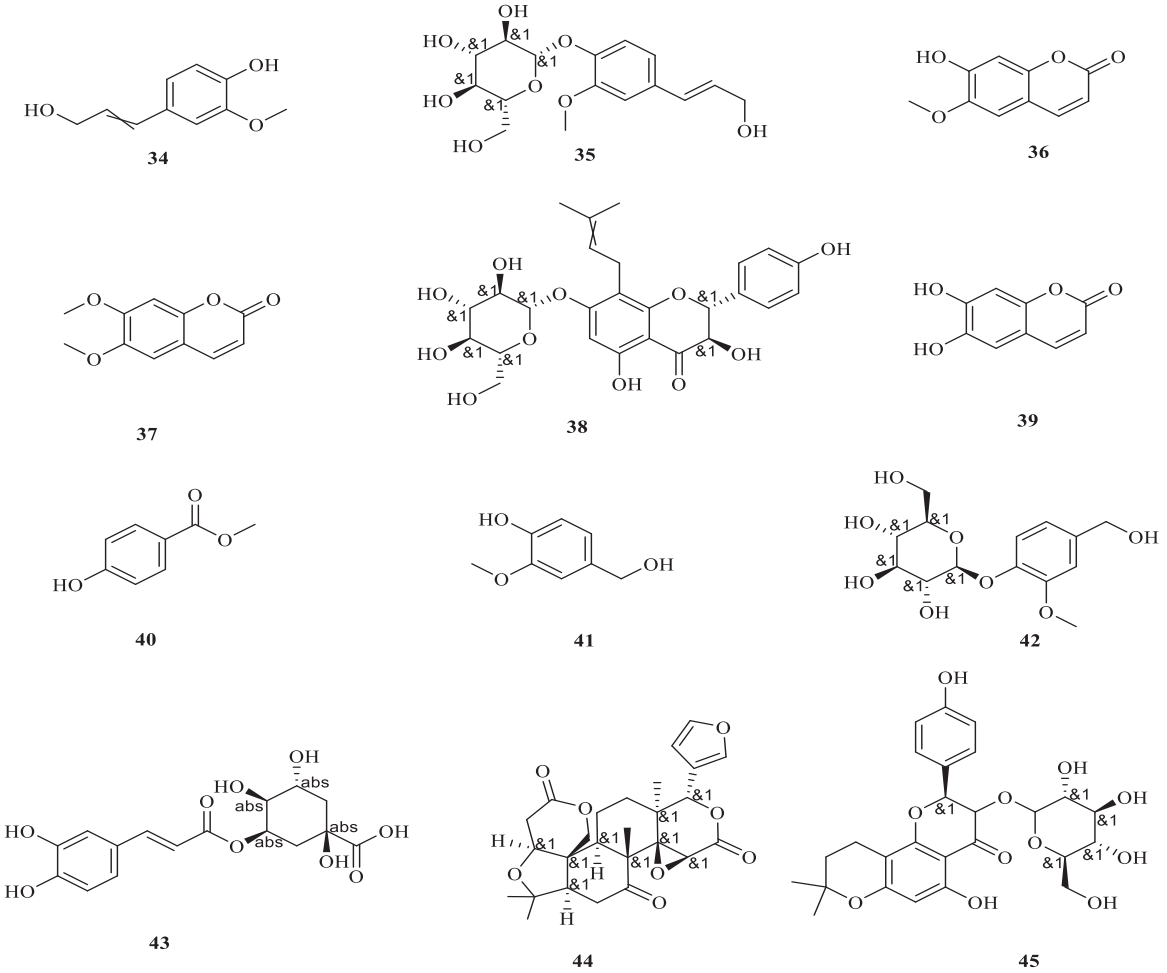


33

Continued Fig. 3

2.3 Phenolics

Studies have shown that phenolics in *P. chinense* mainly include coniferol (**34**), coniferin (**35**), scopoletin (**36**), scoparone (**37**), phellamurin (**38**), aesculetin (**39**), methylparaben (**40**), vanillyl alcohol (**41**), vanilloloside (**42**), chlorogenic acid (**43**), obaculactone (**44**), phellodendroside (**45**), phellopterin (**46**), benzoic acid (**47**), methyl caffeate (**48**), umbelliferone (**49**), caffeic acid (**50**), *p*-coumaric acid (**51**) and *p*-hydroxybenzaldehyde (**52**) [12-16]. The structural formulas of these phenolics are shown in Fig. 4.



34 **35** **36** **37** **38** **39** **40** **41** **42** **43** **44** **45**

Fig. 4 Structures of phenolics isolated from *P. chinense*

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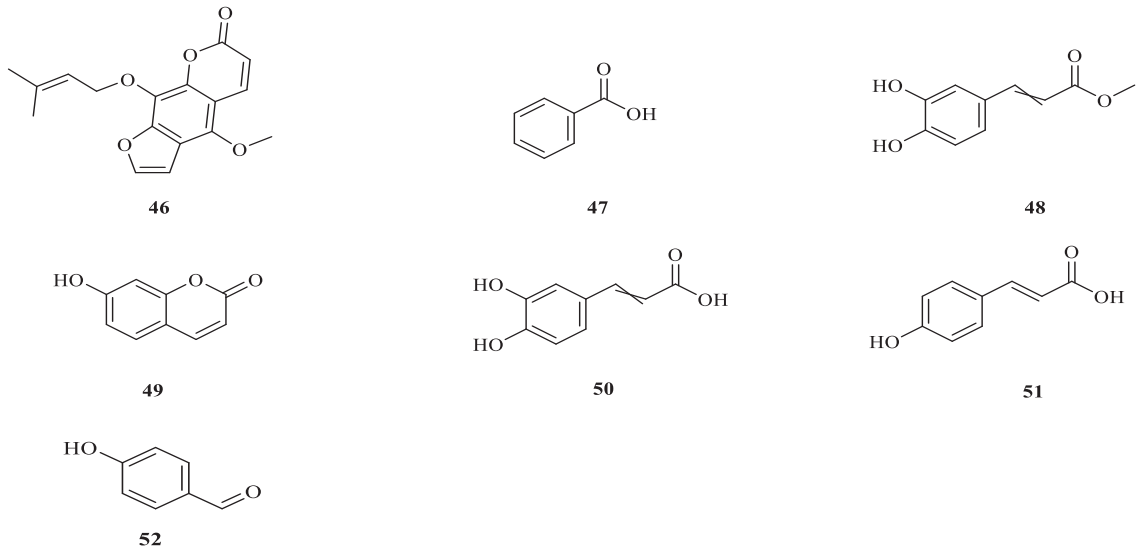

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2.4 Terpenoids

Studies have shown that terpenoids in *P. chinense* mainly include friedelin (**53**), 24-methylenecy cloartanol (**54**), lupenone (**55**), 3-*epi*-Lupeol (**56**), obacunone (**57**), melianone (**58**), limonin (**59**), obamegine (**60**), campesteryl ferulate (**61**) and *α*-phellandrene (**62**) [12-16]. The structural formulas of these terpenoids are shown in Fig. 5.

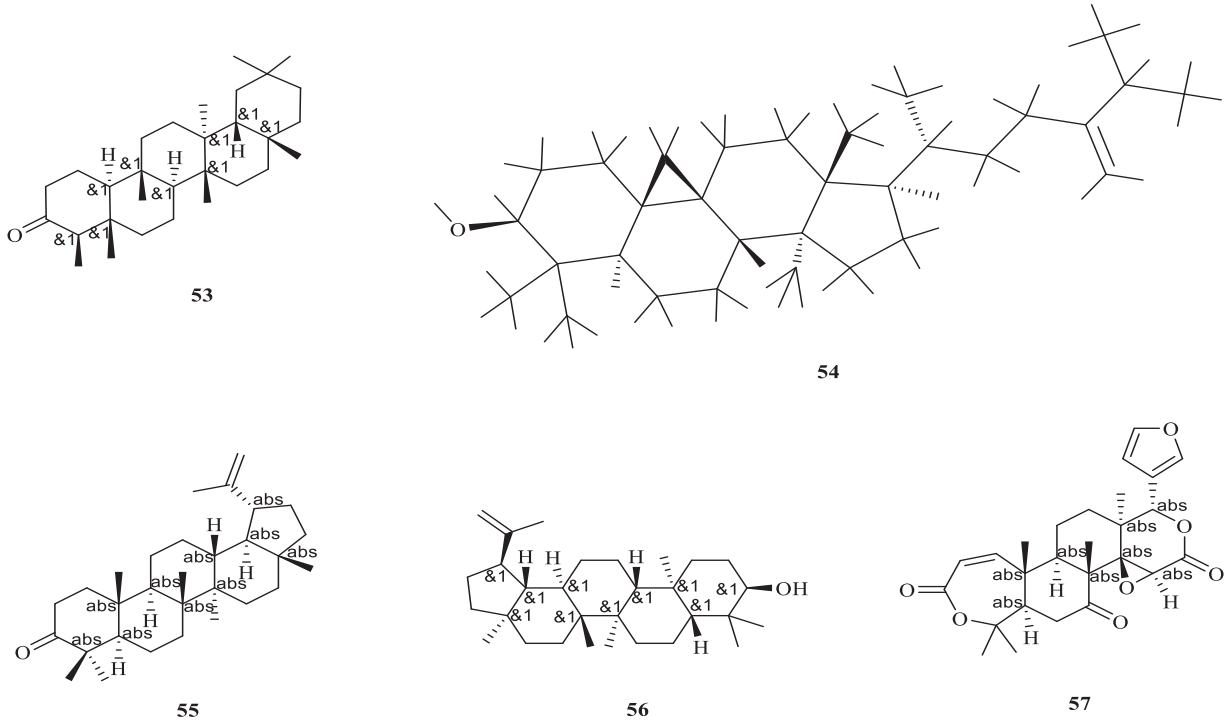

Fig. 5 Structures of terpenoids isolated from *P. chinense*

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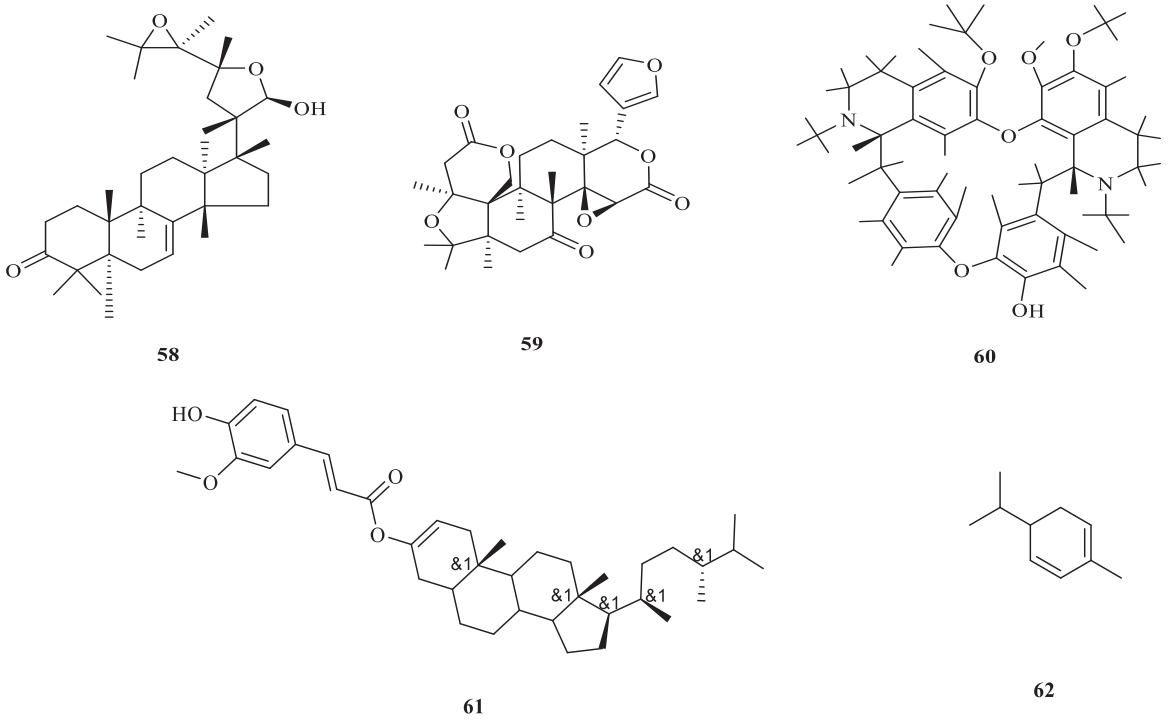

Continued Fig. 5

2.5 Lactones

Studies have shown that lactones in *P. chinense* mainly include hiyodorilactone C (**63**), hiyodorilactone B (**64**) and candletoxin A (**65**) [12-16]. The structural formulas of these lactones are shown in Fig. 6.

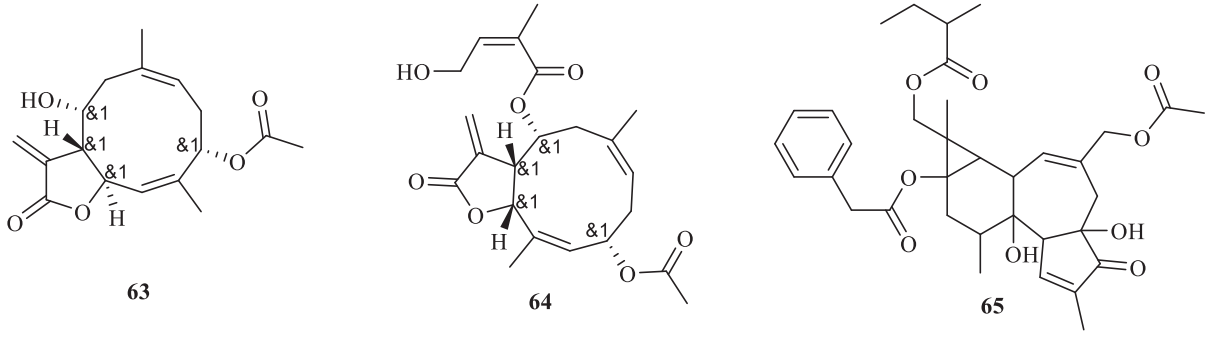

Fig. 6 Structures of lactones isolated from *P. chinense*

2.6 Steroids

Studies have shown that steroids in *P. chinense* mainly include stigmasterol (**66**), 7-dehydrostigmasterol (**67**), *β*-Sitosterol (**68**), campesterol (**69**) and *γ*-sitosterol (**70**) [12-16]. The structural formulas of these steroids are shown in Fig. 7.

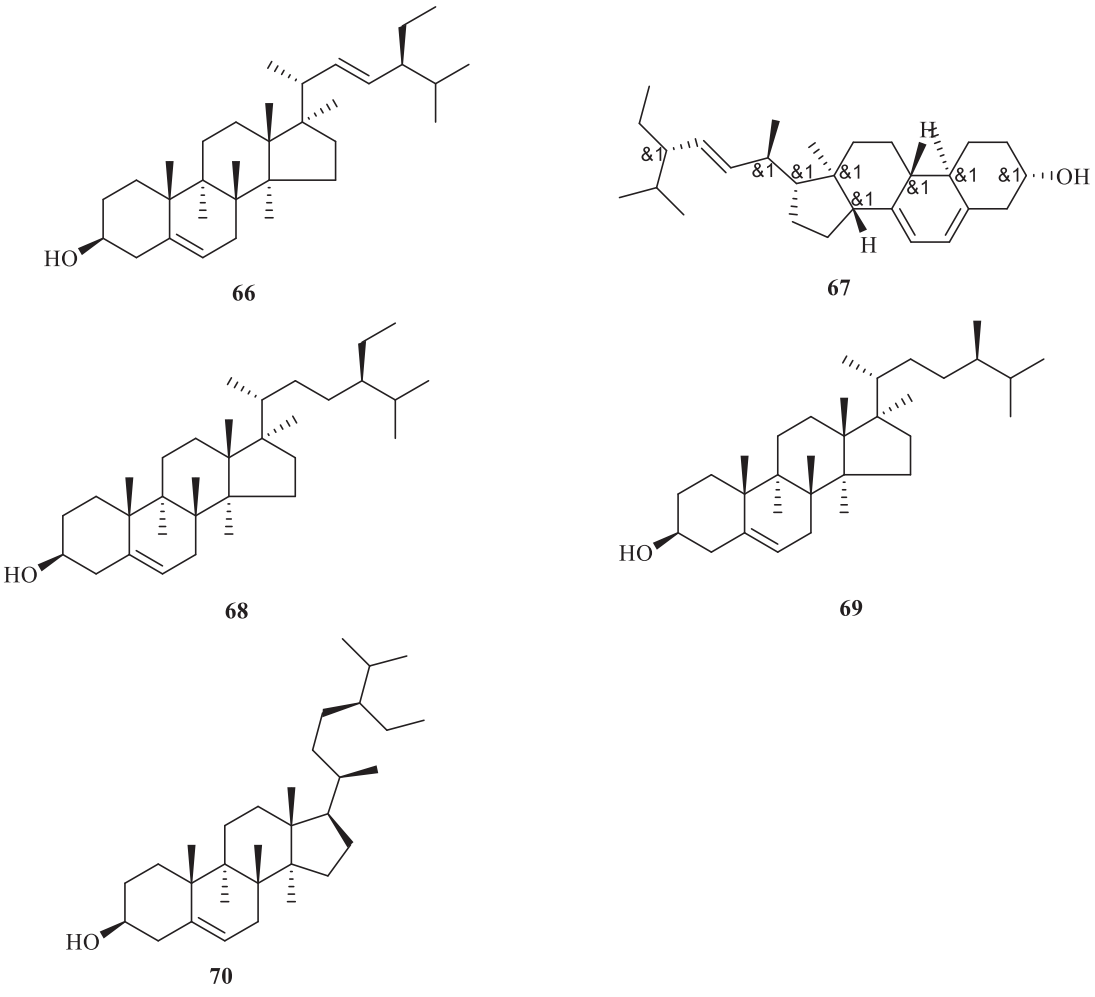

Fig. 7 Structures of steroids isolated from *P. chinense*

2.7 Other compounds

Studies have revealed the presence of other compounds in *P. chinense*, including purpurin 18 methyl ester (**71**), guanidine (**72**) and acetic acid (**73**) [12-16]. The structural formulas of the other compounds are shown in Fig. 8.

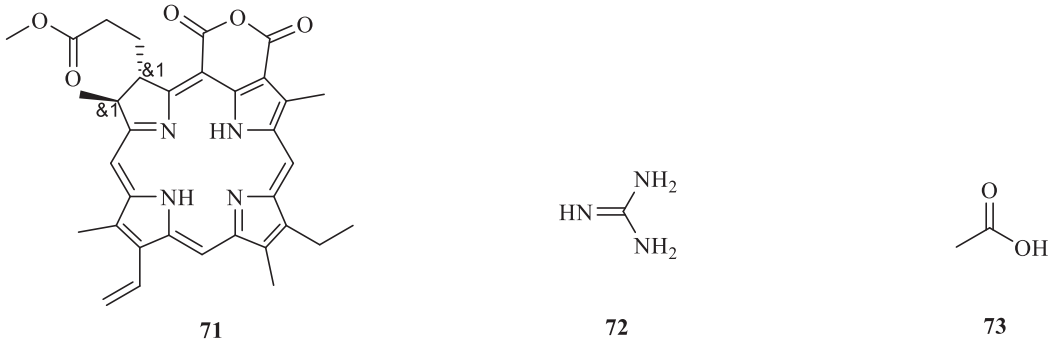

Fig. 8 Structures of the other compounds isolated from *P. chinense*

3 Pharmacological activities

P. chinense, a plant of long-standing repute and veneration in traditional Chinese medicine, has garnered widespread attention in modern scientific research for its unique pharmacological properties. Notably, the array of alkaloids present in *P. chinense*, particularly berberine (**12**), has demonstrated significant biological activity in several cutting-edge scientific studies.

The alkaloid berberine (**12**), in particular, is one of the most studied compounds in this plant. It has anti-liver fibrosis effect by regulating proteins involved in the HIF-1 pathway, such as TNF-α, Timp1 and HO-1. Additionally, berberine (**12**) and other phenolic acids from *P. chinense* have shown significant anti-inflammatory response in animal models.

In terms of monomeric compounds with high content, research has indicated that these compounds, including alkaloids and phenolic acids, are the main active components contributing to the anti-inflammatory properties of *P. chinense.* Moreover, berberine (**12**) has been extensively studied for its broad pharmacological activities, including anticancer, anti-inflammatory and neuroprotective effects. Its protective effect on the central nervous system has been proved, making it a promising agent for treating disorders such as Alzheimer's disease, cerebral ischemia, mental depression, anxiety and schizophrenia.

These activities of *P. chinense* include antibacterial, anti-inflammatory, antioxidative, antitumoral and hypoglycemic effects. The pharmacological activities is shown in Fig. 9. Such research not only underscores the potential of *P. chinense* as a natural therapeutic agent but also provides a scientific foundation for its clinical application.

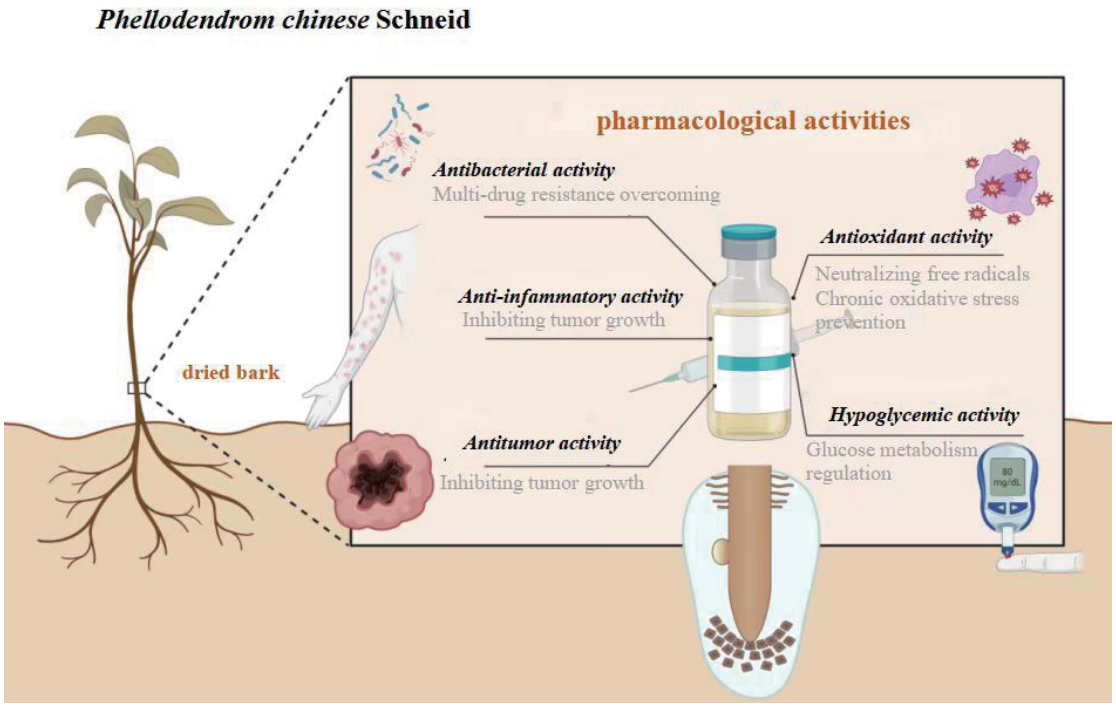

Fig. 9 Pharmacological activities of *P. chinense*

3.1 Antimicrobial activity

Berberine (**12**) is the main alkaloid component in *P. chinense*. It has strong inhibitory effects on various Gram-positive and Gram-negative bacteria, such as *Staphylococcus aureus*, *Bacillus anthracis*, *Streptococcus pneumoniae*, *Corynebacterium diphtheriae* and *Shigella dysenteriae* [17]. The antibacterial mechanism of berberine may be related to its damage to bacterial cell wall and membrane, as well as its inhibition of bacterial oxidative damage activity and energy metabolism [18]. High concentration of berberine has bactericidal effect and is widely used in the treatment of gastroenteritis, bacterial dysentery and other diseases [17].

The water decoction or alcohol extract of *P. chinense* also has antibacterial activity, and has inhibitory effects on *S. pneumoniae*, *C. diphtheriae* and *S. dysenteriae*. Animal model experiments show that the water decoction of *P. chinense* has a protective effect on mice infected with *S. aureus*, and can effectively reduce the mortality rate [19]. The water extract coating catheter of *P. chinense* can reduce urinary tract infection, and the effect is better when combined with antibiotics. The essential oil of *P. chinense* fruit can destroy the integrity of bacterial cell membrane, inhibit the oxidative damage activity and energy metabolism of bacteria [17,18].

The flavonoid glycosides in the leaves of *P. chinense* also have inhibitory effects on some bacteria [20]. The essential oil of Chuanhuangbo can destroy the oxidative damage activity of bacterial cells and the integrity of *Salmonella cell membrane*, and inhibit the energy metabolism of bacteria. The nitrate lotion contains rhubarb, Chuanhuangbo and other ingredients, which can effectively inhibit *Bacillus subtilis*, *Escherichia coli* and *S. aureus* [20,21].

In summary, *P. chinense* and its main component berberine have a broad-spectrum antibacterial activity, which may be related to their effects on bacterial cell wall, cell membrane, oxidative damage activity and energy metabolism. *P. chinense* is clinically used to treat diseases caused by bacterial infection, such as skin infection, showing its application value of antibacterial activity. However, the antibacterial activity and mechanism of *P. chinense* still need to be further studied to clarify its synergistic effect with other antibacterial drugs, as well as its impact on human microbiome.

3.2 Anti-inflammatory activity

The anti-inflammatory effects of *P. chinense* are mainly manifested in the following aspects. First, it inhibits the production of nitric oxide (NO) and inducible nitric oxide synthase (iNOS). NO is an important inflammatory mediator, and excessive NO can cause tissue damage and neuronal death. iNOS is the main synthetic enzyme of NO, which is highly expressed when stimulated by inflammation. Studies have found that the partial alcohol extract of *P. chinense* can effectively regulate the production of NO and iNOS in BV2 cells and mouse microglia induced by lipopolysaccharide, indicating that PAR has anti-inflammatory and neuroprotective effects [22]. In addition, the non-alkaloid components of *P. chinense*, such as limonin (59) and obacunone (57), can also significantly down-regulate NO production and iNOS gene expression through the nuclear factor-κB (NF-κB) mediated pathway [22].

Second, it attenuates the release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). TNF-α and IL-1β are two important pro-inflammatory cytokines, involved in the occurrence and development of various inflammatory diseases. Studies have found that PAR extract can also attenuate the release of TNF-α and IL-1β by LPS-stimulated microglia, among which the inhibitory effect on IL-1β is more significant, indicating that PAR extract may regulate different inflammatory factors through different mechanisms [23]. Another effective component of *P. chinense*, obacunone (**57**), can also reduce the levels of TNF-α, IL-1β, IL-6

and other inflammatory factors in the LPS-induced RAW264.7 macrophage model, and inhibit the expression of iNOS and cyclooxygenase-2 (COX-2) [22]. Moreover, a new isoquinoline alkaloid glycoside isolated from *P. chinense*, phellodendrine (**16**), can also bind to the proteins closely related to inflammation, such as ERK, JNK and p38MAPK, by molecular docking, and effectively reduce the levels of NO, TNF-α, IL-1β and IL-6 in the LPS-induced RAW264.7 macrophage model, and reduce the expression of iNOS and COX-2, indicating that phellodendrine (**16**) has excellent *in vitro* anti-inflammatory effects and may become a potential drug for treating inflammatory diseases [22,23].

Third, it alleviates the inflammatory response and tissue damage in animal models. The anti-inflammatory effects of *P. chinense* are not only verified *in vitro* experiments, but also show good results in various animal models. For example, the partial alcohol extract of *P. chinense* can antagonize the contact delayed-type hypersensitivity (DTH) induced by picryl chloride and oxfendazole, and alleviate the inflammatory response in the mouse ear swelling model [24]. *P. chinense* extract can also reduce the myeloperoxidase (MPO) activity by inhibiting the leukocyte migration rate and/or the secretory activity of berberine, while having little effect on the phospholipase A2 (PLA2) activity and the swelling induced by arachidonic acid (AA) [23]. In addition, PC extract can also reverse the airway inflammation by reducing the infiltration of inflammatory cells and releasing inflammatory mediators into the affected lungs and airways, which can prove its application in infectious pulmonary diseases [24]. In addition, another partial alcohol extract of *P. chinense* can not only reduce the size of edema, but also reduce the MPO activity and reactive oxygen species (ROS) content caused by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). They can also inhibit the levels of TNF-α, Il-1β, IL-6 and COX-2 in TPA-treated mice. It is worth noting that many compounds in *P. chinense*, including palmatine (**6**), berberine (**12**) and phellodendrine (**16**), are regarded as anti-inflammatory activity candidates. In addition, they can cooperate in this respect [24,25].

3.3 Antioxidant activity

P. chinense extract can promote the scavenging of free radicals and exert antioxidant activity. *In vitro* antioxidant analysis showed that A549 cells could effectively remove ROS in the presence of phellodendrine at a mass concentration of 5.25 μg/mL under DPPH·, ABTS+ and oxygen radicals [26]. Another antioxidant experiment indicated that phellodendrine could protect zebrafish embryos from death, heartbeat abnormality and lipid peroxidation induced by APPH. The results of the thiocyanate-iron method for testing anti-lipid oxidation showed that chlorogenic acid had a good antioxidant effect, exhibiting a certain dose-effect relationship [27].

The antioxidant effect of *P. chinense* was positively correlated with the concentration of its extract. Due to the higher content of phenols and flavonoids in the ethanol extract than in the water extract, the ethanol extract had a better antioxidant effect. The alkaloid components in *P. chinense* could exert antioxidant effects by regulating the Akt/NF-κB pathway in zebrafish embryos [27]. In addition, the flavonoids in *P. chinense* were natural antioxidants, which could scavenge superoxide anion radicals in the human body and play roles in anti-aging and enhancing immunity.

3.4 Antitumor activity

P. chinense contains various compounds that can inhibit or kill different types of cancer cells, such as lung, prostate, stomach, pancreatic and osteosarcoma [28,29]. Chlorogenic acid (**43**), a compound found in *P. chinense*, can block the cell cycle of human lung cancer A549 cells at the S phase, preventing cell division and reducing cell viability [28]. Chlorogenic acid (**43**), can also

induce apoptosis of cancer cells by decreasing the mitochondrial membrane potential, increasing the expression level of pro-apoptotic factor Bax, decreasing the expression level of anti-apoptotic factor Bcl-2 and activating capase3. Other compounds in *P. chinense* that have anti-prostate cancer effects include magnoflorine (**8**), berberine (**12**) and palmatine (**6**). Stuidies points out that an extract of *P. chinense* can inhibit the malignant progression of gastric cancer by negatively regulating the STAT3/NF-κB signaling pathway and suppressing the expression of FAK [29]. Palmatine (**6**) also has anti-pancreatic cancer effects by inhibiting glutamate-mediated alterations of GLI signaling in pancreatic cancer cells and blocking the interaction between pancreatic stellate cells and cancer cells [30]. Moreover, some flavonoids in *P. chinense* can inhibit the viability and induce the apoptosis of osteosarcoma cells by inhibiting the PI3K/Akt/mTOR pathway [30]. This suggests that *P. chinense* may serve as a novel potential drug for the treatment of osteosarcoma.

3.5 Hypoglycemic activity

Berberine (**12**), the main active ingredient of *P. chinense*, has the effect of lowering blood glucose and is beneficial for patients with diabetes. Studies have shown that berberine can reduce fasting blood glucose, postprandial blood glucose and hemoglobin A1c levels in adults, as well as lower total cholesterol and low-density lipoprotein cholesterol levels [31]. The hypoglycemic mechanism of berberine may be related to improving insulin sensitivity, increasing insulin secretion, inhibiting fat synthesis and enhancing mitochondrial function. In addition, berberine can also treat KK-Ay diabetic mice, improve their glucose tolerance and reduce the pancreatic islet oxygen consumption induced by hyperglycemia. Different preparations of *P. chinense* can also affect the material and energy metabolism of rats, among which raw *P. chinense* can increase plasma triglyceride levels and decrease the glucose metabolism and glycolysis rate of rats [32].

4 Conclusion

This study reviews the chemical compositions and pharmacological activities of *P. chinense* based on existing studies. As a traditional Chinese herbal medicine, *P. chinense* is very rich in resources and is widely used clinically. It contains a variety of active ingredients, which have antibacterial, antiviral, antiviral and other pharmacological activities. The efficacy of *P. chinense* has been widely recognized by the medical community, but the toxicology research of *P. chinense* needs to be more thorough and systematic. The research results on the toxicity of *P. chinense* highlight its potential as a safe herbal medicine with various pharmacological activities. By studying on the antioxidant and hepatoprotective effect of *P. chinense*, the potential as a hepatoprotective agent in t-BHP-induced liver cell damage was confirmed, which will be beneficial to further clinical application. For instance, a study aimed to produce *P. chinense* green tea leaves (GTL), black tea leaves (BTL) and untreated leaves (UL) to investigate the differences in their flavor substances, functional components, antioxidant activity, alcohol dehydrogenase (ADH) activity and acetaldehyde dehydrogenase (ALDH) activity. The results show that tea products made with *P. chinense* leaves are rich in functional compounds, have satisfactory antioxidant and hepatoprotective activities, and are worth eating every day. Moreover, the hepatoprotective effects of *P. chinense* is related to its potential in treating liver diseases traditionally used by the Chinese Miao minority. Pharmacological research shows its potential liver protective effects in experimental models of chemically-induced liver injury, acute and chronic alcoholic liver injury, non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and viral infection, potentially through antioxidant effects, balancing key liver enzyme

levels, inhibition of hepatic virus DNA replication, inhibition of hepatic stellate cells activation, and inflammation either *in vitro* or *in vivo* [31,32]. However, despite these promising findings, there is a consensus in the scientific community that more thorough and systematic research is needed to fully understand the toxicological profile of *P. chinense*. This includes identifying any potential adverse effects, understanding the mechanisms of action, and establishing safe dosage guidelines for clinical use. The future of *P. chinense* as a widely recognized medicinal plant depends on the results of such rigorous investigations. In conclusion, although *P. chinense* has shown a range of beneficial pharmacological activities, the toxicology research is still in the initial stage and further exploration is needed to ensure its safety and efficacy in clinical applications. The medical community awaits more intensive research to pave the way for its wider acceptance and integration into therapeutic practices. In the future, if its safety, effectiveness and efficacy can be further studied and discussed, *P. chinense* will be more widely recognized.

Acknowledgements

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