Review

Chemical compositions and pharmacological activities of *Xanthium strumarium*

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Abstract

***Xanthium strumarium* (*X. strumarium*) is a traditional Chinese medicine with a long history. In recent years, with the development of modern pharmacology and chemical analysis technology, research on *X. strumarium* has been deepend. This paper aims to systematically summarize the chemical compositions and pharmacological effects of *X. strumarium*, in order to provide theoretical basis and reference for further exploration in its clinical application and drug development.**

Keywords: *Xanthium strumarium*; chemical composition; pharmacological activities

1 Introduction

The fruit of *Xanthium strumarium* (*X. strumarium*), belonging to the *Asteraceae* family, is dried and comprises the bracts of *Xanthium sibiricum* Patr. It is a commonly used traditional Chinese medicinal material. According to pharmacopoeias, *X. strumarium* is pungent, neutral in nature, slightly bitter and warm, belonging to the lung meridian. It is slightly toxic and is known for its effects of dispelling wind-cold, opening nasal passages and expelling wind-dampness. Recent studies have found that its pharmacological activities include anti-inflammatory [1], antimicrobial, antiviral [2] and anti-tumor effects [3]. Folk usage is related to its significant efficacy in the treatment of rheumatoid arthritis-like joint diseases. Previous studies have also revealed the strong anti-inflammatory activity of *X. strumarium* extracts, and systematic chemical isolation of its active components identified quinoline, lignan, glycoside and phenolic acid compounds [4-10]. This paper summarized the chemical compositions and pharmacological effects of *X. strumarium* in order to provide theoretical basis and reference for further exploration in its clinical application and drug development.

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2 Chemical components

2.1 Phenylpropanoids

Research indicates that phenylpropanoids are significantly active ingredients in *X. strumarium*, including *β*-hydroxypropiosyringone (**1**), caffeic acid (**2**), (+)-lirioresinol A (**3**), *p*-coumaroyl ethyleneglycol (**4**), *ω*-hydroxypropioguaiacone (**5**), (+)-jatrointelignan D (**6**), 2-(4-hydroxy-3-methoxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-1-propanol (**7**), (-)- eugenol (**8**), (+)-dihydrophaseic acid (**9**), lyciumin (**10**), caruilignan D (**11**), piperonylic acid glyceride (**12**), (-)-dihydrophaseic acid (**13**), vladinol D (**14**) and threo-buddlenol C (**15**). Compounds **8** and **13** significantly inhibit LPS-induced production of NO in BV-2 cells and exhibit anti-neuroinflammatory activity [11].

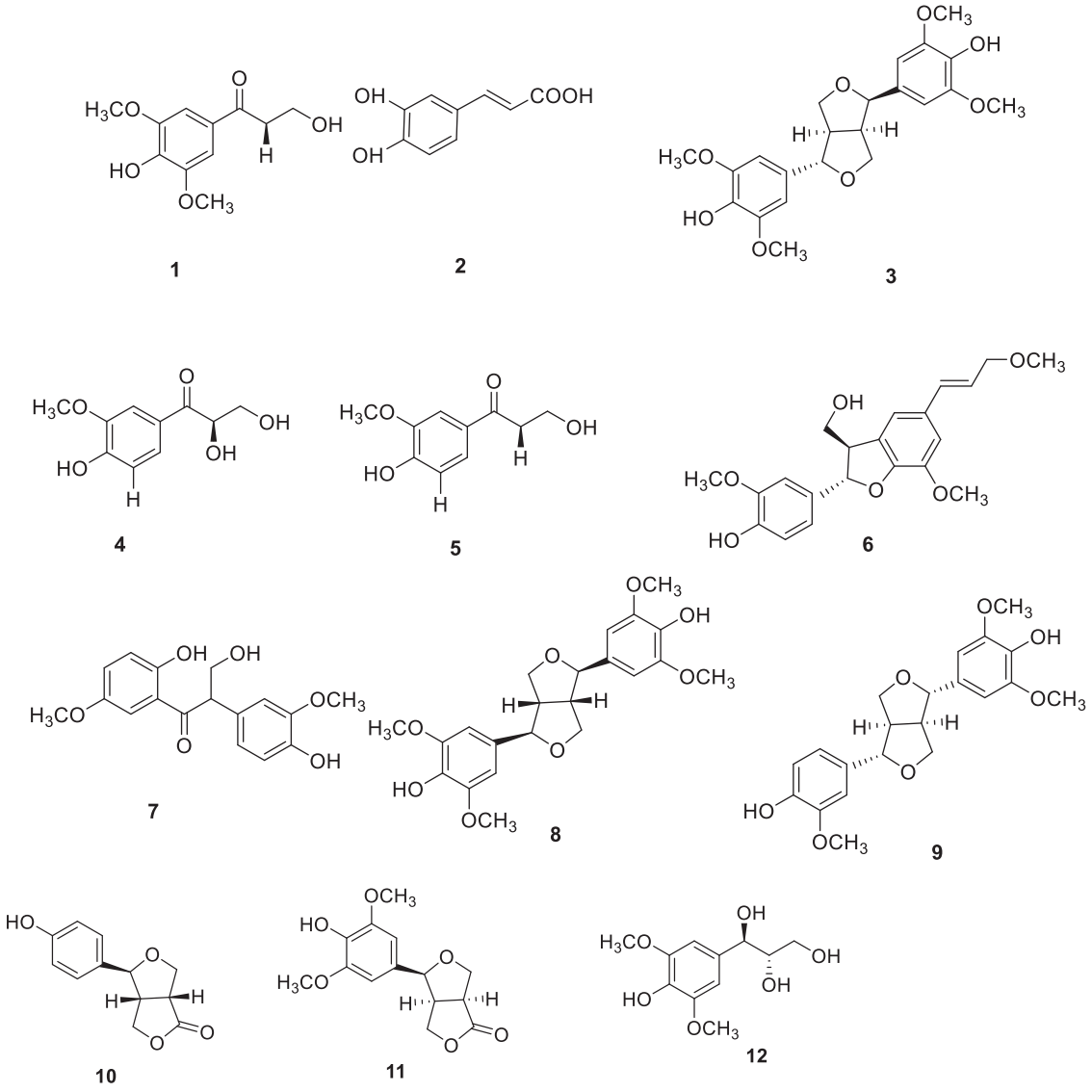

Fig. 1 Structures of phenylpropanoids isolated from *X. strumarium*

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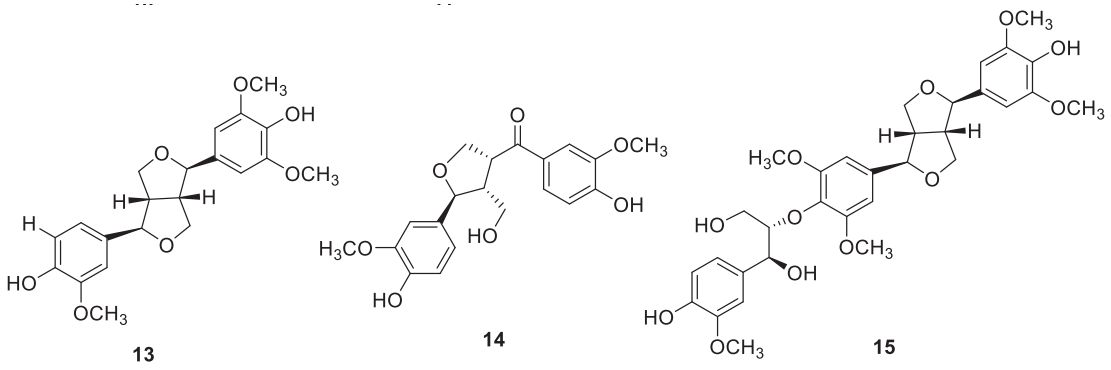

Continued Fig. 1

2.2 Phenolic acids

Research indicates that phenolic acids in *X. strumarium* mainly include Methyl communisoate (**16**), (+)-ent-ficusol (**17**) and (*E*)-3,3'-dimethoxy-4,4'-dihydroxydiphenyl ethylene (**18**).

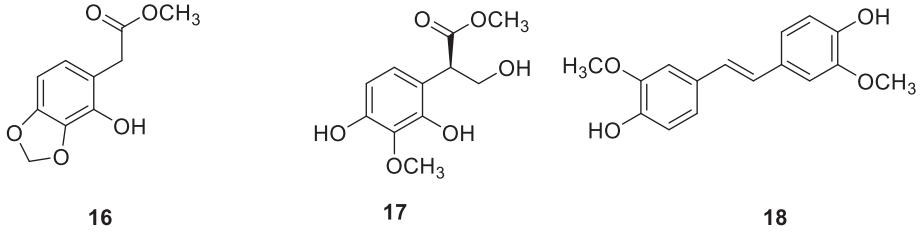

Fig. 2 Structures of phenolic acids isolated from *X. strumarium*

2.3 Alkaloids

X. strumarium contains alkaloids such as deoxyberberine (**19**) and 1H-indole-3-hydroxyacetyl (**20**).

Fig. 3 Structures of alkaloids isolated from *X. strumarium*

2.4 Water-soluble glycoside compounds

The water-soluble glycosides of *X. strumarium* mainly refer to arctiin (**21**) and arctigenin (**22**). Both have toxic effects on hepatocytes.

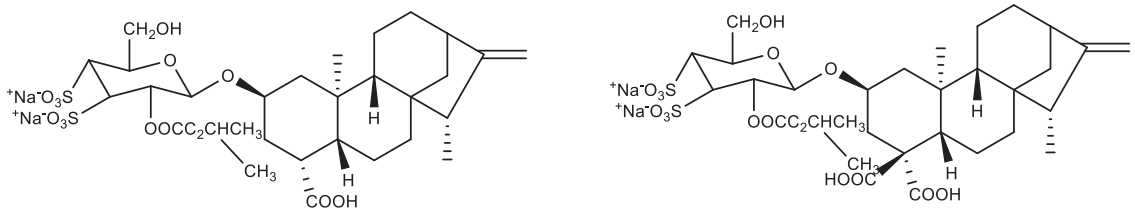

Fig. 4 Structures of water-soluble glycoside compounds isolated from *X. strumarium*

2.5 Guaiac xytene-type sesquiterpenes

Guaiac xytene-type sesquiterpenes mainly contain lasidiolpmethoxybenzoate (**23**), 5-azuleneacetic acid (**24**), xantholide A (**25**) and xantholide B (**26**).

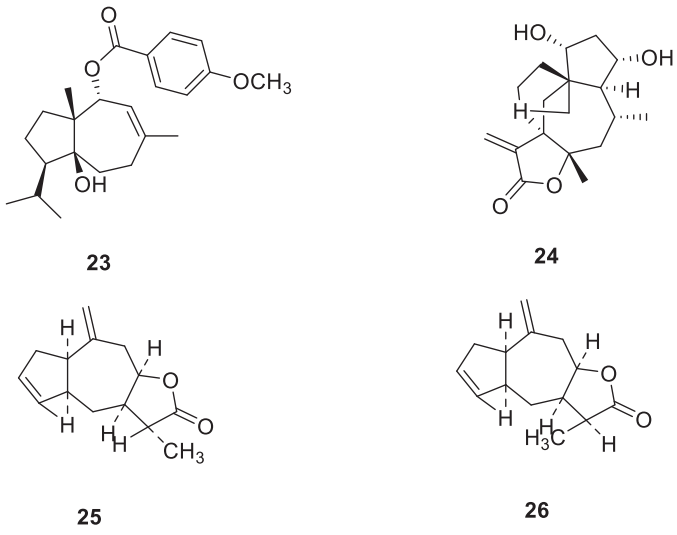

Fig. 5 Structures of guaiac xytene-type sesquiterpenes isolated from *X. strumarium*

2.6 Eucalyptane-type sesquiterpenes

Eucalyptole lactones exhibit anti-inflammatory, anti-tumor, neuro-protective, antibacterial and other activities. These eucalyptole lactones including 4-eudesmene-1β,11-dio (**27**), 4(15)-eudesmene-1β,11-dio (**28**), 3-eudesmene-1β,11-diol (**29**), germacra-5,10(14)-dien- 1β,4β-diol (**30**), β-selinene (**31**), Atractylodes enolactone (**32**), xanthodiene (**33**) and isoalantolactone (**34**).

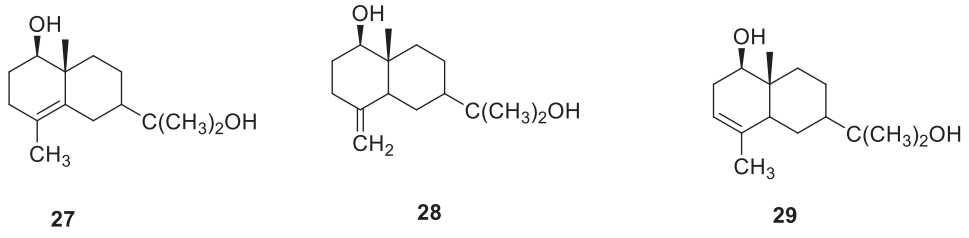

Fig. 6 Structures of eucalyptane-type sesquiterpenes isolated from *X. strumarium*

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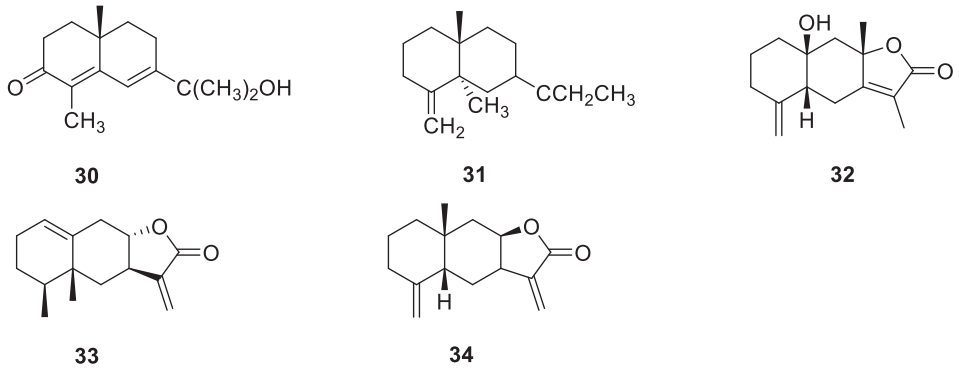
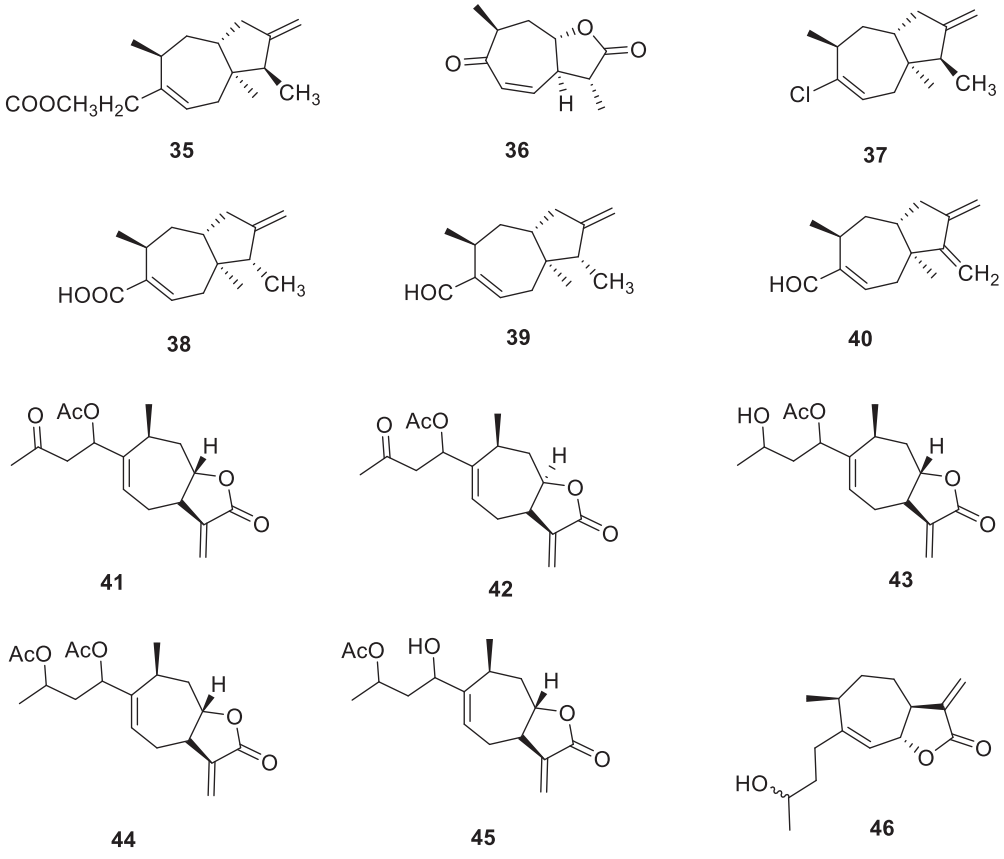


30 31 32 33 34

Continued Fig. 6

2.7 Split-guaiacane-type sesquiterpenes

Other compounds in *X. strumarium* include norxanthantolide A (**35**), norxanthantolide B (**36**), norxanthantolide C (**37**), norxanthantolide D (**38**), norxanthantolide E (**39**), norxanthantolide F (**40**), xanthinin (**41**), xanthumin (**42**), xanthanol (**43**), xanthanol Acetate (**44**), isoxanthanol (**45**), 4,*O*-dihydroinusoniolide (**46**), xanthatin (**47**), xanthinosin (**48**), tomentosin (**49**), 8-epi-tomentosin (**50**), 11α,13-dihydro-xanthuminol (**51**) and desacetylxanthanol (**52**).



35 36 37 38 39 40 41 42 43 44 45 46

Fig. 7 Structures of split-guaiacane-type sesquiterpenes isolated from *X. strumarium*

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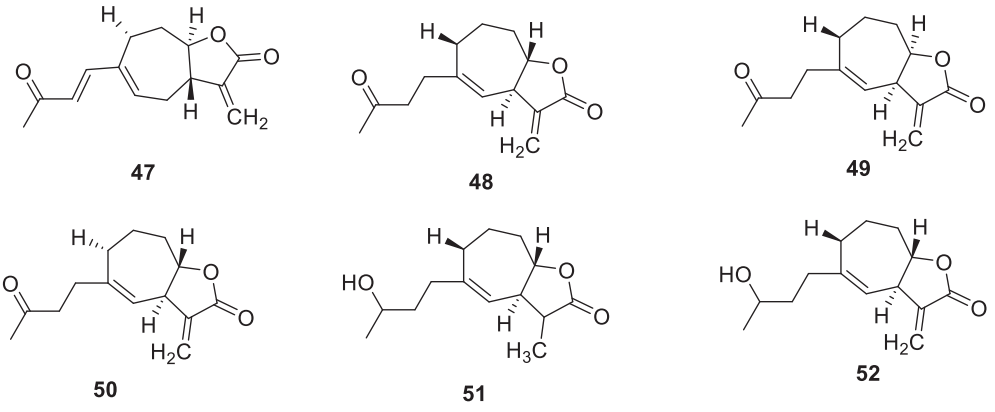

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3 Pharmacological activities

X. strumarium is mainly used for the treatment of diuresis, emetic, laxative, prostate disease, fever, lymph node tuberculosis, hepatitis and cancer, itchy skin and leprosy [12]. It has anti-inflammatory activity, anti-bacterial activity, anti-viral activity, anti-tumor activity, anti-allergic activity, blood glucose-lowering activity and anti-diabetic effects. It is also a good medicine for the treatment of nasal abyss and rhino-sis, and is widely used in clinical practice [13-20].

3.1 Anti-inflammatory activity

The ether extraction and n-butanol extraction of *X. strumarium* showed better anti-inflammatory effects [21-23]. Sun *et al.* demonstrated that the n-butanol fraction of *X. strumarium* significantly reduced the increase of capillary permeability in mouse peritoneal cavity, exhibiting a remarkable anti-inflammatory effect [24]. Through the mouse writhing test, it was observed that *X. strumarium* significantly reduces the number of writhes induced by acetic acid, showing analgesic effects. Yeom *et al.* found that *X. strumarium* blocked NF-κB activation, regulated the expression of c-Jun N-terminal kinase (JNK) and p38 protein activities in the mitogen-activated protein kinase (MAPK) signaling pathway, reduced MAPK activity, enhanced heme oxygenase-1 (HO1) expression in macrophages, and inhibited the inflammatory response induced by lipopolysaccharide [25]. Some conclusions have been made about the relationship between its structure and drug effect. Xanthinosin is *α*, *β*-unsaturated *γ*-lactone ring conjugated system, making it easy to bind to the cell wall and membrane so that the compound can enter the cell and achieve antibacterial or antibacterial effects. Studies have also shown that Xanthine has obvious antibacterial effects on *Bacillus cereus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Salmonella*, and its minimum inhibitory concentration (MIC) values are 31.3, 62.5, 125 and 125 μg/mL, respectively [26]. It was found that *Xanthium* had a good effect on the inhibition of plant pathogens. The water decoction of *Xanthium* has good activity in inhibiting microorganisms such as *Bacillus anthracis* and *Bacillus diphtheria* [27].

3.2 Antibacterial activity

X. strumarium, as a traditional herbal medicine, has been widely used in the treatment of infectious diseases, and its antibacterial activity has attracted much attention. Its antibacterial activity is mainly attributed to its rich chemical composition. Liu et *al.* found that *X. strumarium* extract inhibited various bacteria such

as *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, with a broad antibacterial spectrum and strong antibacterial effects [28]. Zhao et *al.* conducted antibacterial experiments with *X. strumarium* and its processed products with fatty oils and found that they exhibited significant antibacterial effects against *Staphylococcus aureus* and *Streptococcus pneumoniae* [29].

3.3 Antiviral activity

Compounds **58**, **61**, **64** and **51** isolated from *X. strumarium* exhibit certain antiviral activity against *Coxsackie virus* B3, with IC_{50} values of 57.74, 16.78, 8.70 and 3.70 μmol/L, respectively. In addition, compounds **10**, **17**, and **18** also exhibit inhibitory effects against *Coxsackie virus* B3 and have antiviral effects against influenza A virus, with IC_{50} values of 6.4, 8.4, and 8.4 μmol/L, respectively, and SI values of 7.5, 6.8, and 11.9 μmol/L, respectively. *X. strumarium* ethanol extracts also exhibit certain antiviral activity, such as inhibiting the growth of herpes simplex virus type 1 [30]. High dose of *X. strumarium* extracts can alleviate liver pathological damage caused by duck hepatitis B virus [31].

3.4 Anti-tumor activity

Xantine in *X. strumarium* is the main anti-tumor active substance. Xantine can inhibit proliferation and induce apoptosis of a variety of tumor cells, including non-small cell lung cancer cells, human gastric cancer MKN-45 cells, and human breast cancer MDA-MB-231 cells [32,33]. Li et al. demonstrated its anti-tumor mechanism using *in vitro* and *in vivo* co-experiments [34]. Xantine inhibited mouse melanoma cells *in vitro* and *in vivo*. The effects of Xantine on mouse melanoma B16-F10 cells in terms of time and dose were studied by MTS cell proliferation assay, and the results showed that the IC_{50} values of Xantine at 12 h and 4 h on B16-F10 cells were 14.20 and 7.36 μmol/L, respectively. In the *in vitro* trial, the tumor suppression rate of Xantine administration group was 30.81%. Further experiments have shown that Xantine can kill tumor cells around blood vessels, thereby helping to reduce microvascular density. All experimental results suggest that the inhibition of the proliferation of mouse melanoma B16-F10 cells may be related to the activation of the Wnt/β-catenin pathway, and its activity against melanoma is also associated with inhibition of angiogenesis. Wei et al. used serum pharmacological methods to investigate the anti-tumor effect of *Xanthium* aerticum extract, and the results showed that the drug serum of *Xanthium* inhibited the proliferation of human hepatocellular carcinoma cells, and the number of cell clones in the drug serum (low, medium and high doses) group and the 5-fluorouracil group was significantly lower than that in the control group, and the inhibition rates of clone formation were 18.30%, 49.34%, 68.12% and 53.2%, respectively [35].

3.5 Anti-allergic activity

The main active compounds of *X. strumarium* are mostly involved in anti-tumor and antibacterial activities, and the research on allergic diseases is limited. Studies have shown that *X. strumarium* 70% ethanol extract dose-dependently inhibits mouse allergic shock and passive cutaneous anaphylactic reaction induced by ovalbumin. *In vitro* experiments have showed that *X. strumarium* extract reduces histamine and β-hexosaminidase release from rat mast cells in a concentration-dependent manner, indicating that the effective components of *X. strumarium* extract stabilize mast cell membranes, reduce the release of allergic mediators such as histamine, and inhibit mast cell-dependent immediate-type allergic reactions [36]. There are abundant sesquiterpene compounds in

X. strumarium, suggesting that sesquiterpenes may have anti-allergic effects. Wang *et al.* found that *X. strumarium* (40 mg/kg) significantly inhibited ear swelling in ACD mice and markedly reduced the levels of TH2 cytokines IL-4 and IL-5 in ear homogenates [37]. Pathological sections showed that it significantly improved the degree of ear swelling and infiltration of inflammatory cells. *In vitro* experiments showed that 0.1 μmol/L *X. strumarium* had a significant inhibitory effect on TSLP produced by epithelial cells, and 1 μmol/L *X. strumarium* significantly inhibited TNF-α production by RAW264.7 cells. *X. strumarium* can also improve allergic dermatitis and allergic asthma, and has a good inhibitory effect on FITC-induced mouse TH2-type allergic contact dermatitis and HDM-induced mouse allergic asthma models. It can also reduce the production of key initiating factor TSLP by epithelial cells and reverse the transformation of TSLP to NK2 by NK cells. Its mechanism is related to the inhibition of STAT3 activation, indicating that *X. strumarium* has a significant inhibitory effect on allergic reactions. Shao *et al.* used systematic solvent and water-alcohol precipitation methods to extract *X. strumarium* and conducted experiments on anti-allergic intestinal muscle contraction response in sensitized guinea pigs and histamine-induced allergic shock in guinea pigs [38]. The results showed that *X. strumarium* 70% ethanol extract was the effective part for anti-allergy. Dai *et al.* found that *X. strumarium* 70% ethanol extract could inhibit compound **48**/**80**-induced mouse allergic shock and ovalbumin-induced skin allergy [39]. Its anti-allergic mechanism may be related to stabilizing mast cell membranes, inhibiting intracellular calcium ion (Ca^{2+}) influx and increasing cyclic adenosine monophosphate (cAMP) content. Therefore, *X. strumarium* is widely used in the prevention and treatment of allergic diseases in traditional Chinese medicine, showing promising medicinal prospects.

3.6 Blood glucose-lowering activity

X. strumarium can lower blood glucose through different pathways. Yoon *et al.* found that 3,5-*O*-dicaffeoylquinic acid methyl ester isolated from *X. strumarium* significantly inhibited aldose reductase and sorbitol formation in the lenses of mice fed with high-glucose diet, thereby reducing the complications caused by diabetes [40]. It can also lower blood glucose by increasing tolerance and improving insulin resistance. Li *et al.* found that *X. strumarium* water extract improved glucose tolerance and insulin resistance in rats fed with high-fat diet, reducing fat production while increasing fat oxidation [41]. Caffeic acid isolated from *X. strumarium* has a concentration-dependent blood glucose-lowering effect in a certain dose range, with no effect on normal mice. However, carboxylated arctiin components can increase blood glucose caused by adenosine tetraphosphate. This component can inhibit adrenaline-induced hyperglycemia by promoting the breakdown of liver glycogen. Studies have shown that the polysaccharide components in *X. strumarium* can significantly reduce blood glucose and serum insulin levels, improve insulin sensitivity, alleviate insulin resistance, and have certain therapeutic effects on diabetes. Zhang *et al.* studied the effects of *X. strumarium* water extract on mice with high blood sugar levels [42]. After continuous administration for 10 d, blood plasma was collected, and blood glucose levels were measured by using the glucose oxidase method. The results showed that all dose groups of *X. strumarium* could lower blood glucose level in mice with high blood sugar and improve glucose tolerance. Hwang *et al.* have found that 3,5-dimethylcaffeoylquinic acid is an active component of *X. strumarium* in lowering blood glucose [43]. Song *et al.* found that *X. strumarium* could lower blood glucose by inhibiting nuclear transcription factor-κB (NF-κB) activation, preventing cytokine-induced damage

to pancreatic β cells, repairing pancreatic β cell function, and promoting regeneration of damaged pancreatic β cells [44]. Therefore, *X. strumarium* is widely used in traditional Chinese medicine for the treatment of diabetes and its related complications, showing broad development prospects.

4 Conclusion

Based on existing studies, the chemical compositions and pharmacological activities of *X. strumarium* were reviewed in this paper. As an important Chinese herbal medicine, *X. strumarium* has been widely utilized in traditional medicine and has attracted increasing attention from modern scientific research in recent years. Studies have shown that *X. strumarium* contains rich active ingredients, including lactones, polysaccharides, volatile oils, and other compounds. These components impart multiple pharmacological activities to *X. strumarium*, including but not limited to antimicrobial, anti-inflammatory, anti-tumor and immune-regulatory effects. Among them, the antimicarobial activity of *X. strumarium* is manifested in its significant inhibitory effect on various bacteria and fungi, providing an alternative for the treatment of various infectious diseases. Further study on its safety, efficacy, and toxicology will promote the application and development of *X. strumarium* in the medical field.

Acknowledgements

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