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Review article

# Progress in the study of chemical composition, biological activity, and its metabolism of the *Picrasma quassioides*

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ABSTRACT

*Picrasma quassioides* (D.Don) Benn is a member of the Simaroubaceae family, which has a long history of medicinal use in China, the composition of compounds is complex, mainly including alkaloids, lignin, triterpenoids, and other compounds. As a traditional Chinese medicine, *P. quassioides* has pharmacological effects such as anti-inflammatory, antipyretic, antiviral, blood pressure lowering and anticancer. Scholars at home and abroad have been studying *P. quassioides* for about 50 years. In the present review, the research status of the chemical composition, pharmacological activity and pharmacokinetics of *P. quassioides* was provided, as a reference for further developing the value of *P. quassioides*.

*Picrasma quassioides* (D.Don) Benn is a member of the Simaroubaceae family, is a traditional Chinese herb with a long history of medicinal value, which is bitter, cold in nature, and belongs to the lung and large intestine meridians. According to the 2020 edition of the Chinese Pharmacopoeia, *P. quassioides* has the effect of clearing heat and removing dampness which is used for wind-heat colds, sore throats, damp-heat diarrhea and dysentery, eczema, sores, and snake and insect bites [1]. The chemical composition of *P. quassioides* is complex and rich, containing triterpenoids, volatile oils, flavonoids, sterols, saponins, coumarins, and phenolic glycosides in addition to the characteristic *P. quassioides* alkaloids and bittersweet components [2]. Modern pharmacological studies have shown that *P. quassioides* has anticancer, anti-inflammatory, antibacterial, antihypertensive, antipyretic, antivenom, antimalarial, and stomachic effects [3]. Clinically, a variety of active ingredients in *P. quassioides* have been used in herbal preparations, such as *P. quassioides* injection, *P. quassioides* combination, compound *P. quassioides* anti-inflammatory capsule, lotus gall bladder anti-inflammatory tablets, and anti-inflammatory and cholagogue tablets, and have achieved good efficacy in the treatment of various inflammatory diseases such as upper respiratory tract infections, cholecystitis, and enteritis [4–6]. In addition to its significant anti-inflammatory effects, *P. quassioides* contains components such as *P. quassioides* alkaloids and bittersweet, which have various pharmacological activities such as anti-tumor, blood pressure lowering, and anti-pathogenic microorganisms [7,8]. This study reviews the chemical composition, pharmacological activity, and pharmacokinetic studies of *P. quassioides* in the past 50 years to provide a basis for better development and utilization of the Chinese medicine *P. quassioides*.

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## 1. Chemical composition of *P. quassioides*

The chemical composition of *P. quassioides* is relatively complex. A β-carboline alkaloid was first isolated and identified from *P. quassioides* by Japanese scholars Kondo and Takemoto [9] in 1973, and subsequently, its chemical composition has been extensively studied by domestic and foreign scholars. It was found that the main chemical composition of *P. quassioides* are alkaloids and bittersweet substances, and the *P. quassioides* alkaloids have received wide attention due to their significant pharmacological activity and have been used as marker compounds for quality control of *P. quassioides* and its related preparations.

### *1.1. Alkaloids*

*P. quassioides* alkaloids are classified into β-carboline alkaloids, canthin-6-one alkaloids, and alkaloid dimers. According to the literature, 86 alkaloids have been identified in the *P. quassioides*, including 60 β-carbolines, 15 canthin-6-ones, and 11 alkaloid dimers.

#### *1.1.1. β-carboline alkaloids*

The most abundant alkaloids in *P. quassioides* plants are the β-carboline alkaloids, of which there are 60 species [9–29]. Among them, there are 58 compounds with the parent nucleus structure in Fig. 1 A and two compounds with the parent nucleus structure in Fig. 1 B.

#### *1.1.2. Canthin-6-one alkaloids*

There are 15 canthin-6-one alkaloids [16,9,18,21–23,26,27,30,31] in the *P. quassioides* plant, as shown in Fig. 2. There are 11 compounds with the parent nucleus structure in Fig. 2 A, one with the parent nucleus structure in Fig. 2 B, and three with the parent nucleus structure in Fig. 2 C.

#### *1.1.3. Alkaloid dimers*

There are four parent nucleus structures of alkaloid dimer compounds in *P. quassioides* plants, totaling 11 compounds [24,26, 31–36]. Among them, there are two, two, three, and four compounds with the parent nucleus structures of Fig. 3 A, B, C, and D, respectively, and the structures are shown in Fig. 3.

### *1.2. Quassinoids*

Quassinoids chemicals are characteristic components in the Chinese herbal medicine *P. quassioides* plant, and 64 quassinoids structures have been identified [37–50]. There are three types of their parent nucleus structures, hemiacetals and lactones. There are 24 compounds with the parent nucleus structure of Fig. 4 A, one compound with the parent nucleus structure of Fig. 4 B, and 39 compounds with the parent nucleus structure of Fig. 4 C. Their structures are shown in Fig. 4.

### *1.3. Triterpenoids*

A total of 42 triterpenoids were identified in *P. quassioides* [51–55], with two parent nucleus structures, as shown in Fig. 5. Among them, one compound with the structure of parent nucleus Fig. 5 A and 41 compounds with the structure of parent nucleus Fig. 5 B were identified.

### *1.4. Other substances*

So far, other compounds isolated from *P. quassioides* include volatile oils, phenylpropanoids, flavonoids, phenolic glycosides, phenolic acids, and violetone derivatives of cyclohexanone [56–58], including sesquiterpenes [12], cinnamamide derivative [15], neolignans [59,60], phenolic derivatives [61], and cyclization ionone derivative [62], which have been newly discovered in recent

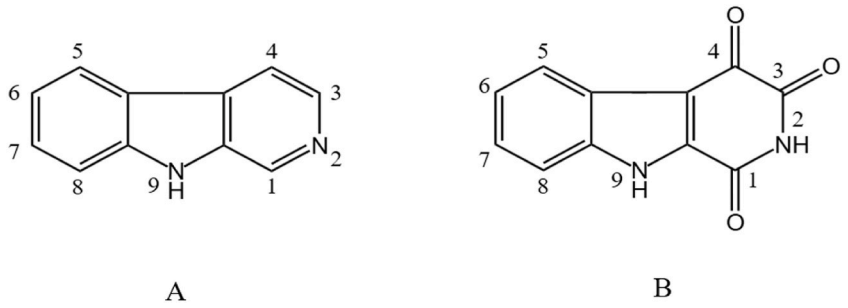


**Fig. 1.** Parent nucleus structure of β-carboline alkaloids in *P. quassioides*. (A) The parent nucleus structure of 58 β-carboline alkaloid compounds. (B) The parent nucleus structure of two other β-carboline alkaloid compounds.

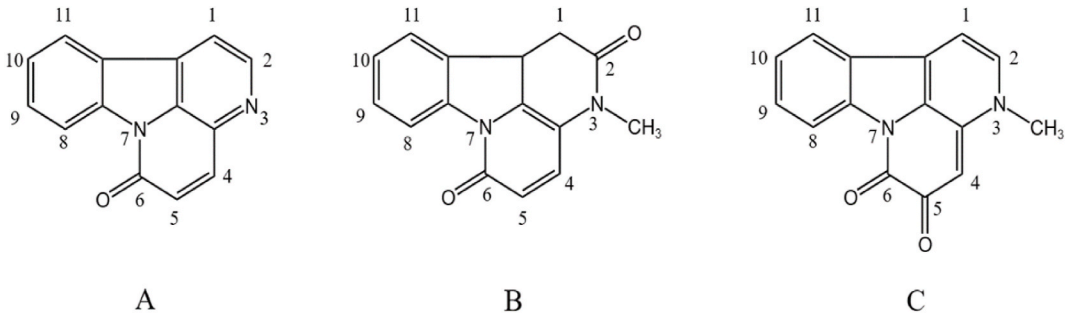


**Fig. 2.** Parent nucleus structure of canthin-6-one alkaloids in *P. quassioides*. (A) The parent nucleus structure of 11 canthin-6-one alkaloid compounds. (B) The parent nucleus structure of one canthin-6-one alkaloid compound. (C) The parent nucleus structure of three other canthin-6-one alkaloid compounds.

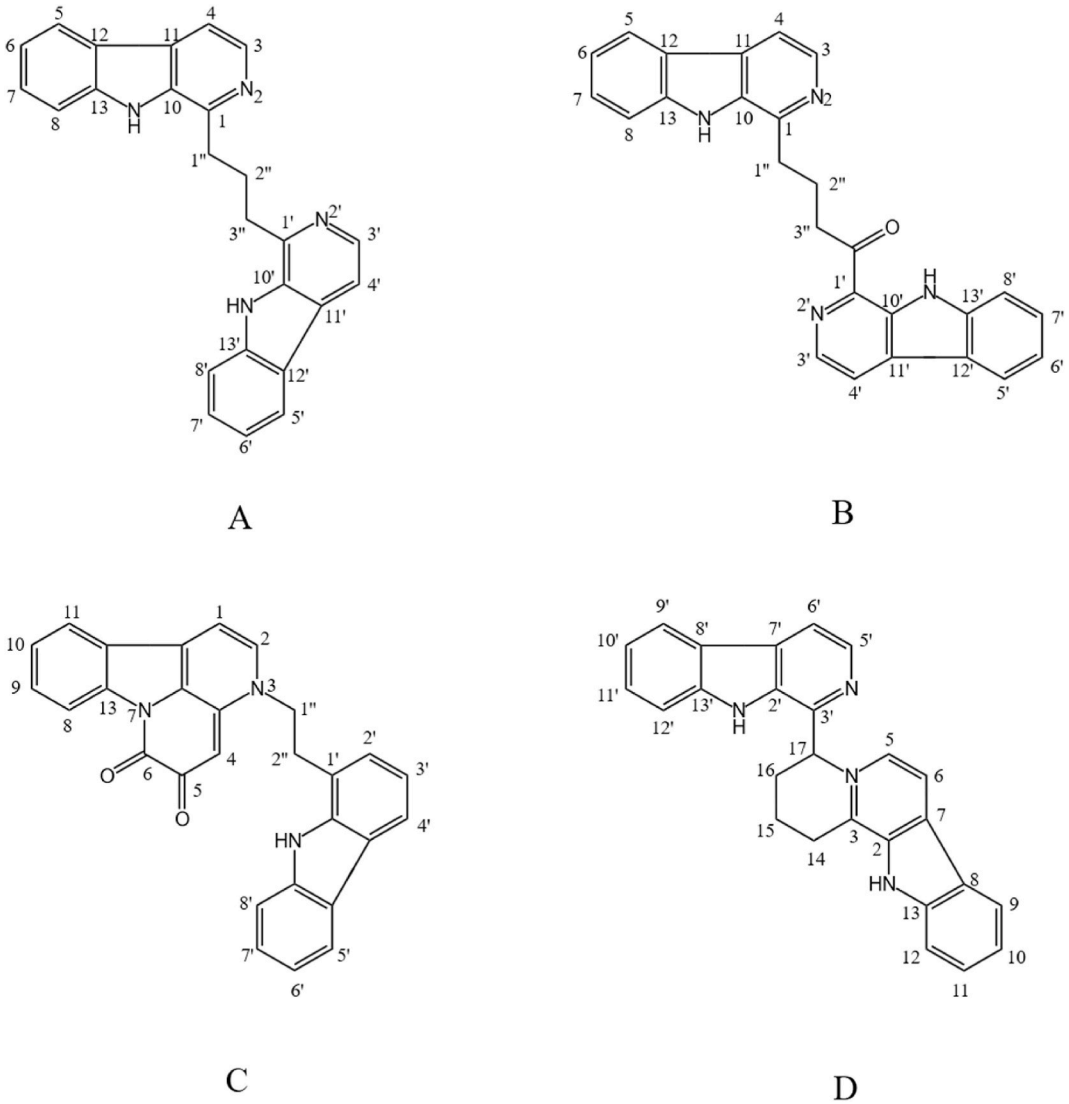


**Fig. 3.** Parent nucleus structure of alkaloid dimer in *P. quassioides*. (A) The parent nucleus structure of two alkaloid dimer compounds. (B) The parent nucleus structure of two alkaloid dimer compounds among them. (C) The parent nucleus structure of three alkaloid dimer compounds. (D) The parent nucleus structure of four other alkaloid dimer compounds.

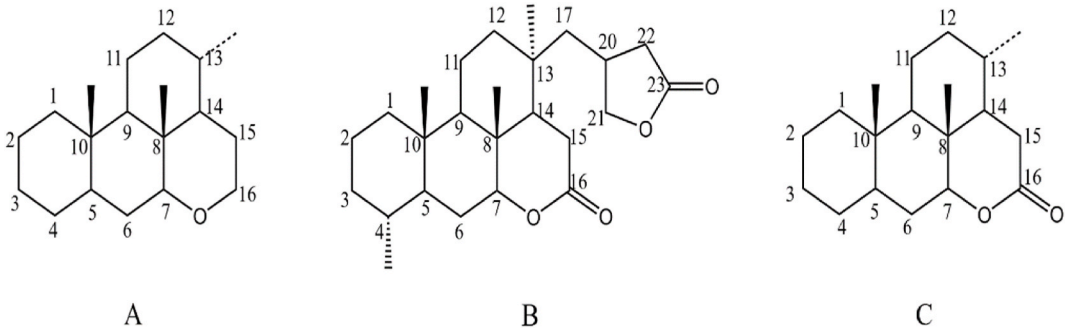


**Fig. 4.** Parent nucleus structure of quassinoids in *P. quassioides*. (A) The parent nucleus structure of 24 quassinoid compounds. (B) The parent nucleus structure of one quassinoid compound. (C) The parent nucleus structure of 39 other quassinoid compounds.

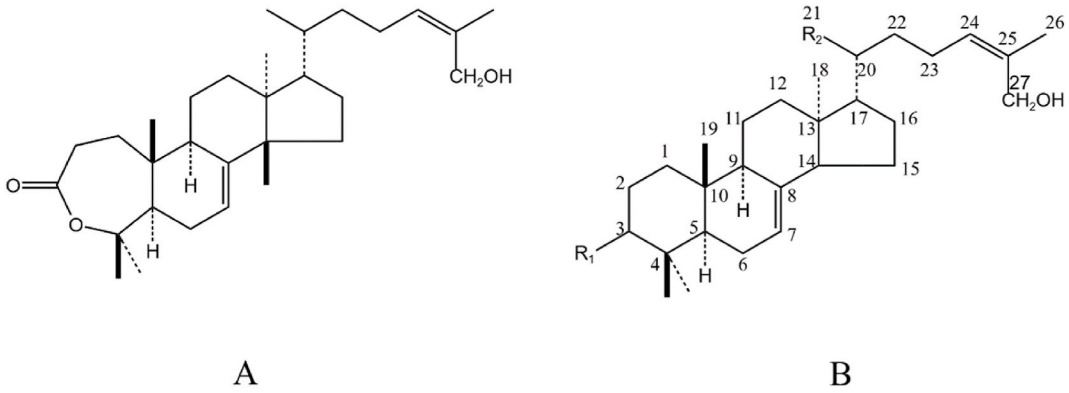


**Fig. 5.** Parent nucleus structure of triterpenoids in *P. quassioides.* (A) The parent nucleus structure of one triterpenoid compound. (B) The parent nucleus structure of 41 other triterpenoid compounds.

years.

### *1.5. Structural activity relationship (SAR) of P. quassioides*

The structural activity relationship (SAR) of *P. quassioides* refers to the relationship between the structure of a specific chemical component in *P. quassioides* and its biological activity. The SAR of *P. quassioides* is mainly reflected in the close relationship between the structure of its chemical composition and its biological activity. The structural characteristics of these chemical components, such as containing nitrogen atoms and aromatic rings, give them unique pharmacological activities, such as antihypertensive, anti-cancer, anti-inflammatory and so on. Through the in-depth study of *P. quassioides* SAR, it can further reveal its pharmacological mechanism, and provide scientific basis for the quality control and clinical application of *P. quassioides*.

For example, alkaloids in *P. quassioides*, such as quassa, have an inhibitory effect on cAMP phosphodiesterase, which can affect intracellular signaling and thus affect blood pressure. In addition, the total alkaloids of *P. quassioides* promote the synthesis and release of vasodilator NO by endothelial cells through increasing the protein expression of eNOS, which makes blood vessels dilate and blood pressure decrease. In addition, the growth of lymphocytic leukemia P388 cell line was inhibited by picroside B in *P. quassioides*, which may be related to the specific structure of the compound, such as aromatic ring and nitrogen atom [37,63,64].

## 2. Biological activity of *P. quassioides*

### *2.1. Anti-cancer*

According to recent literature, the anticancer effects and mechanisms of *P. quassioides* are as follows: treatment of lung cancer cells with *P. quassioides* extracts increases intracellular reactive oxygen species, decreases cell proliferation and migration capacity, and causes autophagy and apoptosis [65]. Compound d of the 4-methoxy-5-hydroxy-canthin-6-one (CAN1) backbone, an analog of canthin-6-one isolated from *P. quassioides*, exhibited stronger anti-tumor cell proliferative activity than 5-FU and induced apoptosis of human cancer cell lines, HepG2 and HCT116 more effectively [66]. *P. quassioides* extract can inhibit the growth of tumors in mice with gastric cancer by upregulating the p21 gene and improving the immune capacity of the body [67].

It was found that *P. quassioides* extract tonics have some efficacy in primary liver cancer, probably by modulating the levels of AFP,

VEGF, nm23, CD44, and Bcl-2 in the serum of patients to achieve the antitumor effect [68]. In addition, β-carboline enantiomers extracted from *P. quassioides* were able to reduce the expression of H-Ras, inhibit the viability of hepatocellular carcinoma cells, and affect ROS accumulation and mitochondrial function in HepG2 cells with H-ras mutations [69]. The compounds isolated from *P. quassioides* can have antitumor effects by significantly and selectively inhibiting hepatocellular carcinoma cell activity and inducing apoptosis leading to hepatocellular carcinoma cell death [16,70].

Picrasidine F, which also has therapeutic effects in cervical cancer, can exert antitumor effects by mediating the miR-331-3p/PSME3 axis to inhibit the proliferation of cervical cancer HeLa cells and promote apoptosis [71]. *P. quassioides* ethanol extract can inhibit ATP synthesis and induce apoptosis in cervical cancer SiHa cells, and the P38MAPK signaling pathway is key to the induction of apoptosis [72]. β-CCE (a β-carboline alkaloid in *P. quassioides*) can increase ROS levels in cervical cancer cells, damage mitochondria, induce apoptosis, and activate p38/MAPK and mitochondria-dependent apoptotic signaling pathways [73]. Furthermore, the three β-carboline alkaloid components isolated from the ethanolic extract of the stem of *P. quassioides* showed inhibitory effects on both cervical and other cancer cells, further confirming the anticancer effects of *P. quassioides* [8].

Dehydrohumanoside extracted from *P. quassioides* induces cell cycle arrest and apoptosis in nasopharyngeal carcinoma cells by regulating JNK and ERK signaling pathways [74]. Picrasidine G (PG), a natural dimeric alkaloid of *P. quassioides*, reduces the viability of the MDA-MB468 cell line (TNBCEGFR+), increases apoptotic markers, and inhibits transcription of STAT3 target gene survivin, which may contribute to targeted therapy in patients with triple-negative breast cancer (TNBC) [75]. In addition, the *P. quassioides* alkaloid 1-methoxycarbonyl-β-carboline (MCC) inhibited the viability, migration, invasion, and lumen formation of human umbilical vein endothelial cells (HUVECs) and suppressed the growth of tumor masses and metastasis of DU145 tumor cells [76].

### 2.2. Anti-inflammatory

The alkaloid component of *P. quassioides* is the main effective anti-inflammatory substance, and a large number of β-carboline alkaloid compounds isolated from the branches, stems, and roots of *P. quassioides* exhibited good anti-inflammatory biological activity [77]. For example, the alkaloid picrasidine I in *P. quassioides* can inhibit osteoclastogenesis and exert anti-inflammatory effects [78]. The carboline alkaloids in *P. quassioides* also have potential anti-inflammatory and antimicrobial activities, with studies finding the highest inhibitory effect of 1-formyl-4-methoxy-β-carboline and 1-formyl-β-carboline [79]. In addition, *P. quassioides* lipotropin A, boldenolA, boldenolC, and Fustin also inhibit the release of inflammatory factors and achieve anti-inflammatory effects [80,81]. It was also found that total *P. quassioides* alkaloids had a significant effect on collagen-induced arthritis, reducing the degree of swelling and joint damage. It reduced TNF-α, IL-6, foot and plantar swelling and joint damage in rats [82].

Clinical trials on the anti-inflammatory properties of *P. quassioides* are as follows: *P. quassioides* injection combined with azithromycin provides synergistic and additive inhibition of the inflammatory factors NO and TNF-α [63]. The combination of oral compound *P. quassioides* anti-inflammatory tablets with topical Lankefuning can safely and effectively treat acne vulgaris with an efficiency of 95 % in the treatment group [83]. *P. quassioides* injection nebulized inhalation adjunct to conventional treatment significantly increased the overall efficiency of acute upper respiratory tract infections in pediatric patients [84]. Intramuscular injection of *P. quassioides* injection in the treatment of acute upper respiratory tract infections in pediatric patients has an overall efficiency of 97.8 % and a high safety profile [4].

Lotus gall injection can relieve fever caused by mixed typhoid and paratyphoid bacteria in rabbits [85,86], and also has a counteracting and antipyretic effect on fever caused by tripterygium vaccine [87]. In addition, the active ingredients in *P. quassioides* have analgesic effects, among which the β-carboline alkaloid Dehydrocrenatidine can achieve analgesic effects by inhibiting neuronal excitability [88]. In addition, the β-carboline alkaloid dehydrocretidine (DHCT) also has analgesic effects and has demonstrated a reduction in mechanical nociceptive hypersensitivity in a rat model of neuropathic pain from chronic compression injury of the sciatic nerve [89].

### 2.3. Antibacterial

*P. quassioides* alkaloids have shown varying degrees of inhibition in vitro against a variety of bacteria, such as Streptococcus haemolyticus B, Staphylococcus aureus, Bacillus sonnei dysentery, Bacillus subtilis, and Bacillus octococci [90,91].

*P. quassioides* aqueous decoction and lipid-soluble total alkaloids showed antibacterial effects against four experimental bacteria in vitro, and topical application of *P. quassioides* aqueous decoction relieved ear redness and lowered serum IgE and IL-6 levels in mice with atopic dermatitis, indicating its antibacterial and anti-inflammatory effects [92]. One study determined that lipid-soluble *P. quassioides* alkaloids had a strong inhibitory effect on *E. coli* strains C249, WM, and YL in vitro [93]. Chen M. et al. [94] found that 4, 5-Dimethoxycanthin-6-one had a significant inhibitory effect on Pneumococcus pneumoniae, and 5-Hydroxy-4-methoxycanthin-6-one and 3-methyl-canthin-2,6-dione also had an inhibitory effect. Methanolic substances extracted from the leaves, seeds, stems and root bark of *P. quassioides*, as well as fractions petroleum ether, methylene chloride, ethyl acetate, and n-butanol, all have broad-spectrum antibacterial activity against a variety of fungi [95]. In an in vitro evaluation of the anti-tuberculosis activity, foreign scholars found that the methanolic extract of *P. quassioides* also had an inhibitory effect on *Mycobacterium tuberculosis*. Shi G. et al. [8] isolated three β-carboline alkaloid components picrasidine F, G and S from the ethanol extract of *P. quassioides* stem, which showed significant antibacterial and cytotoxic activity against *Staphylococcus aureus*.

The combination of *P. quassioides* injection and azithromycin may synergistically inhibit a variety of bacteria such as *Staphylococcus aureus*, including drug-resistant strains, by activating NF-κB and MAPKs signaling pathways and inhibiting the release of NO, TNF-α, and IL-6. In addition, combination therapy improves *Klebsiella pneumoniae* induced lung histopathy and alleviates clinical symptoms

[63,64].

### 2.4. Treatment of cardiovascular diseases

*P. quassioides* increased serum nitric oxide and superoxide dismutase SOD levels in essential hypertensive rats and dilated blood vessels and lowered blood pressure by increasing the content of vasodilatory factor NO [96]. Several studies have shown that total alkaloids of *P. quassioides* have hypotensive effects in both normal and renal hypertensive rats, while slowing heart rate, improving myocardial blood flow and inhibiting sympathetic discharge [97]. The study of acute hypotensive and rat hypotensive experiments revealed that the total alkaloids of *P. quassioides* have obvious hypotensive effects and certain detoxifying effects, with good long-term efficacy and mild side effects [98]. The Chinese patent medicine of *P. quassioides* has also been shown to have antihypertensive effects similar to those of hypocretin, while *P. quassioides* lactone A may achieve hypotension through central α receptors [99,100]. Researchers isolated the quassinoid compound *P. quassioides* lactone A (I) from the stems of *P. quassioides* by aqueous extraction and found it to have significant antihypertensive effects and also showed better efficacy in clinical trials [101].

Total alkaloids of *P. quassioides* have significant hypotensive and heart rate-slowing effects in anesthetized dogs. Intravenous administration of total *P. quassioides* alkaloids to anesthetized dogs, significantly lowered blood pressure, slowed heart rate, reduced coronary blood flow, decreased cardiac output, reduced left ventricular work, and decreased myocardial oxygen consumption [102]. Perfusion experiments on the isolated heart of toads showed a slowing of heart rate, but did not affect myocardial contractility; perfusion experiments on the isolated rabbit ear and toad vessels both showed vasodilatation; different doses of total alkaloids had different degrees of heart rate slowing effects on anesthetized dogs by sedation while prolonging the P–R interval and slightly slowing atrioventricular conduction [103].

Therefore, the comprehensive literature shows that the antihypertensive mechanism of *P. quassioides* is multi-fold, including the direct action, blocking of a receptor, inhibiting superoxide dismutase activity, increasing the expression of nitric oxide synthase and NO production, and inhibiting the sympathetic nerve center.

### 2.5. Effects on the gastrointestinal tract

It was found that Canthin-6-one and β-Carboline-1-propanoic acid from *P. quassioides* increased gastrointestinal blood flow rate in rabbits, whereas 4,5-Dimethoxycanthin-6-one, 5-Hydroxy-4-methoxycanthin-6-one, and Methyl β-carboline-1-carboxylate increased intestinal blood flow rate only [104]. In addition, the active components of *P. quassioides* have a protective effect on the gastric mucosa and are effective against gastric ulcers and mucosal damage. The alkaloids in *P. quassioides* can reduce the inflammatory reaction of gastric mucosa by inhibiting the production and release of inflammatory factors, so as to achieve the purpose of protecting gastric mucosa. The picrogens in *P. quassioides* have anti-inflammatory and antibacterial effects, which can reduce the damage and death of gastric mucosa cells, promote the repair and regeneration of gastric mucosa cells, and thus improve the symptoms of gastric mucosa damage and gastric ulcer [105]. Wei Mingqiang et al. [5] showed that *P. quassioides* injection was significantly more effective than traditional methods in the treatment of pediatric enteritis. Also, *P. quassioides* injection at acupuncture points is an effective method for the treatment of pediatric diarrhea, especially for autumn and winter diarrhea in children over 1 year of age [106,107].

### 2.6. Antiviral

Clinical trials have shown that *P. quassioides* injection has the effect of clearing heat and detoxifying, dispelling dampness, and relieving pain, and is more effective than virazole injection in the treatment of blistering, pain relief, crusting, and healing time [108]. In addition, *P. quassioides* injection has been suggested to have a possible inhibitory effect on novel coronaviruses and is expected to be a new drug against novel coronaviruses [109].

### 2.7. Protective effect on poisoned animals

A study by Du [110] et al. showed that *P. quassioides* alkaloids had no effect on normal rabbits, but could significantly reduce the serum alanine aminotransferase and mortality of rabbits with toxic hepatitis induced by severe subcutaneous injection of carbon tetrachloride. The experiments of Liang Wen [111] found that *P. quassioides* injection had significant protective effects on both mice and dogs injected with lethal doses of snake venom, reaching 75.6 % protection in mice and up to 100 % protection in dogs.

### 2.8. Anti-malarial

Saiin et al. [112] found that the n-hexane extract of *P. quassioides* has anti-malarial activity. Pavanand et al. [113], on the other hand, found that compounds 6-hydroxy-4-methoxy-1-vinyl-B-carboline and 4-methoxy-1-6-carboline extracted from the stem bark of Thai *P. quassioides* produced inhibitory activity against a variety of Plasmodium falciparum species.

### 2.9. Antioxidant

The roots, stems, branches, and leaves of *P. quassioides* have antioxidant effects, with the leaves being the most effective and can be used as an antioxidant stress agent in animal production [114].Yang et al. [115] found that *P. quassioides* had significant antioxidant

activity, demonstrating that 4-methoxy-5-hydroxy-6-one was the only compound with antioxidant activity, which provides a basis for further development of *P. quassioides* as an antioxidant. 4-methoxy-5-hydroxycanthin-6-one exhibited obvious 1,1-diphenyl-2-picryl--hydrazyl free radical scavenging activity with an IC50 value of 84.037 μM.

### *2.10. Anti-metabolic disorder effects*

Naturally occurring compounds dimeric alkaloid picrasidine N in *P. quassioides* have been reported to stimulate receptors such as PPARγ and PPARβ/δ, which play important roles in the regulation of energy metabolism, inflammation, and other physiological processes such as obesity, diabetes, and hyperlipidemia [116]. In addition, the dimeric β-carboline type alkaloid compound Picrosinine C from *P. quassioides* root is also a PPARα activator with potential applications for the treatment of metabolic diseases such as hyperlipidemia [117].

### *2.11. Protective effects on the nervous system*

The Canthin-6-one alkaloids (CO) in *P. quassioides* have potential anti-neuroinflammatory effects and may be protective against astrocyte-mediated pro-inflammatory responses and associated endothelial barrier disruption [118]. In addition, the ethyl acetate extract of *P. quassioides* stem improved memory and cognition in mice with amyloid β-peptide-induced AD and was neuroprotective in a neuronal cell model, and its anti-AD mechanism may involved inhibition of neuroinflammation and reduction of Aβ1-42 deposition [119].

## 3. Toxicity

Many studies have demonstrated that total *P. quassioides* alkaloids have no significant effects on the growth and development of rats, nor do they cause significant adverse effects on the blood indicators and organs of rats [120].However, a study by Gong et al. [9] showed that the 5-hydroxy-4-methoxycanthin-6-one (CAN) component of *P. quassioides* has toxic effects on zebrafish embryos, which may lead to reduced survival, delayed hatching, and malformation of zebrafish embryos, as well as causing oxidative stress. And a

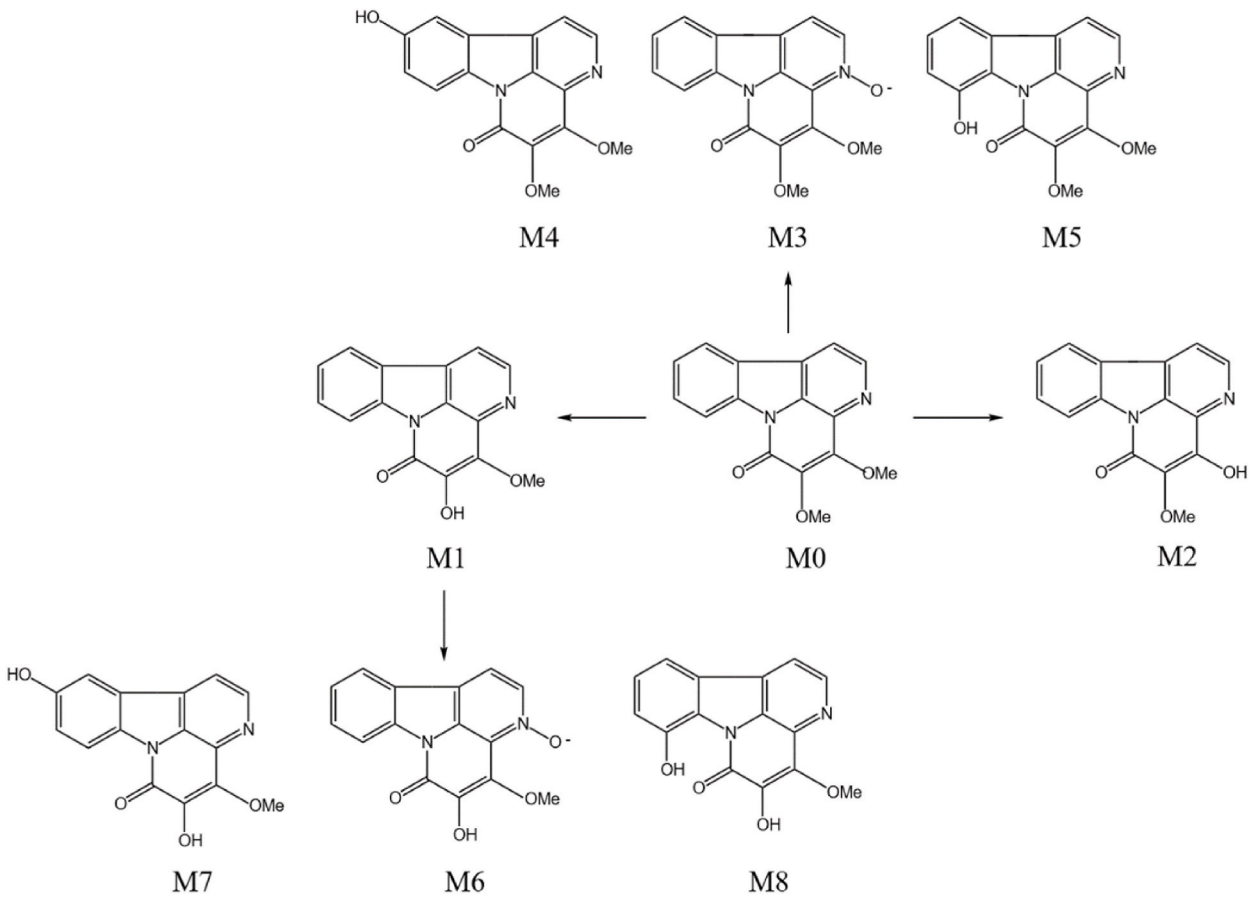


**Fig. 6.** Metabolic pathway of 4,5-Dimethoxylcanthin-6-one in liver microsomes in vitro.

series of derivatives containing the CAN1 framework were designed, synthesized, and evaluated for anti-proliferative activity against two human cancer cell lines, HepG2 and HCT116, IC50 values of 5.05 μM (HepG2) and 6.65 μM (HCT116).

## 4. Metabolic studies

In recent years, there have been new developments in metabolic studies on *P. quassioides*. Miao et al. [121–123] studied the metabolites (M1-M8, as shown in Fig. 6) of 4,5-Dimethoxycanthin-6-one in liver microsomes of different animals (rats, mice, dogs and humans) and analyzed the tissue distribution and pharmacokinetic characteristics of the major metabolites in rats. In addition, the results showed that 4,5-dimethoxycanthin-6-one could uncompetitively inhibit CYP1A2 mediated phenacetin O-deethylation with an IC50 value of 1.7 μM and a Ki value of 2.6 μM. Shi et al. [124,125] studied the concentrations of 4,5-Dimethoxycanthin-6-one and 5-Hydroxy-4-methoxycanthin-6-one in rat plasma after oral administration of *P. quassioides* by LC-MS and their pharmacokinetic characteristics, and found that 4,5-Dimethoxycanthin-6-one was eliminated faster in rats (as shown in Fig. 7). A total of 17 metabolites were identified, and a new CAN metabolic pathway was identified using LC-Q-TOF-MS and other techniques to screen and characterize CAN metabolites in rats. Zhao et al. [126] determined the content of 5-Methoxycanthin-6-one in rat plasma by LC-MS/MS and investigated its pharmacokinetic characteristics, which showed that 5-Methoxycanthin-6-one was rapidly absorbed and had a moderate elimination half-life in rats, but had low bioavailability (as shown in Table 1). Meixiang Cai et al. [127] analyzed the alkaloid chemical composition of *P. quassioides* and its conversion pattern in SD rats and found that the 4,5-carbon double bond and 6,7-lactam bond could be broken in vivo to form β-carboline type alkaloids. It was demonstrated that 5-hydroxy-4-methoxycanthin-6-one could be converted to 1-Methoxycarbonyl-β-carboline in rats. Fan et al. [128] used Cunninghamella blakesleeana CGMCC was applied as a microbial system to mimic mammalian metabolism of 4,5-Dimethoxylcanthin-6-one, and seven metabolites of compound 1 were successfully metabolized. The metabolic pathways of 1 were proposed, and the metabolic processes involved phase I and phase II reactions. In addition, *P. quassioides* promotes the metabolism of azithromycin in a rat pneumonia model, reduces tissue accumulation and avoids liver damage, and improves the efficiency of drug utilization [129]. Chen Fengzheng et al. [130] obtained the total alkaloid *P. quassioides* ketone from the ethanol extract of *P. quassioides* by acid solubilization and alkali precipitation, and found that *P. quassioides* ketone undergoes structural changes to the highly active 4,5-Dimethoxycanthin-6-one by the action of human-derived intestinal microorganisms and enzymes secreted by microorganisms.

## 5. Summary and outlook

In recent years, significant progress has been made in the study of the chemical composition, biological activity, and metabolism of the Chinese herbal medicine *P. quassioides*. The chemical composition of *P. quassioides* has been continuously discovered and new techniques have been used to isolate new major constituent substances such as alkaloids, quassinoids, triterpenoids and other substances. Studies have shown that the active substances in *P. quassioides* have anti-cancer, anti-inflammatory and antihypertensive effects, in addition to antiviral, analgesic, and neuroprotective effects, which have potential applications in the treatment of a variety of diseases. And a precise understanding of the pharmacological effects of *P. quassioides* and a solid scientific basis for its application in clinical therapy. Studying the formation, transformation and elimination of its metabolites, we can profounder understand the dynamics of *P. quassioides* drugs in vivo, providing strong support for optimizing drug design and improving therapeutic efficacy. Meanwhile, the study of *P. quassioides* alkaloid metabolites can deeper understand its mechanism of action and provide an important theoretical basis for the drug development of *P. quassioides*. In the future, we need to continue to study the chemical composition, pharmacological effects, and pharmacokinetics of *P. quassioides* in depth to develop new safe and effective drugs.

## Data availability statement

No data are available.

## Fund projects

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## Ethics approval

Review and approval by an ethics committee was not needed for this study because this is a review, there are no experiments and their ethical conflicts.

## CRediT authorship contribution statement

**Yiye Zhao:** Writing – original draft, Investigation. **Dan Ye:** Supervision, Formal analysis. **Chen Xie:** Methodology, Conceptualization. **Haoyang Quan:** Investigation, Data curation. **Min Zheng:** Supervision, Resources. **Xiaolei Miao:** Writing – review & editing, Validation.

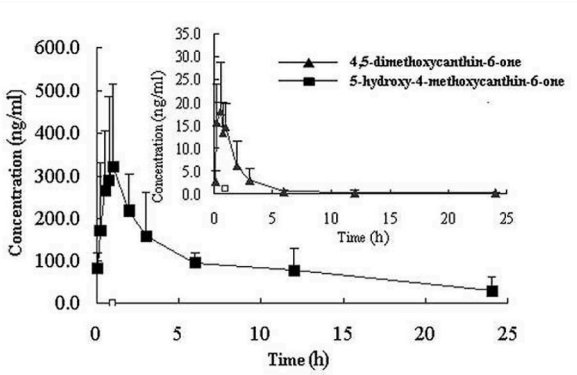


**Fig. 7.** Blood concentration and pharmacokinetic characteristics of 5-Hydroxy-4-methoxycanthin-6-one and 4,5-Dimethoxycanthin-6-one in rats.

**Table 1**
Pharmacokinetic parameters of 5 -hydroxy-4 -methoxy-ferrocinone in rats after oral and intravenous administration.

| Parameters | Unit | 10 mg/kg | Oral<br>25 mg/kg | 50 mg/kg | Intravenous<br>5 mg/kg |
|---|---|---|---|---|---|
| $AUC_{0-t}$ | μg h/L | 294.86 ± 62.40 | 564.98 ± 117.16 | 1003.28 ± 316.08 | 603.55 ± 119.80 |
| $AUC_{0-\infty}$ | μg h/L | 315.53 ± 72.62 | 593.78 ± 134.58 | 1059.62 ± 345.36 | 645.86 ± 108.04 |
| $MRT_{0-t}$ | h | 1.74 ± 0.33 | 1.92 ± 0.33 | 2.03 ± 0.34 | 0.69 ± 0.12 |
| $T_{1/2}$ | h | 1.37 ± 0.44 | 2.11 ± 1.09 | 1.55 ± 0.80 | 0.85 ± 0.14 |
| $T_{max}$ | min | 33.00 ± 6.71 | 36.00 ± 8.22 | 42.00 ± 6.71 | 2.00 ± 0.00 |
| $V_Z/F$ | L/kg | 59.27 ± 32.54 | 132.22 ± 51.12 | 92.57 ± 36.40 | 9.67 ± 1.98 |
| $CL_Z/F$ | L kg/h | 30.12 ± 13.07 | 50.97 ± 25.95 | 55.03 ± 26.25 | 7.94 ± 1.52 |
| $C_{max}$ | ng/mL | 232.80 ± 54.44 | 353.40 ± 91.17 | 484.35 ± 161.31 | 1745.51 ± 109.93 |
| F | % | 24.42 | 18.72 | 16.62 | |

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

[1] Chinese Pharmacopoeia [S], Part 1 (2020).
[2] Zhao Wenna, Xinxin Zhang, Renming Xie, et al., Research progress on chemical constituents and pharmacological effects of *Picrasma quassioides*, Sinobai 34 (7) (2011) 1149–1152.
[3] Hua Gu, Mei Wang, Zhiyang Wang, Modern pharmacology and clinical application of *Picrasma quassioides*, Research of Traditional Chinese Medicine 14 (5) (2001) 55–56.
[4] Wanhui Wu, Clinical observation on the treatment of acute upper respiratory tract infection by atomizing inhalation of *Picrasma quassioides* injection in children, Chinese Community Physician 32 (22) (2016) 119–120.
[5] Wei Mingqiang, Bin Chen, Qianyong Wu, Clinical study of Hai Lixin (*Picrasma quassioides* Injection) in treatment of infantile enteritis, Chinese Medical Guide 16 (34) (2018) 170–171.
[6] Pei Shufei, Zhang Xiangdong, Zhao Xianqun, et al. Clinical study of Xiaoyanlidan Tablet combined with ceftriaxone sodium in the treatment of chronic cholecystitis [J]. New Chinese Medicine,202,54(22):76-79.
[7] Yanqiu Deng, Zhao Lichun, Hongzhen Tang, et al., Research progress on chemical constituents and biological activities of *Picrasma quassioides*, Chinese Patent Medicine 42 (5) (2020) 1291–1296.
[8] Guohua Shi, Weihua Jiao, Yang Fan, et al., Study on three dimerized β-cabalin alkaloids and their bioactivity in Balsam pear, Chinese Herbal Medicine 46 (6) (2015) 803–807.
[9] G. Gong, L. Jiang, Q. Lin, et al., *In vivo* toxic effects of 4-methoxy-5-hydroxy-canthin-6-one in zebrafish embryos via copper dyshomeostasis and oxidative stress, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 204 (2018 Jan) 79–87.
[10] Zhao Wenna, Study on Chemical Constituents and Pharmacological Activities of *Picrasma Quassioides* [D], Northwest University, 2013.
[11] Zhang Qiuyu, Lin Zhaozhan, Yuan Yue, et al. Study on chemical constituents of *Picrasma quassioides* [J]. Chinese Herbal Medicine,20,51(19):4884-4890.
[12] Qinghua Lin, Jian Xu, Feng Feng, Chemical constituents of stem of *Picrasma quassioides*, J. China Pharm. Univ. 48 (6) (2017) 675–679.
[13] J. Zhang, S.S. Zhao, J. Xie, et al., N-methoxy-β-carboline alkaloids with inhibitory activities against Aβ42 aggregation and acetylcholinesterase from the stems of *Picrasma quassioides*, Bioorg. Chem. 101 (2020 Aug) 104043.
[14] H.S. Kwon, H. Lee, J.S. Lee, et al., Two new β-carboline alkaloids from the stems of *Picrasma quassioides*, Arch Pharm. Res. (Seoul) 41 (5) (2018 May) 513–518.
[15] J. Zhang, C.X. Wang, X.J. Song, et al., A new cinnamamide derivative and two new β-carboline alkaloids from the stems of *Picrasma quassioides*, Fitoterapia 139 (2019 Nov) 104375.
[16] W.Y. Zhao, X.Y. Shang, L. Zhao, et al., Bioactivity-guided isolation of β-Carboline alkaloids with potential anti-hepatoma effect from *Picrasma quassioides* (D. Don) Benn, Fitoterapia 130 (2018 Oct) 66–72.
[17] Y. Kondo, T. Takemoto, The structure of a New β-carboline alkaloid from *Picrasma ailanthoides* Planchon, Chem Pharm Bull 21 (4) (1973) 837–839.
[18] Junshan Yang, Shurong Luo, Xiulan Shen, et al., Chemical study on alkaloids of *Picrasma quassioides*, Acta Pharmacy 14 (3) (1979) 167–177.

[19] J.S. Yang, D. Gong, Kumujancine and kumujanrine, two new β-carboline alkaloids from *Picrasma quassioides* (D. DON.) Benn, Acta Chim Sinica 42 (7) (1984) 679–683.
[20] S. Matsumura, H. Enomoto, Indole derivatives [P]. Ger often. CODEN: GWXXBX DE 2941449 19800417, 1980, p. 21pp (German).
[21] Meng Chen, Study on Active Constituents of Alkaloids from Bittern [D], Yantai University, Yantai, 2007 (in Chinese).
[22] T. Ohmoto, K. Koike, Studies on the constituents of *Picrasma quassioides* Bennet.I. On the alkaloidal constituents, Chem Pharm Bull 30 (4) (1982) 1204–1209.
[23] I.V. Bennet, Structures of picrasidines I, J, and K, Chem Pharm Bull 33 (8) (1985) 3356–3360.
[24] T. Ohmoto, K. Koike, Studies on the constituents of *Picrasma quassioides* Bennet. II. On the alkaloidal constituents, Chem Pharm Bull 31 (9) (1983) 3198–3204.
[25] T. Ohmoto, K. Koike, Studies on the constituents of *Picrasma quassioides* Bennet. III. The alkaloidal constituents, Chem Pharm Bull 32 (9) (1984) 3579–3583.
[26] T. Ohmoto, K. Koike, Studies on the alkaloids from *Picrasma quassioides* bennet. V: structures of picrasidines L, M, and P, Chem Pharm Bull 33 (9) (1985) 3847–3851.
[27] H.Y. Li, T. Ohmoto, K. Koike, et al., New alkaloids, picrasidines W, X and Y, from *Picrasma quassioides* and X-ray crystallographic analysis of picrasidine Q, Chem Pharm Bull 41 (10) (1993) 1807–1811.
[28] W.H. Jiao, H. Gao, C.Y. Li, et al., β-Carboline alkaloids from the stems of *Picrasma quassioides*, Magn. Reson. Chem. 48 (6) (2010) 490–495.
[29] K. Koike, T. Ohmoto, K. Ikeda, β-Carboline alkaloids from *Picrasma quassioides*, Phytochemistry 29 (9) (1990) 3060–3061.
[30] J. Liu, R.S. Davidson, R.V.D. Heijden, et al., Isolation of 4-Hydroxy-5-methoxycanthin-6-one from *Picrasma quassioides* and revision of a previously reported structure, Liebigs Ann. Chem. 1992 (9) (1992) 987–988.
[31] T. Ohmoto, K. Koike, Studies on the alkaloids from *Picrasma quassioides* bennet. VI. Structures of picrasidines N, O, and Q, Chem Pharm Bull 33 (11) (1985) 4901–4905.
[32] K. Koike, T. Ohmoto, Studies on the alkaloids from *Picrasma quassioides* bennet, VII. Structures of. BETA.-carboline dimer alkaloids, picrasidines-H and-R [J]. Chem Pharm Bull 34 (5) (1986) 2090–2093.
[33] K. Koike, T. Ohmoto, Picrasidine-U, dimeric alkaloid from *Picrasma quassioides*, Phytochemistry 27 (9) (1988) 3029–3030.
[34] K. Koike, T. Ohmoto, Studies on the alkaloids of *Picrasma quassioides* Bennet. VIII X-ray crystal structure analysis of picrasidine-F, Chem Pharm Bull 34 (8) (1986) 3228–3236.
[35] K. Koike, T. Ohmoto, T. Higuchi, Picrasidine-T, a dimeric β-carboline alkaloid from *Picrasma quassioides*, Phytochemistry 26 (12) (1987) 3375–3377.
[36] K. Koike, T. Ohmoto, Studies on the alkaloids from *Picrasma quassioides* Bennet. IX. Structures of two. BETA.-carboline dimeric alkaloids, picrasidines-G and-S, Chem Pharm Bull 35 (8) (1987) 3305–3308.
[37] J. Xu, D. Xiao, W.W. Song, et al., Quassinoids from the stems of *Picrasma quassioides* and their cytotoxic and NO production-inhibitory activities, Fitoterapia 110 (2016 Apr) 13–19.
[38] C. He, Y. Wang, T. Yang, et al., Quassinoids with insecticidal activity against diaphorina citri kuwayama and neuroprotective activities from *Picrasma quassioides*, J. Agric. Food Chem. 68 (1) (2020 Jan 8) 117–127.
[39] W.Y. Zhao, X.Y. Song, L. Zhao, et al., Quassinoids from *Picrasma quassioides* and their neuroprotective effects, J. Nat. Prod. 82 (4) (2019 Apr 26) 714–723.
[40] C. Liu, R.R. Cheng, L. Yang, et al., Inhibition of CYP450 enzymes by quassinoids from *Picrasma quassioides* leaves, Phytochem. Lett. 30 (2019) 138–142.
[41] M. Okano, T. Fujita, N. Fukamiya, et al., New quassinoid glycosides and hemiacetals from *Picrasma ailanthoides* planchon. Picrasinoside-B,-C,-D,-E,-F, and-G, and picrasinol-A and-B, Chem. Lett. 13 (2) (1984) 221–224.
[42] M. Daido, N. Fukamiya, M. Okano, et al., Picrasinol D, a new quassinoid from the stem wood of *Picrasma ailanthoides*, J. Nat. Prod. 58 (4) (1995) 605–608.
[43] M. Okano, T. Fujita, N. Fukamiya, et al., New quassinoid glucosides, picrasinoside-A,-B,-C,-D,-E,-F, and-G and new hemiacetals, picrasinol-A and-B, from the stem bark of *Picrasma ailanthoides* Planchon, Bull. Chem. Soc. Jpn. 58 (6) (1985) 1793–1800.
[44] T. Matsuzaki, N. Fukamiya, M. Okano, et al., Picrasinoside H, a new quassinoid glucoside, and related compounds from the stem wood of *Picrasma ailanthoides*, J. Nat. Prod. 54 (3) (1991) 844–848.
[45] T. Murae, T. Tsuyuki, T. Ikeda, et al., Bitter principles of *Picrasma ailanthoides* planchon. Nigakilactones A, B, C, D, E and F, Tetrahedron 27 (7) (1971) 1545–1555.
[46] Thaiwei, Chen Zhongliang. Chemistry, biogenesis and anticancer activity of Picrin from momordica armigera [J]. Foreign Medicine. Journal of Pharmaceutical Sciences,1979(1):10-19.
[47] S.P. Yang, J.M. Yue, Five new quassinoids from the bark of *Picrasma quassioides*, Helv. Chim. Acta 87 (6) (2004) 1591–1600.
[48] H. Hikino, T. Ohta, T. Takemoto, Picrasins, simaroubolides of Japanese quassia tree *Picrasma quassioides*, Phytochemistry 14 (11) (1975) 2473–2481.
[49] J.S. Yang, D. Gong, A new bitter principle, kusulactone, from Indian quassiawood(*Picrasma quassioides*), Zhongcaoyao 15 (12) (1984) 531–533.
[50] H. Hirota, A. Yokoyama, T. Tsuyuki, et al., Structure of Nigakilactone O, a new quassinoid from *Picrasma ailanthoides*, Chem. Lett. 17 (4) (1988) 651–652.
[51] W.Y. Zhao, J.J. Chen, C.X. Zou, et al., New tirucallane triterpenoids from *Picrasma quassioides* with their potential antiproliferative activities on hepatoma cells, Bioorg. Chem. 84 (2019) 309–318.
[52] J. Xu, D. Xiao, Q.H. Lin, et al., Cytotoxic tirucallane and Apotirucallane triterpenoids from the stems of *Picrasma quassioides*, J. Nat. Prod. 79 (8) (2016) 1899–1910.
[53] J. Zhang, C.X. Wang, X.J. Song, et al., A pair of new tirucallane triterpenoid epimers from the stems of *Picrasma quassioides*, Chin. J. Nat. Med. 17 (12) (2019 Dec) 906–911.
[54] P.Y. Yang, P. Zhao, M. Bai, et al., Structure elucidation and absolute configuration determination of $C_{26}$, $C_{27}$ and $C_{30}$ tirucallane triterpenoids from the leaves of *Picrasma quassioides* (D. Don) Benn, Phytochemistry 184 (2021 Apr) 112675.
[55] Y. Niimi, H. Hirota, T. Tsuyuki, et al., New 7, 24-tirucalladiene-type triterpenoids from *Picrasma quassioides* bennett, Chem Pharm Bull 37 (1) (1989) 57–60.
[56] K. Yoshikawa, S. Sugawawa, S. Arihara, Phenylpropanoids and other secondary metabolites from fresh fruits of *Picrasma quassioides*, Phytochemistry 40 (1) (1995) 253–256.
[57] Y. Sugimoto, T. Sakita, Y. Moriyam, et al., Structure of nigakialcohol, a new ionone derivative from *picrasma ailanthoides* planchon, Tetrahedron Lett. 19 (44) (1978) 4285–4288.
[58] Chenlan Zhu, Deng Guihua, Lin Study on chemical constituents of bitter wood, Natural Products Research and Development 24 (4) (2012) 476–478 (in Chinese).
[59] L.L. Lou, G.D. Yao, J. Wang, et al., Enantiomeric neolignans from Picrasma quassioides exhibit distinctive cytotoxicity on hepatic carcinoma cells through ROS generation and apoptosis induction, Bioorg. Med. Chem. Lett 28 (8) (2018 May 1) 1263–1268.
[60] G.D. Yao, J. Wang, X.Y. Song, et al., Stereoisomeric guaiacylglycerol-β-coniferyl aldehyde ether induces distinctive apoptosis by downregulation of MEK/ERK pathway in hepatocellular carcinoma cells, Bioorg. Chem. 81 (2018 Dec) 382–388.
[61] R. Xu, D. Zhang, F. Shu, et al., Picraquanines A-C, three new phenolic derivatives from the stems of *Picrasma quassioides*, Nat. Prod. Res. 35 (21) (2021 Nov) 3687–3693.
[62] C. Liu, R.R. Cheng, Z.Z. Han, et al., A new ionone derivative from the leaves of Picrasma quassioides, J. Asian Nat. Prod. Res. 21 (7) (2019 Jul) 652–658.
[63] Zhang Jie, Li Qiao, Guo Wenna, et al. Effects of Kumu Injection and Azithromycin on the release of inflammatory cytokines in vitro [J]. J. Yantai Univ. (Nat. Sci. Eng.),20,33(1):115-119.
[64] M. Yu, X. Gu, Y. Qu, et al., Combination therapy with TCM preparation kumu injection and azithromycin against bacterial infection and inflammation: *in vitro* and *in vivo*, Evid Based Complement Alternat Med 2022 (2022 Mar 16) 8533005.
[65] Jin Yongzhe, Xie Danping, Sun Hunan. Effect of extract of *Picrasma quassioides* on apoptosis of drug-resistant lung cancer cells [J]. Medical Journal of Yanbian University, 20,43(4):243-250.
[66] W. Dai, J. He, F. Ye, et al., Design, synthesis and *in vitro* biological evaluation of novel 4-methoxy-5-hydroxycanthin-6-one derivatives as potential anti-tumor agents, Nat. Prod. Res. 34 (16) (2020 Aug) 2289–2294.
[67] Zhengri Zhu, Wanlu Liu, Aidong Chen, Study on related factors of gastric cancer mice by extract of *Picrasma quassioides*, Foreign Medicine (Antibiotics) 36 (3) (2015) 126–127.

[68] Li Yue, Xin Luo, Li Yufeng, Li Jing, Clinical research of traditional, Chin. Med. 9 (20) (2017) 41–42.
[69] D.P. Xie, Y.X. Gong, Y.H. Jin, et al., Anti-tumor properties of *Picrasma quassioides* extracts in H-Ras$^{G12V}$ liver cancer are mediated through ROS-dependent mitochondrial dysfunction, Anticancer Res. 40 (7) (2020 Jul) 3819–3830.
[70] W.Y. Zhao, J.J. Chen, C.X. Zou, et al., Effects of enantiomerically pure β-carboline alkaloids from *Picrasma quassioides* on human hepatoma cells, Planta Med. 85 (8) (2019 May) 648–656.
[71] Zhang Lin, Deng Guihua, Yang Liang, et al. Study on the mechanism of regulating the proliferation and apoptosis of cervical cancer HeLa cells through the regulation of miR-331-3p [J]. Shaanxi J. Tradit. Chin. Med.,202,43(1):17-22.
[72] Y.X. Gong, Y. Liu, Y.H. Jin, et al., *Picrasma quassioides* extract elevates the cervical cancer cell apoptosis through ROS-mitochondrial Axis activated p38 MAPK signaling pathway, In Vivo 34 (4) (2020 Jul-Aug) 1823–1833.
[73] H.N. Sun, D.P. Xie, C.X. Ren, et al., Ethyl β-carboline-3-carboxylate increases cervical cancer cell apoptosis through ROS-p38 MAPK signaling pathway, In Vivo 36 (3) (2022 May-Jun) 1178–1187.
[74] M.C. Hsieh, Y.S. Lo, Y.C. Chuang, et al., Dehydrocrenatidine extracted from *Picrasma quassioides* induces the apoptosis of nasopharyngeal carcinoma cells through the JNK and ERK signaling pathways, Oncol. Rep. 46 (2) (2021 Aug) 166.
[75] N. Yamashita, M. Kondo, S. Zhao, et al., Picrasidine G decreases viability of MDA-MB 468 EGFR-overexpressing triple-negative breast cancer cells through inhibition of EGFR/STAT3 signaling pathway, Bioorg. Med. Chem. Lett 27 (11) (2017 Jun 1) 2608–2612.
[76] Q.H. Lin, W. Qu, J. Xu, et al., 1-Methoxycarbony-β-carboline from *Picrasma quassioides* exerts anti-angiogenic properties in HUVECs *in vitro* and zebrafish embryos *in vivo*, Chin. J. Nat. Med. 16 (8) (2018 Aug) 599–609.
[77] F. Zhao, Z. Gao, W. Jiao, et al., PlantaMed [M], 2012, p. 1906, 78.
[78] L. Kong, B. Wang, X. Yang, et al., Picrasidine I from *picrasma quassioides* suppresses osteoclastogenesis via inhibition of RANKL induced signaling pathways and attenuation of ROS production, Cell. Physiol. Biochem. 43 (4) (2017) 1425–1435.
[79] Meng Chen, Study on Active Constituents of Alkaloids from *Picrasma quassioides* [D], Yantai University, 2007.
[80] Weihua Jiao, Hao Gao, Zhao Feng, et al., Study on anti-inflammatory active constituents of *Picrasma quassioides* [C]//Chinese chemical Society, National natural science Foundation of China. Proceedings of the 8th Symposium on Natural Organic Chemistry of the Chinese Chemical Society, 2010, p. 230 [Publisher unknown].
[81] Chiao Weihua, Study on Anti-inflammatory Active Constituents of Chinese Herb *Picrasma quassioides* [D], Shenyang Pharmaceutical University, 2010.
[82] Bowen Liu, Fulei Liu, Ruyi Wang, et al., Analysis of Chemical constituents of total alkaloids from *Picrasma quassioides* and their effects on Collagen-induced arthritis in rats, J. China Pharm. Univ. 50 (5) (2019) 585–592.
[83] Mi Ning, Huanying Chen, Effect of Compound *Picrasma quassioides* anti-inflammatory tablets combined with Lankefuning in the treatment of acne vulgaris, Dermatology and Venereal Diseases 38 (3) (2016) 217–219.
[84] Ci Cheng Chen, Li Zhenrong, Xiaochun Liu, Therapeutic effect of *Picrasma quassioides* injection on acute upper respiratory tract infection in children, China Prescription Drugs 14 (5) (2016) 40–41.
[85] Chinese Herbal Medicine Information Station, in: National Medicine Administration (Ed.), Active Ingredient Manual of Botanical Medicine [M], People's Medical Publishing House, Beijing, 1986, pp. 875–876.
[86] Liandan injection, Chinese pharmaceutical, Journal (7) (1988) 440.
[87] Kunqin Zheng, Experimental study on liandan injection, Guangdong Medical Journal (6) (1987) 50.
[88] H.Y. Ho, C.C. Lin, Y.C. Chuang, et al., Apoptotic effects of dehydrocrenatidine via JNK and ERK pathway regulation in oral squamous cell carcinoma, Biomed. Pharmacother. 137 (2021 May) 111362.
[89] F. Zhao, Q. Tang, J. Xu, et al., Dehydrocrenatidine inhibits voltage-gated sodium channels and ameliorates mechanic allodia in a rat model of neuropathic pain, Toxins 11 (4) (2019 Apr 18) 229.
[90] Zhenyu Song, Modern Study of Chinese Herbal Medicine [J], vol. I, Beijing Medical University, Peking Union Medical University Associated Press, Beijing, 1995, p. 100.
[91] Study on the toxicity of total alkaloids of Picrasma quassioides, Chinese Herbal Medicine Bulletin (6) (1977) 34–35+49.
[92] Zhao Wenna, Cui Ying, Jing Bai, et al., Study on antibacterial activity and anti-inflammatory effect of extracts of *Picrasma quassioides* in vitro, Northwest Pharmaceutical Journal 34 (4) (2019) 505–508.
[93] He Ying, Wei Liu, Zhongwei Chen, et al., Study on the inhibitory effect of alkaloids from *Picrasma quassioides* on Escherichia coli in vitro, Journal of Anhui Agricultural Sciences (7) (2008) 2777–2778.
[94] Meng Chen, Huaying Fan, Shengjun Dai, et al., Study on antibacterial active components of alkaloids of *Picrasma quassioides* [C]. Proceedings of the Symposium on Research and Development of Innovative Drugs and New Varieties, 2006, pp. 315–321 [Publisher unknown].
[95] M.R. Khan, M. Kihara, A.D. Omoloso, Antibacterial activity of *Picrasma javanica*, Fitoterapia 72 (4) (2001 May) 406–408.
[96] Zhao Wenna, Su Qi, Jiao He, et al., Study on antihypertensive effect of extract of *Picrasma quassioides* on essential hypertension rats, Pharmacology and Clinic of Traditional Chinese Medicine 28 (5) (2012) 108–111.
[97] Ma Shude, Xie Renming, Miao Airong, et al. Effects of total alkaloids of *Picrasma quassioides* on cardiovascular system [J]. Acta Medica Sinica,1982(5):327-330.
[98] Zhide Du, Aiwu Zhang, Yufeng Wang, Study on antihypertensive effect and toxicity of total alkaloids of *Picrasma quassioide*, Chinese Journal of Pharmacy (6) (1981) 5–7.
[99] Cheng Zhuan-quan, Yin Chuan-xiu, Wang Su-xia, et al. Clinical observation of 52 cases of hypertension treated with Balsam herb [J]. Shaanxi New Medicine,1980(7):9-10.
[100] Cheng Zhunquan, Wang Suxia, Wang Zonghe, et al. Treatment of hypertension with picrolactone A in 136 patients [J]. New Drug and Clinical,1987(5):275-278.
[101] Zhang Zhenjie, Li Suiying, Guo Li, et al. Isolation and identification of antihypertensive components of *Picrasma quassioide* [J]. Acta Botanica Sinica of Northwest China,1986(2):138-140.
[102] Xie Renming, Miao Airong, Shen Yaqin, et al. Effects of total alkaloids of *Picrasma quassioide* on coronary circulation and cardiac hemodynamics in dogs [J]. Chinese Journal of Traditional Chinese Medicine,1982,13(11):30-32+34.
[103] Du Zhi-De, Zhang Ai-wu, Pharmacologic study on total alkaloids of *Picrasma quassioide*, Pharmaceutical Industry (6) (1982) 21–26.
[104] T. Ohmoto, Y.I. Sung, K. Koike, et al., Effect of alkaloids of simaroubaceous plants on the local blood flow rate, J. Pharmaceut. Sci. 39 (1) (1985) 28–34.
[105] N. Yujiro, K. Koike, et al., Gastric aniulcer components from the woods of *Picrasma quassioides* (Simaroubaceae), Nat. Med. 48 (2) (1994) 116–121.
[106] Wenxing Liu, Report of 60 cases of autumn and winter diarrhea treated by acupoint injection of hailixin brand *Picrasma quassioides* injection, World Latest Medical Information Abstracts 15 (14) (2015) 125.
[107] Chunxia Zhang, Clinical observation of acupoint injection of *Picrasma quassioides* injection in the treatment of diarrhea in children, Inner Mongolia Traditional Chinese Medicine 34 (6) (2015) 81.
[108] Weixuan Xie, Effect of *Picrasma quassioides* injection on herpes zoster, Journal of Youjiang Medical College for Nationalities (6) (2000) 967.
[109] Zhao Guangjian, Deshe Zhai, Yu Rilei, et al., Study on the inhibition of SARS-CoV-2 by the composition of *Picrasma quassioides* Injection, J. Ocean Univ. China 51 (1) (2021) 70–75.
[110] Du Zhi-De, Zhang Ai-wu, Pharmacologic study on total alkaloids of *Picrasma quassioides*, Pharmaceutical Industry (6) (1982) 21–26.
[111] Liang Jianhua. Study on antivenom of *Picrasma quassioides* [J]. Bulletin of Chinese Traditional Medicine,1987(4):56.
[112] C. Saiin, R. Rattanajak, S. Kamchonwongpaisan, et al., Isolation and *in vitro* antimalarial activity of hexane extract from Thai *Picrasma javanica* B1 stembark, Southeast Asian J Trop Med Public Health 34 (Suppl 2) (2003) 51–55.
[113] K. Pavanand, K. Yongvanitchit, H.K. Webster, et al., *In vitro* antimalarial activity of a Thai medicinal plant *Picrasma javanica* Bl, Phytother Res. 2 (1) (1988) 33–36.

[114] Huang Huaxi, Feng Lixin, Li Jinhua, et al. Study on antioxidant activity of different medicinal parts of *Picrasma quassioides* [J]. Feed Res.,202,45(15):67-70.
[115] N. Yang, Y. Shi, A. Xiong, et al., Preparation and purification of canthinone and β-carboline alkaloids from *Picrasma quassioides* based on bioautography and mass-spectrometry-directed autopurification system, J Sep Sci 41 (15) (2018 Aug) 3014–3021.
[116] S. Zhao, Y. Kanno, W. Li, et al., Picrasidine N is a subtype-selective pparβ/δ agonist, J. Nat. Prod. 79 (4) (2016 Apr 22) 879–885.
[117] F. Li, H. Wang, Y. Wang, et al., Computational investigation reveals Picrasidine C as selective PPARα lead: binding pattern, selectivity mechanism and ADME/tox profile, J. Biomol. Struct. Dyn. 38 (18) (2020 Nov) 5401–5418.
[118] Q. Yue, Y. Xu, L. Lin, et al., Canthin-6-one (CO) from *Picrasma quassioides* (D.Don) Benn. ameliorates lipopolysaccharide (LPS)-induced astrocyte activation and associated brain endothelial disruption, Phytomedicine 101 (2022) 154108.
[119] E. Guo, Y. Hu, T. Du, et al., Effects of *Picrasma quassioides* and its active constituents on Alzheimer's disease *in vitro* and *in vivo*, Bioorg. Chem. 92 (2019 Nov) 103258.
[120] Guo Xiaozhuang, La Wanying, Shufeng Zhang, et al., The Dictionary of Toxic Chinese Herbal Medicine [M], Tianjin Science and Technology Translation and Publishing Company, Tianjin, 1992, p. 290.
[121] Miao Xiaolei, Study on Metabolism and Mechanism of 4,5-Dimethoxycanthin-6-One in Vitro and in Vivo [D], Hubei University, 2016.
[122] X. Miao, J. Wang, L. Chen, et al., Identification of *in vivo* and *in vitro* metabolites of 4,5-dimethoxycanthin-6-one by HPLC-Q-TOF-MS/MS, J Chomatogr B Analyt Technol Biomed Life Sci 1020 (2016 May 1) 78–84.
[123] X. Miao, J. Wang, Y. Chen, Pharmacokinetics and tissue distribution of 4,5-dimethoxycanthin-6-one and its major metabolites in rats, J. Pharm. Biomed. Anal. 139 (2017 May 30) 22–29.
[124] Y. Shi, Y. Xia, J. Wang, et al., Metabolic profile of 5-hydroxy-4-methoxycanthin-6-one, a typical canthinone alkaloid, in rats determined by liquid chromatography-quadrupole time-of-flight tandem mass spectrometry together with multiple data processing techniques, J. Pharm. Biomed. Anal. 129 (2016 Sep 10) 60–69.
[125] Y. Shi, C. Hong, J. Xu, et al., Simultaneous quantification of two canthinone alkaloids of *Picrasma quassioides* in rat plasma by liquid chromatography-tandem mass spectrometry and its application to a rat pharmacokinetic study, J Chromatogr B Analyt Technol Biomed Life Sci 986–987 (2015 Apr 1) 100–107.
[126] L. Zhao, Y. Zhao, L. Guo, et al., Pharmacokinetic and bioavailability study of 5-hydroxy-4-methoxycanthin-6-one, a typical canthinone alkaloid, in rats using ultra-high performance liquid chromatography/electrospray ionization tandem mass spectrometry, Biomed. Chromatogr. 34 (7) (2020 Jul) e4830.
[127] Meixiang Jiang, Yingjun Zhou, Qunfang Mao, Study on chemical composition and biotransformation of *Picrasma quassioides* alkaloids, J. Tradit. Chin. Med. 28 (1) (2022) 56–58+76.
[128] H.X. Fan, Z.Q. Zhou, J. Peng, et al., A microbial model of mammalian metabolism: biotransformation of 4,5-dimethoxyl-canthin-6-one using Cunninghamella blakesleeana CGMCC 3.970, Xenobiotica 47 (4) (2017 Apr) 284–289.
[129] Sun Faxin, Xu Xiaomeng, Feng Yingying, et al. Effects of kumu injection and azithromycin distribution in rats with pneumonia [J]. J. Yantai Univ. (Nat. Sci. Eng.), 201,34(3):295-301.
[130] Chen Fengzheng, Long Jie, Sun Guofeng, et al. Isolation of main alkaloid components from *Picrasma quassioides* and transformation of intestinal microorganisms [J]. Journal of Leshan Normal University, 201,36(8):14-19.