Review

Chemical composition and biological activity of *Houttuynia cordata*

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Abstract

Houttuynia cordata **is an important traditional Chinese medicine. It is widely used for clearing heat and detoxification, reducing swelling and treating sores, diuresis and dehumidification. It is also used to treat lung carbuncles, ulcers, hemorrhoids, rectal bleeding, spleen and stomach heat, which are caused by excess heat, heat toxicity, dampness, and disease heat. Modern pharmacological experiments have shown that *H. cordata* has antibacterial, antiviral, immune enhancing, diuretic and other effects. This article reviews the chemical components and biological activities of *H. cordata* to provide reference for clinical application.**

Keywords: *Houttuynia cordata*; chemical composition; biological activity

1 Introduction

Houttuynia cordata is a medicinal herb included in Chinese Pharmacopoeia, which comes from the dry aboveground part of *H. cordata* Thunb. It often grows beside ditches, streams, ridges, shaded slopes and wetland grasslands. It is harvested in summer and autumn with lush stems, leaves, and numerous flower clusters and the residual roots are removed. It is washed, dried or used fresh. It is mainly produced in provinces south of the Yangtze River Basin in China. Modern pharmacological research has shown that *H. cordata* has the effect of clearing heat and detoxifying, especially used to treat respiratory diseases, and has good anti-radiation effects and air pollution resistance. This study reviewed the chemical components and biological activities of *H. cordata*, and laid the foundation for its clinical application.

2 Chemical composition

The volatile oil and flavonoids contained in *H. cordata* are the main medicinal components. In addition, *H. cordata* also contains alkaloids, organic acids, fatty acids, etc. The whole plant of *H. cordata* is edible, and its nutritional components include

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protein, fat, carbohydrates, vitamins, amino acids, inorganic salts and various trace elements.

2.1 Volatile oil

With the rapid development of chromatographic separation technology, more and more components have been isolated from Houttuynia cordata, such as methyl nonone (**1**), *β*-Pinene (**2**), Pinene (**3**), Borneol acetate (**4**), *β*-Laurenene (**5**) and 4-terpeneol (**6**), with the contents of 14.56%, 14.56%, 14.56%, 10.4%, 8.55% and 8.1%, respectively [1-6]. The structures are shown in Fig. 1.

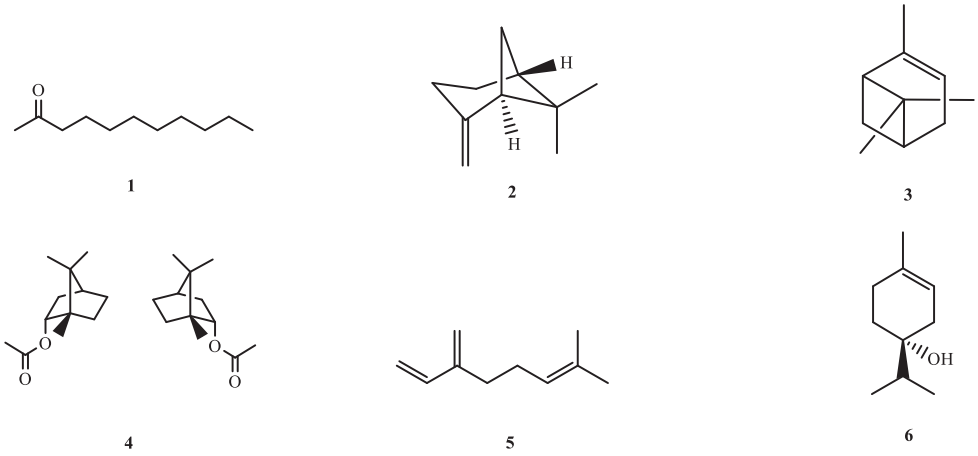

Fig. 1 Structures of Volatile oil from *H. cordata*

2.2 Flavonoids

The content of total flavonoids in *H.cordata* is about 0.1%. As the main effective components of *H. cordata*, flavonoids have received increasing attention in recent years. These flavonoids include quercetin (**7**), isoquercetin (**8**), quercetin (**9**), rutin (**10**), hyperoside (**11**), *β*-Sitosterol (**12**), chlorogenic acid (**13**), 6-methoxy-7-hydroxycoumarin (**14**), rutin (**15**), quercetin-3-*O*-*β*-D-galactose-7-*O*-*β*-D-glucoside (**16**), quercetin (**17**), hyperoside (**18**), rutin (**19**), resveratrol (**20**) and aflatoside (**21**). The structures are shown in Fig. 2.

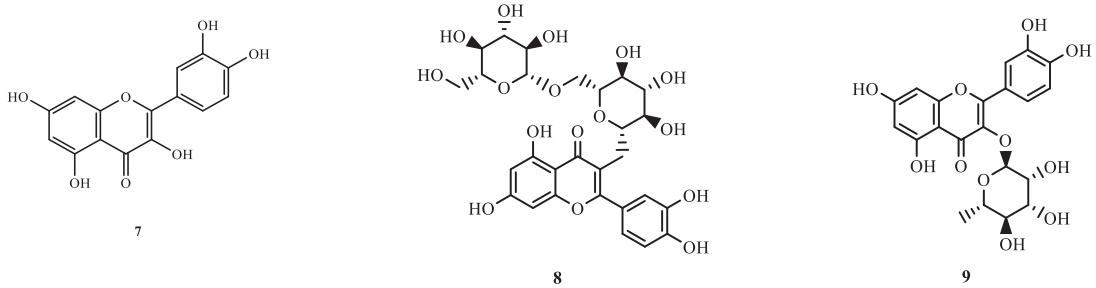

Fig. 2 Structures of Flavonoids from *H. cordata*

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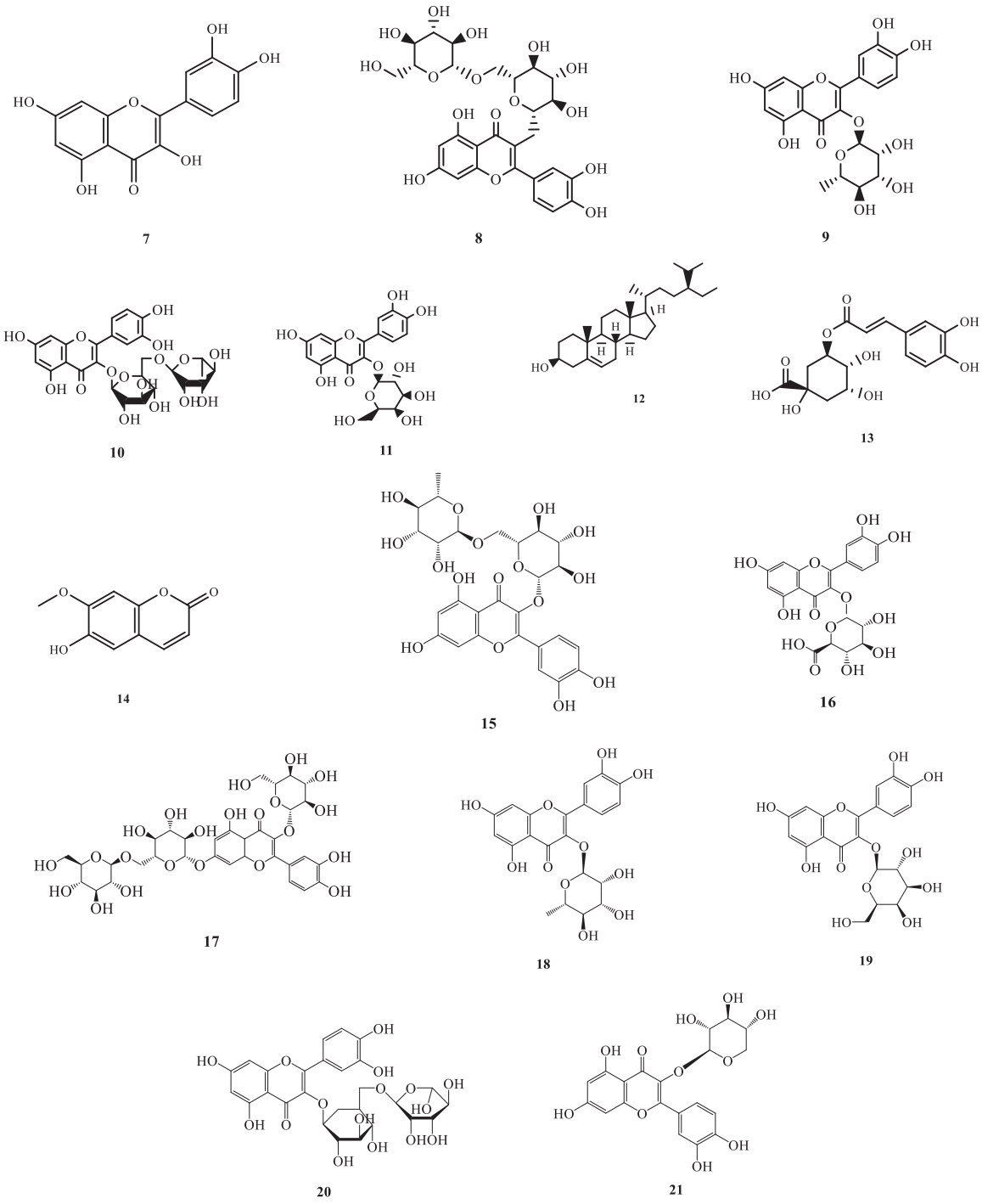

Continued fig. 2

2.3 Alkaloids

Houttuynia cordata contains many alkaloids, such as benzoamide (**22**), heart-shaped alkaloids (**23**), triptolide (**24**), aristolochic lactone BII (**25**), demethylated cauliflower berberine B (**26**) and piperolactone (**27**) [6]. The structures are shown in Fig. 3.

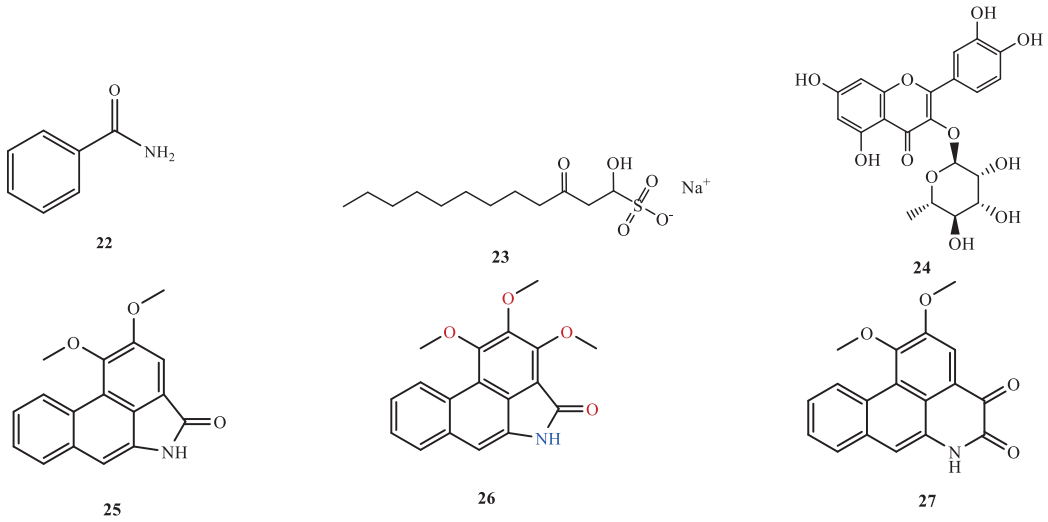

Fig. 3 Structures of alkaloids from *H. cordata*

2.4 Organic acids

H. cordata contains organic acids, such as oleic acid (**28**), aristolochic acid (**29**), chlorogenic acid (**30**), linoleic acid (**31**), 3,4-dihydroxybenzoic acid (**32**), decanoic acid (**33**), octanoic acid (**34**), stearic acid (**35**) and palmitic acid (**36**) [7]. It also contains 16 essential amino acids, including phenylalanine (**37**), methionine (**38**), leucine (**39**), lysine (**40**) and threonine (**41**), as well as three semi essential amino acids: histidine (**42**), arginine (**43**) and tyrosine (**44**), as well as eight non essential amino acids, namely asparagine, aspartate, glycine, serine, glutamine, proline, alanine and valine [8]. The structures of these organic acids are shown in Fig. 4.

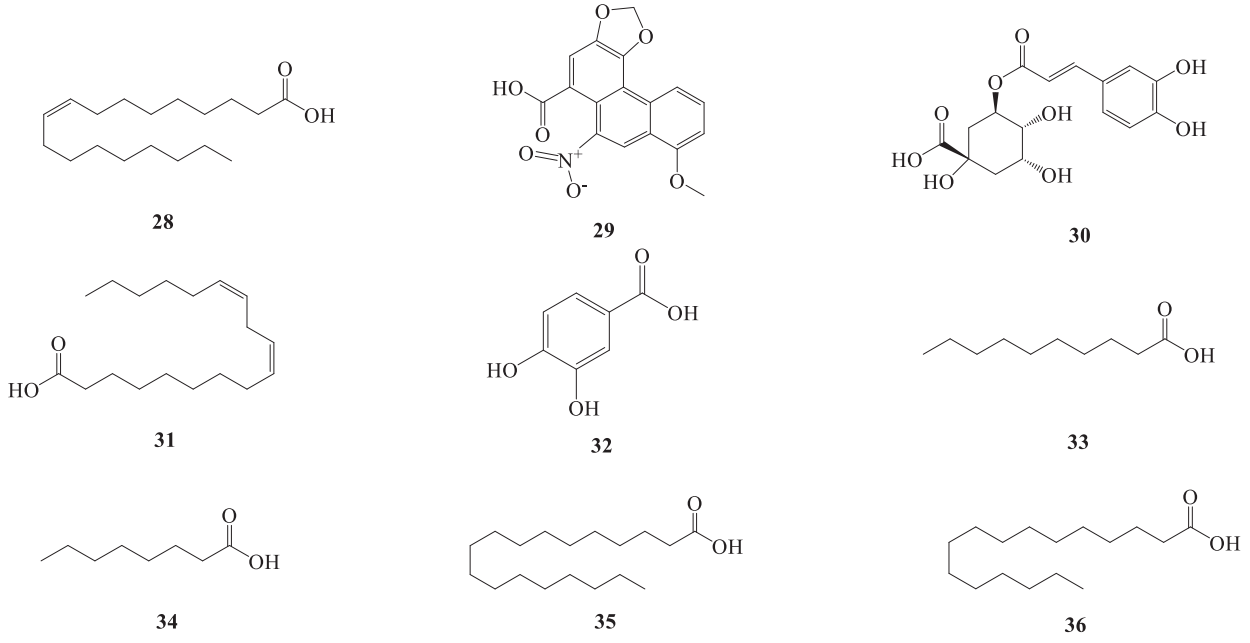

Fig. 4 Structures of organic acids from *H. cordata*

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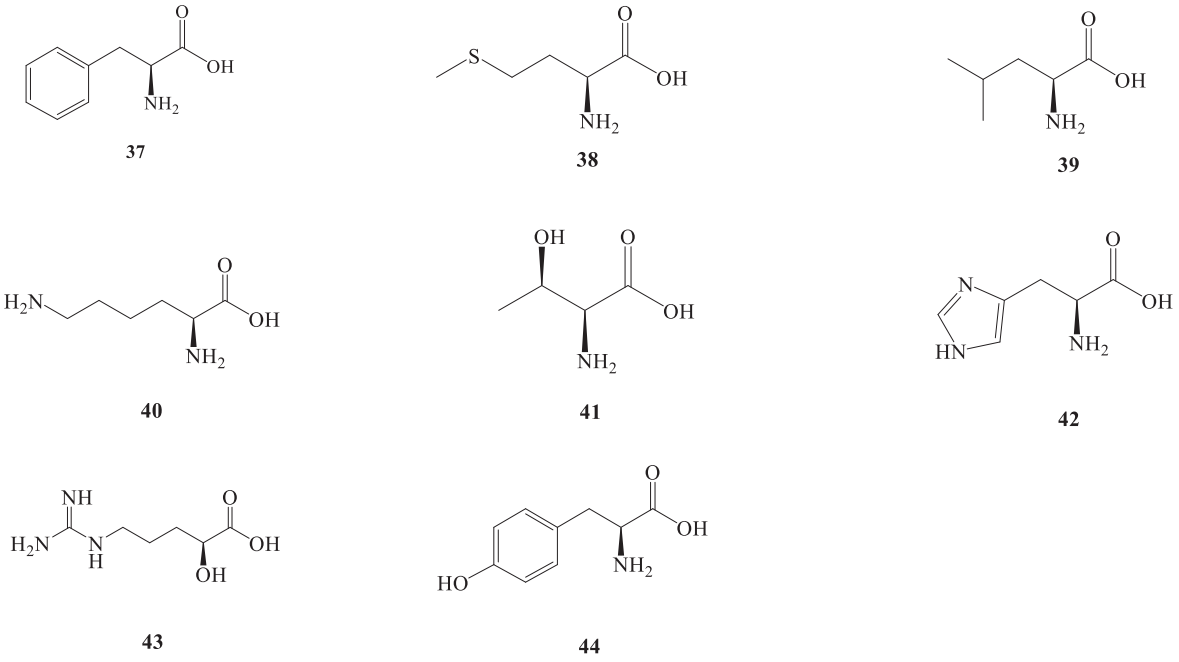

Continued fig. 4

2.5 Other compounds

H. cordata contains polysaccharides, vitamins, inorganic salts and metal elements. The polysaccharides in *H. cordata* are mostly water-soluble sugars, including glucose (**45**), arabinose (**46**), fructose (**47**), xylose (**48**), galactose (**49**) and rhamnose (**50**). The stems and leaves of *H. cordata* are rich in vitamin C (**51**), vitamin P (**52**) and vitamin B_2 (**53**). *H. cordata* contains inorganic salts such as potassium chloride and potassium sulfate, as well as elements such as sodium, magnesium, calcium and phosphorus. It also contains trace elements, such as iron, manganese, zinc and tin. In addition, fresh *H. cordata* stems and leaves contain 5% carbohydrates (**54**), 2.29% protein and 0.4% fat. Every 100 g fresh *H. cordata* stem and leave also contains 2.59 mg carotene (**55**). The structures of other compounds are shown in Fig. 5.

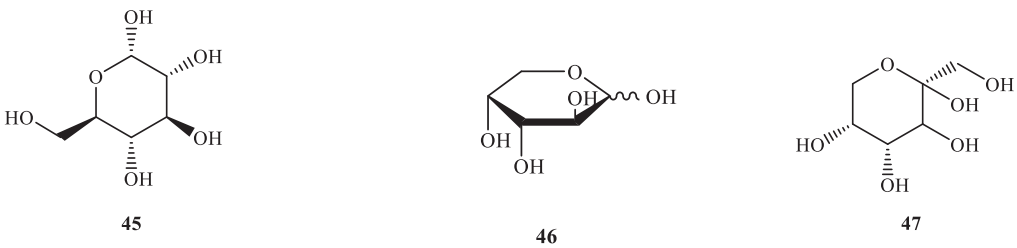

Fig. 5 Structures of other compounds from *H. cordata*

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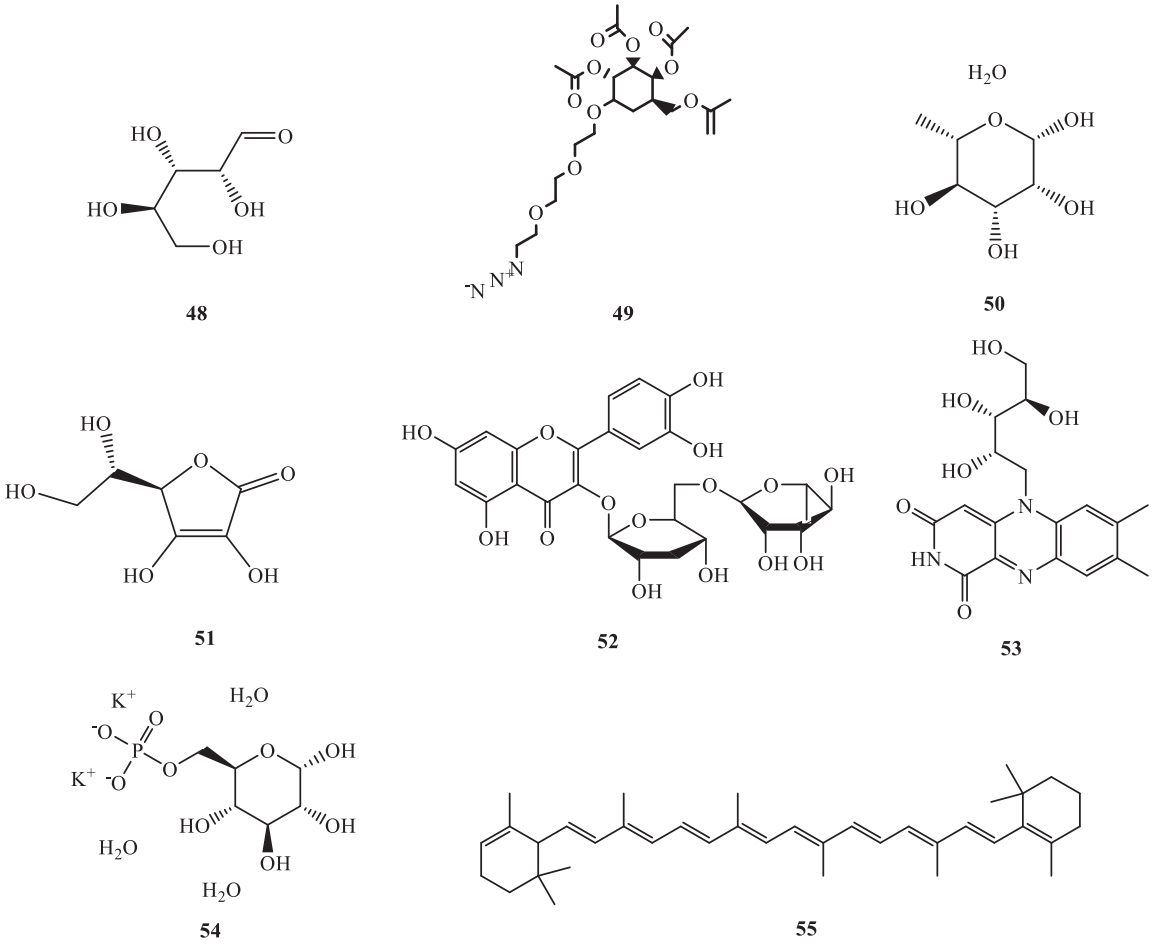

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3 Pharmacological effects of *H. cordata*

3.1 Antibacterial effects

The volatile oil in *H. cordata* is an active ingredient with antibacterial effects. It inhibits the formation of bacterial cell membranes, increases the phagocytic ability of phagocytic cells, and thus exerts antibacterial effects. The volatile oil of *H. cordata* has the strongest inhibitory effect on Staphylococcus aureus, Staphylococcus aureus and Candida albicans, followed by different degrees of inhibition on hemolytic streptococcus, Staphylococcus aureus, influenza bacteria, catarrhal bacteria, pneumococcus, Escherichia coli, dysentery bacteria and typhoid bacteria. The minimum inhibitory concentrations of Houttuynia cordata volatile oil on Staphylococcus aureus, Escherichia coli and Bacillus subtilis were reported to be 0.25%, 1% and 2%, respectively, while the minimum inhibitory concentrations on Penicillium, Aspergillus niger and yeast were reported as 8%. In contrast, its inhibitory effect on other Gram negative bacteria is not significant. The combination of *H. cordata* and other antibacterial drugs can also increase the antibacterial effect. For example, the combination of *H. cordata* and trimethoprim enhances the antibacterial effect.

3.2 Anti-inflammatory effects

The relevant literature in the past 10 years

has shown that the main components of *H. cordata* with anti-inflammatory effects are volatile oil and flavonoids, among which methyl nonone and quercetin have good anti-inflammatory activities. In addition, studies have shown that the alkaloids and polysaccharide components may also have anti-inflammatory effects. Related studies have found that the water extract of Houttuynia cordata can inhibit TNF at mass concentrations of 0.0625 and 0.125 mg/mL, and the inhibitaion rate can reach 30%.

3.2.1 H. cordata volatile oil

The anti-inflammatory mechanism of the volatile oil components of *H. cordata* is similar to that of non steroidal anti-inflammatory drugs (NSAIDs). In a mouse peritoneal macrophage model induced by lipopolysaccharide (LPS), *H. cordata* volatile oil inhibited the release of prostaglandin E2 (PGE2) [IC_{50} value: 44] eight μg/mL, dose-dependently inhibited cyclooxygenase (COX)-2 enzyme activity (IC_{50} value: 30) nine μg/mL and reduced the expression of COX-2 mRNA and protein, but did not affect the expression of COX-1 [9]. In a mouse model of lung tumor induced by benzo [a] pyrene (B [a] P) and human normal lung epithelial cells (BEAS-2B), a mixture of *H. cordata* volatile oil and water extracts, as well as methyl nonone, activated the nuclear transcription factor E2 related factor - heme oxygen-1/quinone oxidoreductase 1 (Nrf2-HO-1/NQO-1) signaling pathway, inhibited the generation of reactive oxygen species (ROS) in BEAS-2B cells, and reduced DNA damage and inflammatory response induced by B [a] P stimulation [10]. In a BALB/c mouse model infected with Salmonella typhimurium, sodium *H. cordata* regulated nuclear factor (NF)-κB signal transduction pathway, significantly reduced intestinal pro-inflammatory cytokines, such as TNF-α and Interleukin-1β, and inhibited the production of IL-6 and inflammation related enzymes, such as inducible nitric oxide synthase (iNOS) and COX-2. At the same dose, the anti-inflammatory activity of sodium *H. cordata* is better than that of methyl nonone[11]. *H. cordata* sodium can be converted into methyl nonone under certain *in vitro* conditions, but it is relatively stable during the *in vivo* process and exhibits anti-inflammatory effects as a prototype [12].

3.2.2 H. cordata alcohol water extract

In vitro and *in vivo* experiments have shown that the 70% ethanol water extract of *H. cordata* has cough relieving, phlegm resolving, anti-inflammatory and analgesic effects [13]. It is used to treat acute lung injury (ALI) induced by pulmonary epithelial cells (A549), alveolar macrophages (MH-S) and LPS.

In a mouse model, the 70% ethanol water extract of *H. cordata* and three flavonoid components (aflatoside, hyperoside and quercetin) have shown potential therapeutic value in treating pulmonary inflammatory diseases. Among them, quercetin has the best activity at 100 *u*g/mL, reducing the inflammatory response in mice and inhibiting the production of inflammatory biomarkers IL-6 and nitric oxide (NO) in two types of cells [14]. A mouse acute inflammation model was established by intraperitoneal injection of LPS, and the anti-inflammatory activity of *H. cordata* ethanol water extract in different proportions was compared. It was found that 50% ethanol water extract of *H. cordata* had the best effect and the content of the pro-inflammatory factors, such as TNF-α, IL-1β and IL-6 significantly decreased [15].

3.2.3 Other water extracts of Houttuynia

Cordata improves the therapeutic effect of endothelial progenitor cells (EPCs) on LPS induced acute lung injury (ALI) in rats. By inhibiting

the production of inflammatory cytokines, the inflammatory response is reduced. Combined with EPCs, the expression of iNOS and endothelin-1 (ET-1) is reduced to prevent lung injury [16]. In a LPS-induced chronic inflammatory lung injury model in rats, high-dose polysaccharides from *H. cordata* reduced the number of white blood cells, monocytes and serum high-sensitivity C-reactive protein (hs CRP) content, increased the levels of malondialdehyde (MDA), NO, iNOS and total nitric oxide synthase (tNOS). The level of cytokine IL-6, IL-1β and TNF-α significantly decreased, and the treatment group with *H. cordata* polysaccharides improved pathological morphology, such as pulmonary edema, and the antioxidant enzyme activity of lung tissue significantly increased [17]. 21 alkaloids were isolated from the aboveground part of *H. cordata*, and their inhibitory effects on NO production were tested. It was found that the anti-inflammatory activity of ryegranine was better, with an IC_{50} value of 8.7 μmol/L [18].

3.3 Antitumor effects

H. cordata has inhibitory effects on the proliferation of various tumor cells. At present, we mainly study its effect on the proliferation of lung cancer, breast cancer, liver cancer and other cancer cells. Results show that *H. cordata* volatile oil, alcohol extract, and alkaloid components have anti-tumor activity.

3.3.1 H. cordata volatile oil

Using Lewis lung cancer mice as a model, the volatile oil of *H. cordata* can kill tumor cells both *in vivo* and *in vitro* and inhibit tumor growth [19]. The volatile oil of *H. cordata* can inhibit the growth and proliferation of large B diffuse non Hodgkin's lymphoma cells SUDHL-4 through the apoptotic pathway both *in vivo* and *in vitro*, and its toxic side effects are less than those of the commonly used drug vincristine [20]. In human breast cancer cells (MCF-7), the volatile oil of *H. cordata* Thunb promotes cell apoptosis by down-regulating the expression of B lymphocyte tumor (Bcl)-2 protein. It has a certain inhibitory effect on the growth of MCF-7 mouse transplanted tumors in a dose-dependent manner [21]. The *in vivo* pharmacological study of *H. cordata* volatile oil against colon cancer showed that the tumor inhibition rates of the high, medium and low concentration groups of *H. cordata* volatile oil were 52.86%, 40%, 71%, for the hydroxycamptothecin group 14%. Significant lesions can be observed in the tumor tissue of the treatment group compared to the negative control group. Organ tissue sections indicate that both hydroxycamptothecin and *H. cordata* volatile oil have certain liver and kidney toxicity, and hydroxycamptothecin has greater renal toxicity [22].

3.3.2 H. cordata alcohol extract

H. cordata ethanol extract can induce wrinkling and rounding of human lung cancer cell A549, while regulating G0/G1 blockade, increasing Fas/CD95 protein levels, activating the expression of caspase-8 and Caspase-3, and inducing cell apoptosis [23]. In MDA-MB-231 and MCF-7 cells of breast cancer, the low concentration ethanol extract of *H. cordata* decreased the expression of cyclin D1 and CDK4, inhibited colony formation, and induced G1 cell cycle arrest.

MMP-9 secretion reduces the migration and invasion of cancer cell lines, and high concentration alcohol extracts induce cell apoptosis. The alcohol extract can not only stimulate the activity of Caspases, but also up-regulate the expression of Caspases and apoptosis, promoting Bcl-2 family proteins in breast cancer cells [24]. 95% ethanol extract of *H. cordata* induces programmed cell death of A375 human melanoma cells. and

activation of Caspases dependent pathways and p38 phosphorylation pathways is associated with high mobility histone B1 (HMGB1) reduction [25].

3.3.3 H. cordata alkaloids

The cytotoxicity study of HCT-15 found that Aristolochia lactam B had significant cytotoxicity on human tumor cell line XF-498, and Splendidine had certain cytotoxicity on five types of tumor cells [26]. *H. cordata* alkaloids inhibit the proliferation of human lung cancer cell line H460, causing cell atrophy, death, nuclear fragmentation and the appearance of apoptotic bodies, with an IC_{50} value of 17 μmol/mL, and cell cycle arrest at G0/G1 phase induces cell apoptosis [27].

3.3.4 Others

When the mass concentration of total flavonoids of *H. cordata* Thunb was 6 g/L, the apoptosis of human breast cancer cell line MCF-7 was the strongest. PI3K, Bcl-2 mRNA and PI3K, phosphorylated protein kinase B (*p*-Akt) and Bcl-2 protein expression are down-regulated, and Bcl-2 related x proteins are also down-regulated.

(Bax) mRNA and protein expression are up-regulated [28]. The ethyl acetate fraction of *H. cordata* significantly up-regulates the mRNA and protein expression of serum hypoxia inducible factor 1a (HIF-1A) and FOXO3 in human liver cancer cells HepG2, and stimulates the expression of muscle cell enhancing factor 2A gene (MEF2A). Within 24 h, it increases the apoptosis rate of cells, inhibits the growth of human liver cancer xenografts in nude mice, and activates the HIF-1A-FOXO3 and MEF2A pathways to induce apoptosis in human HepG2 liver cancer cells [29]. *H. cordata* water-soluble pectin polysaccharide induces cell cycle arrest and apoptosis in human lung cancer cell line A549, while the expression of apoptotic genes Caspase 3 and CyclinB1 is up-regulated [30].

3.4 Antivirus

H. cordata has inhibitory effects on various viruses, with the most studied viruses being herpes simplex virus (HSV) and influenza A virus H1N1. *H. cordata* extract, flavonoids, and polysaccharides have antiviral activity, among which quercetin, quercetin, and hyperoside have better activity.

3.4.1 H. cordata water extract

The water extract of *H. cordata* has anti herpes simplex virus (HSV) activity, among which quercetin, quercetin, and isoquercetin have significant activity. *H. cordata* A-E also has certain anti HSV activity. Mechanism and inhibition of NF-κB is related to the activation of B [31-33]. In a mouse model of acute lung injury induced by influenza A virus H1N1, flavonoids from *H. cordata* have both antiviral and anti-inflammatory effects. Among them, hyperoside and quercetin have the best activity and can inhibit neuraminidase activity and Toll like receptor signal transduction [34]. If the water extract of Houttuynia cordata directly interacts with DENV-2, it exerts antiviral effects by inhibiting its viral RNA replication, with an effective dose of 0.8 μg/mL. The water extract of *H. cordata* has anti SARS coronavirus activity, significantly inhibiting the expression of SARS virus 3CL protease (3CLpro) and RNA dependent RNA polymerase (RdRp) [35].

3.4.2 H. cordata polysaccharides

In the lung and intestinal injury model of mice infected with influenza A virus (H1N1), *H. cordata* polysaccharides can improve the survival rate of H1N1 infected mice, improve lung and intestinal injury, and reduce virus replication. Inhibiting

inflammation, protecting the intestinal barrier and regulating mucosal immunity may be related to the regulation of the gut lung axis [36]. *H. cordata* polysaccharides can reduce the formation of mouse norovirus 1 (MNV-1) virus plaques, with a better effect than alcohol extracts but worse than water extracts. 500 μmol/mL polysaccharide can reduce the infection rate of MNV-1 to below the lower detection limit. The deformation and expansion of viral particles inhibit the penetration of the virus into target cells [37]. The inhibitory effect of *H. cordata* on respiratory syncytial virus (RSV) and Coxsackie virus B3 (CV-B3) is positively correlated with the content of *H. cordata* polysaccharides [38].

3.5 Anti-radiation effect

In 1945, the Hiroshima atomic bomb incident occurred in Japan, resulting in over 88000 deaths and over 51000 injuries and missing persons on that day. In the central area of the atomic bomb explosion, only 56 people survived from 21000 victims, of which 2 were able to recover from treatment with *H. cordata*. The anti-radiation effect of *H. cordata* was discovered and utilized. In addition, a crystalline substance was extracted from *H. cordata* in foreign countries, and experimental studies have shown that this substance has a significant adjuvant therapeutic effect on lung inflammation after radiotherapy for cancer. It also alleviates the adverse reactions caused by radiotherapy in cancer patients [39].

3.6 Toxic Reactions

H. cordata has relatively low toxicity and a clear foul odor after oral administration, which has a certain stimulating effect on the vaginal mucosa. *H. cordata* is a medicinal and food homologous substance. In addition to medicinal use, it is also eaten as a cold dish in the folk. In Guangdong and Guangxi, it is also used to make herbal tea, which is one of the condiments on southern tables. Although there are no reports of poisoning, the adverse reactions caused by *H. cordata* injection cannot be ignored. In clinical practice, there are also some cases of nausea, vomiting, rash, dizziness, headache, high fever, allergic shock and local phlebitis [40].

3.7 Other functions

H. cordata has good antioxidant activity. The polysaccharides and flavonoids in *H. cordata* can effectively eliminate superoxide and hydroxyl radicals in the body. The alkaloids in *H. cordata* have anti-platelet aggregation and hypoglycemic effects [41]. The total flavonoids of *H. cordata* can reduce the levels of inflammatory factors, reduce cell apoptosis, and have anti Mycoplasma pneumoniae infection effects. *H. cordata* also has anti-radiation effects. The volatile oil of *H. cordata* has anti-allergic, anti-asthma, and anti-cough effects. The extract of *H. cordata* has diuretic effects. The water-soluble substance of *H. cordata* has mild sedative and anti shock effects. *H. cordata* flavonoids have significant antidepressant effects [42].

4 Conclusion

H. cordata is a commonly used traditional Chinese medicinal herb in China, with abundant medicinal resources, high yield, various effective ingredients and nutrients, and low toxicity and side effects. It has been developed into a healthy product. As a dual-use dietary therapy plant, *H. cordata* has great application and popularization value. There are abundant fishy resources in China. Although the toxic side effects of *H. cordata* and its preparations are minimal, there are many reports of allergic reactions in the widely used *H. cordata* injection in clinical practice, which should be taken seriously. We need to strengthen the research on the germplasm resources, harvesting and processing of *H. cordata*,

and develop quality management standards for *H. cordata* production, in order to produce high-quality, high-yield and pollution-free raw materials and ensure that *H. cordata* and its preparations enter the international market. We should further deepen the research on the pharmacology and chemical components of *H. cordata*, explore its effective ingredients and mechanisms of action, study the feasibility of different administration routes of *H. cordata*, and develop new modern Chinese medicine formulations.

Acknowledgements

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