Review Article

The Fruits of *Xanthium sibiricum Patr*: A Review on Phytochemistry, Pharmacological Activities, and Toxicity

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Abstract

In recent years, drug development and research have gradually shifted from chemical synthesis to biopharmaceutical and natural drugs. Natural medicines, such as traditional Chinese medicine, have been among the first studied because of their long medicinal history, simplicity, and the relatively low cost of research. Among them, *Xanthii Fructus* (XF) is famous for the treatment of sinusitis. In this article, the achievements of research on XF from 1953 to 2020 are systematically reviewed, focusing on the aspects of chemical constituents, pharmacological effects, clinical applications, toxicity and side effects, and processing methods. To date, there have been significant advances in both the phytochemistry and pharmacology of XF. Some traditional uses have been validated and clarified in modern pharmacological studies. However, its mechanism of action in the treatment of allergic diseases has not been satisfactorily explained. Further *in vitro* and *in vivo* studies are required to rationally develop new drugs and to elucidate the therapeutic potential of XF. A comprehensive evaluation of XF and an understanding of network pharmacology are also needed.

Keywords: Pharmacological activities, phytochemistry, toxicity, *Xanthii Fructus*

Introduction

More than 20,000 kinds of plants are used in traditional medicines worldwide. Traditional Chinese medicine (TCM) is famous for its unique curative effects. *Xanthii Fructus* (XF), or "cangerzi" in Chinese, is widely studied as a traditional Chinese medicinal agent. XF is the dried fruit of the composite plant *Xanthium sibiricum Patr.* With involucre as shown in Figure 1. The fruit ripens in autumn, is harvested and dried, and the impurities such as stems and leaves are removed. XF was first described in Shennong's *Classic of Materia Medica* (during the Qin and Han Dynasties) and was later recorded in the *Compendium of Materia Medica* (Ming Dynasty). XF is often used to treat rhinitis, headache due to a cold, limb cramps and numbness, ulcers, and itching.[1] Modern pharmacological research has shown that XF also exerts hypoglycemic, anti-inflammatory, and other effects.[2-4] Although XF has high efficacy, its toxicity cannot be ignored. Cases of poisoning induced by accidental ingestion of XF are often reported, mainly resulting from drug-induced liver injury.[5] This toxicity limits the clinical use of XF. To reduce the toxicity of XF and improve its therapeutic effects, processed, especially stir-fried, products are often used in China.

In recent years, there have been many reports on XF. The main chemical constituents of XF are sesquiterpenoid lactone, glycoside, and phenolic acid; it also contains unsaturated fatty acids and other substances.[6-11] In the 2015 edition of

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Pharmacopoeia of the People's Republic of China (ChP), carboxyl atractyloside was used as an index to evaluate the toxicity of XF, while chlorogenic acid content was used to evaluate quality. Some methods, such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS), can provide a reference for optimizing quality and safety controls of XF.[12,13]

This article systematically reviews recent studies on the phytochemistry, pharmacology, and toxicology of XF. The purpose was to study XF in depth in order to elucidate its application and pharmacological activity and to discuss the limitations of current studies. Future research directions for XF are considered in order to provide a scientific basis for the development of new drugs and to elucidate its full therapeutic potential.

Phytochemistry

XF contains an abundance of chemical constituents. Increasing research activity has enhanced our understanding of its chemical constituents. Thus far, chemical constituents including phenolic acid, sesquiterpenes, glycosides, thiazine, and lignans have been discovered

Phenylpropanoids

Phenylpropanoids are important chemical components in XF, and phenolic acids are the most common phenylpropanoids. There are many phenolic acid compounds, and chlorogenic acid is the most abundant organic acid in XF. Phenolic acid plays an important role in the clinical effects of XF. It has favorable antioxidant, anti-inflammatory, antimicrobial, enzyme inhibitory, liver cell protective, and platelet aggregation inhibitory activities, as well as other biological activities.[14-20] In addition to chlorogenic acid, other phenolic acids exist in XF, such as neochlorogenic acid, cryptochlorogenic acid, caffeic acid (1), ferulic acid (2), isochlorogenic acid (3), protocatechuic acid (4), and caffeoylquinic acids.[21-25] Other studies have shown that the phenolic acid content in these medicinal materials is related to factors such as origin, harvest time, processing time, and temperature.[22] The names and chemical structures of other phenylpropanoids are shown in Table 1 and Figure 2.

Glycoside

Glycosides are widely distributed in the roots, stems, leaves, flowers, and fruits of plants.[40] They are mostly colored crystals that dissolve in water.[41] They are generally bitter and some are highly toxic. Sugars and other substances are formed by hydrolysis.[41] The toxic components of XF are mainly water-soluble glycosides.[34] Jiang (2017) isolated and identified the toxic parts based on their selection by pharmacological screening. Experiments have shown that the toxic components of XF are carboxyatractyloside (1), atractyloside (2), and 3',4'-dedisulfated-atractyloside (3).[35-37] After stir-frying, the content of atractyloside decreases, and the toxicity of XF decreases.[36] The glycosides in XF include hemiterpene glycosides, monoterpene glycosides, and diterpenoid glycosides. Details of the glycoside compounds are shown in Table 2. The corresponding chemical structures are shown in Figure 3.

Sesquiterpenoid

The characteristic components of Compositae are sesquiterpenoid lactones.[45,46] More than 300 sesquiterpenoid lactones have been isolated from Compositae alone. These compounds have anti-inflammatory, analgesia, antitumor, anti-allergic, antibacterial, antiulcer, and other activities, and they affect the central nervous system and cardiovascular system.[47-54] Most of the sesquiterpene lactones in XF have been extracted with petroleum ether, methanol, ethanol, chloroform, acetone, and other organic solvents. These organic solvents have been further extracted, removed, and extracted by column chromatography to obtain sesquiterpene lactones.[55] To date, approximately forty sesquiterpene lactones have been identified in XF [Table 3]. The detailed chemical structure is shown in Figure 4. Xanthatin is the main active substance of XF, which exerts antitumor effects.[54]

Lignanoids

Twenty lignans have been identified in XF since 2017. As shown in Figure 5. They include xanthiumnolic B (1), leptolepisol D (2), fructusol A (3), (-)-1-O-β-D-glucopyranosyl-2-{2-methoxy-4-[1-(E)-propen-3-ol] phenoxyl}-propane-3-ol (4), and dihydrode-hydrodiconiferyl alcohol (5); the other components are shown in Table 4. Among them, in 2017, xanthiumnolic B was shown to have anti-inflammatory effects.[66]

Thiazides

Ten thiazide compounds have been reported to date: xanthiazone (1), 2-hydroxy-xanthiazone (2), 7-hydroxymethyl-8,8-dimethy l-4,8-dihydrobenzol - [1,4]-thiazine-3,5-dione-11-O-β-D-glucopyranoside (3), 2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside (4), 7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol-[1,4]-thiazine-3,5-dione-(2-O-caffeoyl)-β-D-glucopyranoside (5), xanthialdehyde (6), chrysophanic acid (7), emodin (8), aloe emodin (9), and 7-[(β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl) oxymethy]-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione (10). The detailed chemical structures are shown in Table 5 and Figure 6.

Others

Ahuja and Nigam reported that XF contains anthraquinones. In addition, flavonoids, alkaloids, heterocyclic compounds, adenosine, sterols, fatty acids, coumarins, and other compounds have been identified in XF.[31,71,72]

Analytical Methods

Presently, in ChP, the quality of XF is controlled by HPLC and the content of chlorogenic acid is at least 0.25%. Among the abovementioned analytical methods, HPLC is the most frequently used, and is the main method used for the analysis of other compounds.[12] Although HPLC is a simple and

Table 1: Phenylpropenoids reported from *Xanthii Fructus*

Compound name	Part of plant	Reference
(1S,2R)-1,2-bis (4-hydroxy-3-methoxypenyl-1,3-propanediol	Fruits	[26]
1,3,5-tri-O-caffeoylquinic acid	Fruits	[27]
1,3-di-O-caffeoylquinic acid	Fruits	[28]
1,4-di-O-caffeoylquinic acid	Fruits	[29]
1,5-di-O-caffeoylquinic acid	Fruits	[22]
2,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one	Fruits	[30]
3,4-di-caffeoylquinic acid methyl ester	Fruits	[31]
3,5-di-caffeoylquinic acid methyl ester	Fruits	[31]
3,5-di-O-caffeoylquinic acid	Fruits	[27]
3-hydoxy-1-(4-hydroxy-phenyl)-propan-1-one	Fruits	[32]
3-methoxy-4-hydroxy-transcinnamaldehyde	Fruits	[24]
4,5-di-O-caffeoylquinic acid	Fruits	[29]
4-hydroxy-3-methoxycinnamaldehyde	Fruits	[31]
4-O-caffeoyl quinic acid methyl ester	Fruits	[33]
5-O-caffeoylquinic acid	Fruits	[28]
Arbutin	Fruits	[34]
Caffeic acid	Fruits	[22]
Caffeic acid choline ester	Fruits	[33]
Caffeic acid ethyl ester	Fruits	[24]
Chlorogenic acid	Fruits	[28]
Coniferine	Fruits	[35]
Erythro-guaiacylglycerol-8-O-4'-(coniferyl alcohol) ether	Fruits	[36]
Erythro-guaiacylglycerol-β-coniferyl aldehyde ether	Fruits	[26]
Ferulic acid	Fruits	[26]
Icariside D1	Fruits	[37]
Icariside F2	Fruits	[32]
Isovanillic acid	Whole plants	[37]
Methyl-3,5-di-O-caffeoylquinic acid	Fruits	[29]
Methylchlorogenate	Fruits	[38]
Neochlorogenic acid methyl ester	Fruits	[28]
p-hydroxybenzaldehyde	Fruits	[39]
Protocatechuic acid	Fruits	[24]
rel-(2α,3β)-7-O-methylcedrusin	Fruits	[40]
Threo-1-phenyl-(4-hydroxy-3-methoxy)-2-phenyl-(4"-hydroxy-3"-methoxy)-1,3-propanediol	Fruits	[38]
Threo-guaiacylglycerol-8-O-4'- (coniferyl alcohol) ether	Fruits	[26]
Threo-guaiacylglycerol-β-coniferyl aldehyde ether	Fruits	[26]
Xanthiumnolic A	Fruits	[39]
Xanthiumnolic C	Fruits	[39]
Xanthiumnolic D	Fruits	[39]
Xanthiumnolic E	Fruits	[39]
ω-hydroxypropioguaiacone	Fruits	[32]

accurate method, it does not provide a comprehensive method for the quality control of drugs. Detection of chlorogenic acid content only when determining the content of XF is also a disadvantage because the content of other chemical components in XF has not been determined, which is not favorable for quality control.

Recently, with the development of analytical instruments, there have been many reports on the quality control methods for XF. For phenolic acids and glycosides, commonly used analytical methods include HPLC, high-performance capillary electrophoresis, ultra-performance liquid chromatography (UPLC), ultra-HPLC-triple quadrupole-linear ion trap mass spectrometry (UPLC-QTRAP-MS/MS), and HPLC-photodiode array. For anthraquinones and flavonoids in XF, UPLC-QTRAP-MS/MS is an effective method for the simultaneous determination of these two compounds.[73,74] Volatile oils can be detected by HPLC-evaporative light-scattering detector and GC-MS. Other methods, such as liquid chromatography-diode array spectrometry/electrospray ionization mass spectrometry (HPLC-DAD/ESI-MS) and UPLC coupled with time-of-fight mass spectrometry (UPLC/Q-TOF-MS), have also been used to determine the chemical content of

Table 2: Glycosides reported from *Xanthii Fructus*

Compound name	Part of plant	Reference
Hemiterpene glycoside		
2-methyl-3-buten-2-ol-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	Fruits	[42]
everlastoside C	Fruits	[43]
Monoterpene glycoside		
(6E)-3-hydroxymethyl-7-methylocta-1,6-dien-3-ol8-O-β-D-glucop yranoside	Fruits	[7]
(6Z)-3-hydroxymethyl-7-methylocta-1,6-dien-3-ol8-O-β-D-glucopyranoside	Fruits	[7]
3β-norpinan-2-one 3-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	Fruits	[7]
xanmonoter A	Fruits	[44]
xanmonoter B	Fruits	[44]
Diterpenoid glycoside		
3',4'-dedisulphated-atractyloside	Fruits	[40]
atractyloside	Fruits	[36]
carboxyatractyloside	Fruits	[38]
Fructusnoid A	Fruits	[44]
Fructusnoid B	Fruits	[44]
Fructusnoid C	Fruits	[44]

Figure 1: The plant *Xanthium sibiricum Patr.* and *Xanthii Fructus*

XF.[40,68] Furthermore, these methods can detect changes in the active and toxic components of XF with sensitivity before and after processing. In recent years, researchers have studied the relationship between pharmacological activity and the content of chemical constituents in plants. This analytical method may bring about a great change in the quality control of XF.

Pharmacological Activities and Clinical Application

Pharmacological activities

The earliest application of Xanthium in China can be traced back to the Qin dynasty. The roots, stems, leaves, flowers, and fruits of Xanthium have been reported to have medicinal effects in classical works, including XF.[74]

Antimicrobial activity

In vitro, XF has been shown to exert a strong inhibitory effect on many microorganisms, such as *Staphylococcus aureus*, *Pneumococcus*, and Group b *Streptococcus*.[75,76] It has demonstrated clear bacteriostatic effects on *Escherichia coli* and *Bacillus subtilis*, whereby the bacteriostatic effect on *E. coli* is greater than that on *B. subtilis*.[77]

Acetone and ethanol extracts of XF have also demonstrated inhibitory effects on *Trichoderma rubra*. Chloroform extract and n-butanol extract of XF can inhibit *Demodex oculi*, and mucous toxicity tests found no irritation.[78] The inhibition rate of hepatitis B virus (HBV) DNA by XF polysaccharides was 25%–50%.[63] XF extracts can control the pathological changes caused by HBV without affecting transaminase levels.[79] In addition, an ethanol extract of XF can completely inhibit the growth of herpes virus at 0.1 mg/mL, and has no toxic effect on normal cells.[80]

Anti-inflammatory and analgesic activities

Intraperitoneal injection of methanol extract of XF at 250 mg/kg increased analgesia by 30%–60%. XF has some anti-inflammatory and analgesic effects on writhing reaction induced by subcutaneous injection of 1000 mg/kg acetic acid in mice.[64,81] The anti-inflammatory mechanism of action has been discussed in recent years. Studies have shown that the product of the MEXS gene is a potent inhibitor of nitric oxide, prostaglandin E2, and tumor necrosis factor-alpha (TNF-α) production. Inducible nitric oxide synthase, cyclooxygenase-2 expression, and TNF-α release were inhibited through the blockade of nuclear factor-kappa B activation by MEXS. XF has an inhibitory effect on the above inflammatory factors to a certain extent.[8,82]

Anti-allergy effect

Among the various extracts of XF, a 70% alcohol extract was found to have the best anti-allergic effect, and its anti-allergy mechanism may be related to the inhibition of Ca^{2+} influx in mast cells and the intracellular cyclic adenosine monophosphate (cAMP) content.[83-85] Dai *et al*. (in 2008) showed that xanthium can inhibit allergic reactions rapidly. Accordingly, 70% alcohol extracts of XF inhibit anaphylactic shock in mice, passive skin reactions in rats *in vivo*, and reduce histamine and beta-aminohexase release by rat mast cells *in vitro*. It was found to have no significant effect on the skin

Table 3: Sesquiterpenoids reported from *Xanthii Fructus*

Compound name	Part of plant	Reference
(2E,4E,1'S,2'R,4'S,6'R)-dihydrophaseic acid	Fruits	[24]
(3S,5R,6R,7E,9S)-megastigman-7ene-3,5,6,9-tetrol-3-O-β-D-glucopyranoside	Aerial parts	[56]
(3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmene-9-one	Fruits	[24]
11α,13-dihydro-8-epi-xanthatin	Aerial parts	[57]
11α,13-dihydroxanthatin	Aerial parts	[58]
11α,13-dihydroxanthuminol	Leaves	[59]
1β,4β, 4α,5α-diepoxyxanth-11(13)-en-12-oic acid	Aerial parts	[58]
1β,4β,4α,5α-diepoxyxanth-11	Fruits	[58]
1β-hydroxyl-5α-chloro-8-epi-xanthatin	Aerial parts	[55]
2-hydroxy xanthinosin	Aerial parts	[60]
2-hydroxytomentosin	Aerial parts	[61]
2-hydroxytomentosin-1β,5β-epoxide	Aerial parts	[58]
4-epi-isoxanthanol	Aerial parts	[58]
4-epi-xanthanol	Aerial parts	[58]
4-oxo-bedfordia acid	Aerial parts	[58]
4β,5β-epoxyxanthatin-1α,4α-endoperoxide	Aerial parts	[58]
5-azuleneacetic acid	Aerial parts	[60]
6β,9β-dihydroxy-8-epi-xanthatin	Fruits	[63]
8-epi-tomentosin	Leaves	[57]
8-epi-xanthatin	Aerial parts	[62]
Desacetylxanthanol	Leaves	[65]
Dihydrophaseic acid sodium salt 4'-O-β-D-glucopyranoside	Fruits	[56]
Inusoniolide	Aerial parts	[60]
Lasidiol p-methoxybenzoate	Fruits	[59]
Norxanthantolide A	Fruits	[45]
Norxanthantolide B	Fruits	[45]
Norxanthantolide C	Fruits	[45]
Norxanthantolide D	Fruits	[45]
Norxanthantolide E	Fruits	[45]
Norxanthantolide F	Fruits	[45]
Pungiolide A	Aerial parts	[64]
Pungiolide D	Aerial parts	[64]
Pungiolide E	Aerial parts	[64]
Sibirolide A	Fruits	[45]
Sibirolide B	Fruits	[45]
Tomentosin	Leaves	[53]
Xanthatin	Leaves	[53]
Xanthinosin	Leaves	[53]
Xanthnon	Aerial parts	[60]

response to histamine or serotonin in rats. These results showed that XF can stabilize hypertrophic cell membranes, reduce the release of histamine and other allergic mediators, and inhibit mast cell-dependent anaphylaxis.[82,83]

Antioxidant effect

Free radicals have a great influence on oxidation reactions. Extracts of XF have been shown to scavenge superoxide radicals and hydroxyl radicals; they have also been shown to delay and reduce lipid peroxidation.[54] In addition, XF extracts can reduce the lipid peroxide content in tissues and increase the activity of superoxide dismutase. The antioxidant activity of an XF extract was better at scavenging superoxide free radicals, while that of an alcohol extract was better at scavenging hydroxyl free radicals.[86]

Antitumor effect

Using a serum pharmacology method, Wei *et al*. treated human liver cancer cells cultured *in vitro* with low, medium, and high doses of XF in mouse serum and 5-fluorouracil, and used clonogenesis and flow cytometry to examine the effects on cell division, proliferation, and apoptosis.[87,88] The results showed that the XF drug serum had inhibitory and toxic effects on human liver cancer cells. In addition to its effects on human liver cancer cells, XF drug serum displayed clear toxic and inhibitory effects on human brain glioma and S180 sarcoma cells.[4]

Hypoglycemic effect

Monosaccharides are absorbed directly into the bloodstream through the small intestine, whereas disaccharides and

Table 4: Lignanoids reported from *Xanthii Fructus*

Compound name	Part of plant	Reference
(-)-(2R)-1-O-β-D-glucopyranosyl-2-{2-methoxy-4-[(Eformylvinyl] phenoxyl} propane-3-ol	Fruits	[67]
(-)-1-O-β-D-glucopyranosyl-2-{2-methoxy-4-[1-(E)-propen-3-ol] phenoxyl}-propane-3-ol	Fruits	[67]
(-)-7R,8S-dehydrodiconiferyl alcohol	Fruits	[67]
(-)-simulanol	Fruits	[67]
1-(4-hydroxy-3-methoxy)-phenyl- 2-[4-(1,2,3-trihydroxypropyl)-2-methoxy]-phenoxy-1,3-propandiol	Fruits	[67]
2-(4-hydroxy -3-methoxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-1-propanol	Fruits	[67]
4-oxopinoresinol	Roots	[68]
7R,8S-dihydrodehydrodiconiferyl alcohol -O-β-D-glucopyranoside	Fruits	[67]
Balanophonin	Fruits	[67]
Balanophonin A	Fruits	[67]
Chushizisin E	Fruits	[67]
Dehydrodiconiferyl alcohol	Fruits	[67]
Dihydrodehydrodiconiferyl alcohol	Fruits	[67]
Diospyrosin	Fruits	[67]
Fructusol A	Fruits	[68]
Leptolepisol D	Fruits	[67]
Pinoresinol	Fruits	[24]
Syringaresinol	Roots	[31]
Threo-dihydroxydehydrodiconiferyl alcohol	Fruits	[67]
Xanthiumnolic B	Fruits	[33]

Table 5: Thiazides reported from *Xanthii Fructus*

Compound name	Part of plant	Reference
2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside	Fruits	[26]
2-hydroxy-xanthiazone	Fruits	[26]
7-[(β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl) oxymethy]-8,8-dimethyl- 4,8-dihydrobenzo[1,4]thiazine-3,5-dione	Fruits	[26]
7-hydroxymethyl-8,8-dimethy l-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside	Fruits	[26]
7-Hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-(2-O-caffeoyl)-β-D-glucopyranoside	Fruits	[69]
Aloe emodin	Fruits	[42]
Chrysophanic acid	Fruits	[42]
Emodin	Fruits	[42]
Xanthialdehyde	Fruits	[70]
Xanthiazone	Fruits	[22]

polysaccharides are converted into monosaccharides by alpha-glucose liver enzymes.[89] XF can reduce liver glycogen in animals, and a water extract of XF can inhibit the activity of alpha-glucose liver enzymes. The glycosides in XF can significantly reduce the blood glucose level induced by rhamnose, but cannot reduce the hyperglycemia caused by tetrafluorouracil in rats. If rhamnose is injected first, followed by epinephrine, the elevated blood sugar response of epinephrine decreases or is lost. Low, medium, and high doses of an XF decoction can reduce the blood glucose of normal mice, and are able to regulate blood glucose and maintain blood glucose stability. The medium- and high-dose XF decoctions can significantly reduce the blood glucose of hyperglycemia mice and improve the glucose tolerance of hyperglycemia mice.[66,90,91]

Effects on immune function

Animal experiments have shown that XF has an inhibitory effect on both humoral and cellular immunity, with a greater effect on cellular immunity. In addition, XF displayed an inhibitory effect on the immune response of mononuclear macrophages.[92] XF is not conducive to the increase in capillary permeability caused by histamine. XF significantly inhibits the expression of the interleukin-2 receptor, regulates the immune imbalance of Th cells in patients with asthma, and inhibits the release of inflammatory transmitters.[56] Experiments have shown that XF induces different degrees of weight gain in immune organs. Specifically, the weight of the thymus and spleen increased with an increasing dose, and the serum hemolysin value increased in mice.[93]

Effects on other physiological systems

In vitro animal experiments have shown that XF has an inhibitory effect on the heart, and can slow the heart rate and reduce myocardial systolic function. Animal models have revealed different effects of XF on blood vessels, which mainly functions to dilate blood vessels.[94] In addition, XF extracts exerted an obvious antithrombin effect. Methanol extract had good effect on the recovery of cholesterol triglyceride level,

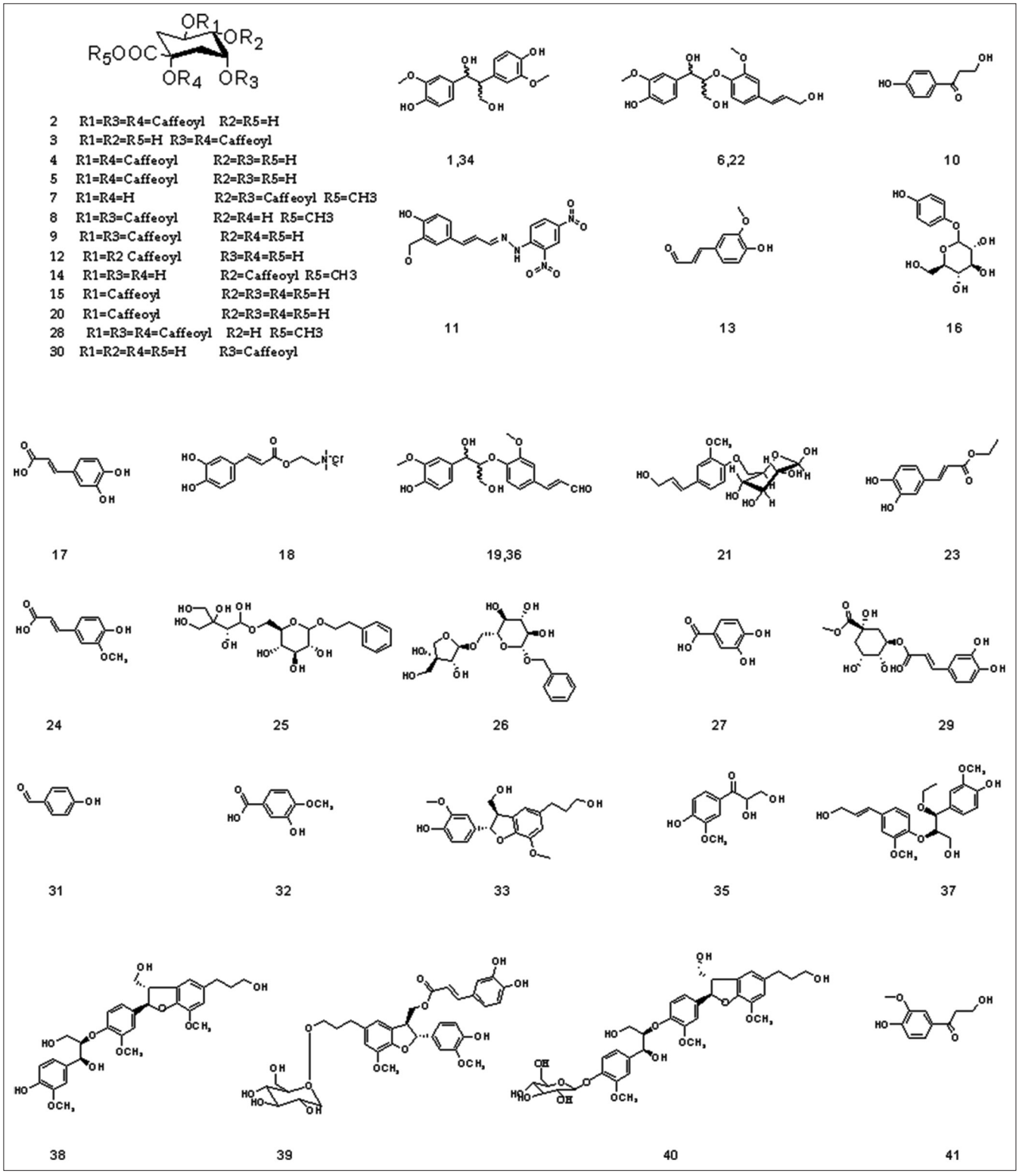

Figure 2: Chemical structure of phenylpropenoids reported from *Xanthii Fructus*

enhanced the phospholipid level, and inhibited the cholesterol and triglyceride level.[95] Moreover, the results of the study by Duan Xiaomao (2006) showed that compared with normal saline, chemical stimulation with XF and alcohol prolonged the latent period of cough in mice, and significantly decreased the number of coughs. Compared with codeine, there was little difference in the antitussive effect. This indicates that XF exerts an antitussive effect.

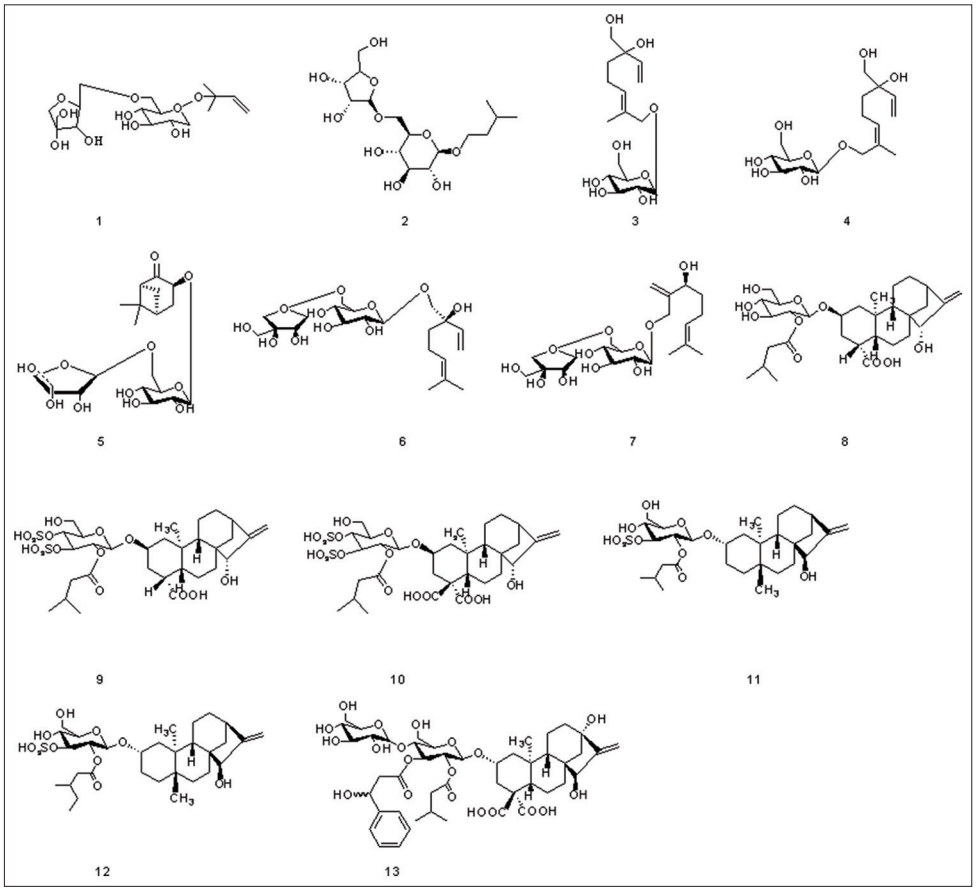

Figure 3: Chemical structure of glycosides reported from *Xanthii Fructus*

Clinical application

XF is used to clinically treat rhinitis, sinusitis, urinary tract infection, upper respiratory infection, hypoglycemia, intractable toothache, malaria, chronic bronchitis, mumps, allergic diseases, urticaria, tumor, dermatitis, diarrhea, and otitis media.[90-98]

Toxicity and Side Effects

The symptoms of XF poisoning are generally the same, regardless of the drug administration route. The activity of laboratory animals decreased upon XF administration.[95] Compared to normal animals, experimental animals were less active and responsive to external stimuli and had irregular breathing and extreme breathing difficulties with paroxysmal convulsion before they died.[96] The absolute lethal dose (LD_{100}) of a 25% XF emulsion intraperitoneally injected into rabbits was 10 mL/kg, and the median lethal dose (LD_{50}) in mice was 7.5 mL/kg.[97] Histopathological examination of the main organs of various animals after poisoning revealed the same lesions, differing only in the degree of severity. Among them, liver injury was the most serious.[98] The livers of dead animals presented degenerative disease or even necrosis, and epithelial turbiditis in the curved tube of the kidney was similar to the symptoms of carbon tetrachloride poisoning.[99] Therefore, the main consequence of XF poisoning is liver necrosis; death may be due to convulsion caused by secondary brain edema. Many studies have found that the toxic components of XF may be related to toxic proteins or xanthium glycosides and alkaloids.[100] The toxicity of XF extract is proportional to the drug concentration.

The toxic components of XF were determined for medicinal xanthium herbs, decoction pieces, and representative formulations containing xanthium (Biyuanshu oral liquid). The results showed that toxicity was observed as follows: decoction pieces > medicinal material > prescription preparation. The results of acute toxicity tests showed that all the three preparations in mice resulted in toxicity as follows: decoction pieces > medicinal material > prescription preparation. The toxicity of decoction pieces was greater than that of medicinal herbs, which was consistent with the trend observed for atractylode content.[99]

Clinical adverse reactions of XF have been reported in clinical studies and mainly manifest in terms of damage to the skin, digestive system, nervous system, and cardiovascular system. The specific performance was as follows:[94,96-101] first, skin lesions manifest as a systemic rash or contact dermatitis; second, digestive system toxicity is characterized by nausea, vomiting, loss of appetite, abdominal distention, diarrhea, hematochezia, liver and kidney pain, liver enlargement, ascites, liver coma, abnormal liver function, and liver failure; third, nervous system symptoms include dizziness, headache, restlessness, convulsions, drowsiness,

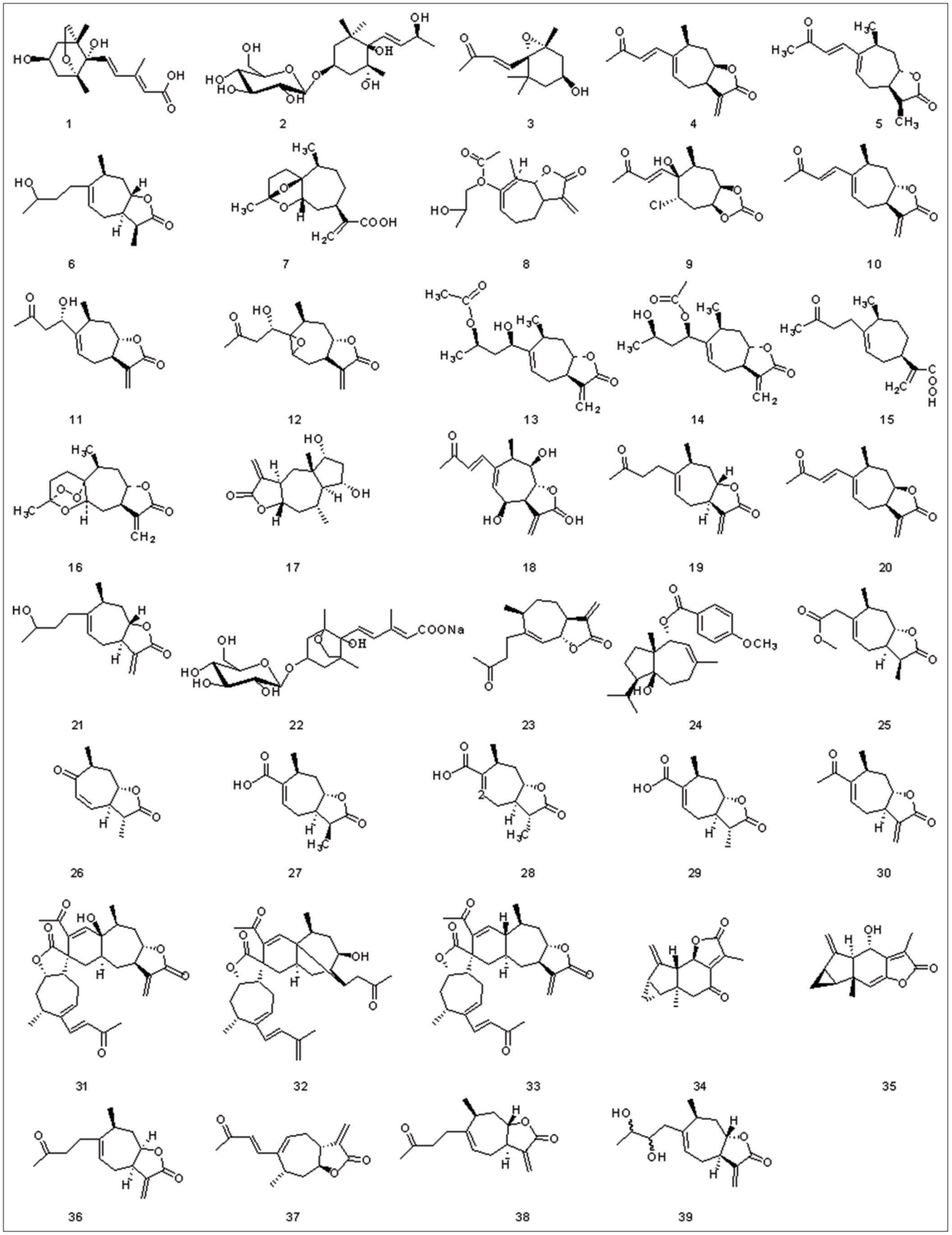

Figure 4: Chemical structure of sesquiterpenoids reported from *Xanthii Fructus*

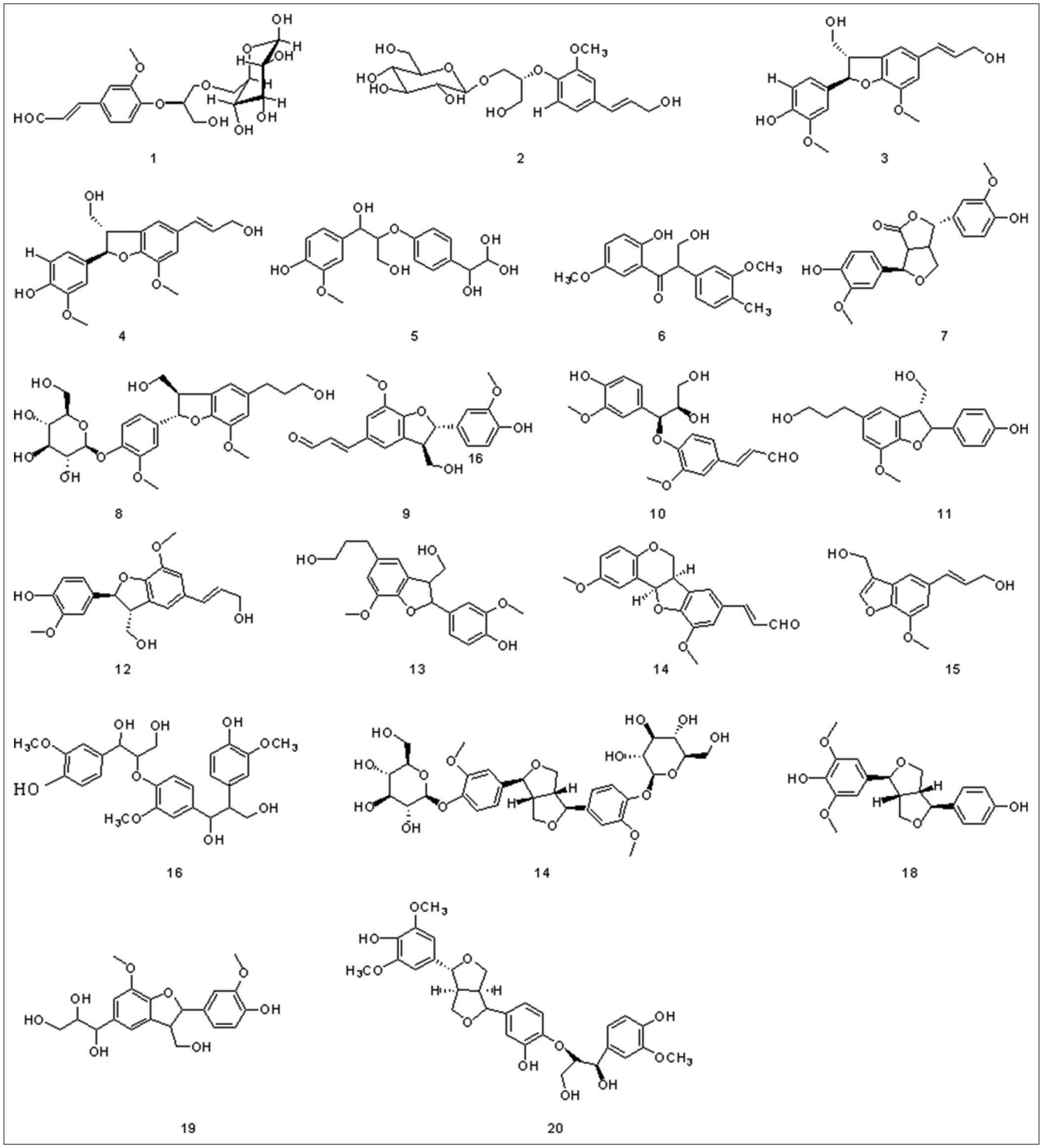

Figure 5: Chemical structure of lignanoids reported from *Xanthii Fructus*

confusion, coma, cerebral edema, and aphasia; fourth, damage to the cardiovascular system includes chest tightness, shortness of breath, decreased blood pressure, arrhythmia, and atrioventricular block; fifth, urinary system toxicity is characterized by edema, oliguria, urinary closure, hematuria, urinary incontinence, renal dysfunction, and acute renal failure; sixth, adverse effects of XF on the respiratory system include dyspnea, irregular respiratory rhythms, and pulmonary edema; and seventh, damage to the hematopoietic system involves thrombocytopenic purpura, gingival bleeding, and cutaneous mucosal bleeding. Other side effects include neuroedema, nosebleed, lip swelling, hoarseness, and difficulty swallowing.

Processing and Reducing Toxicity

XF is toxic to many organs, especially the liver and kidney.[66,101]

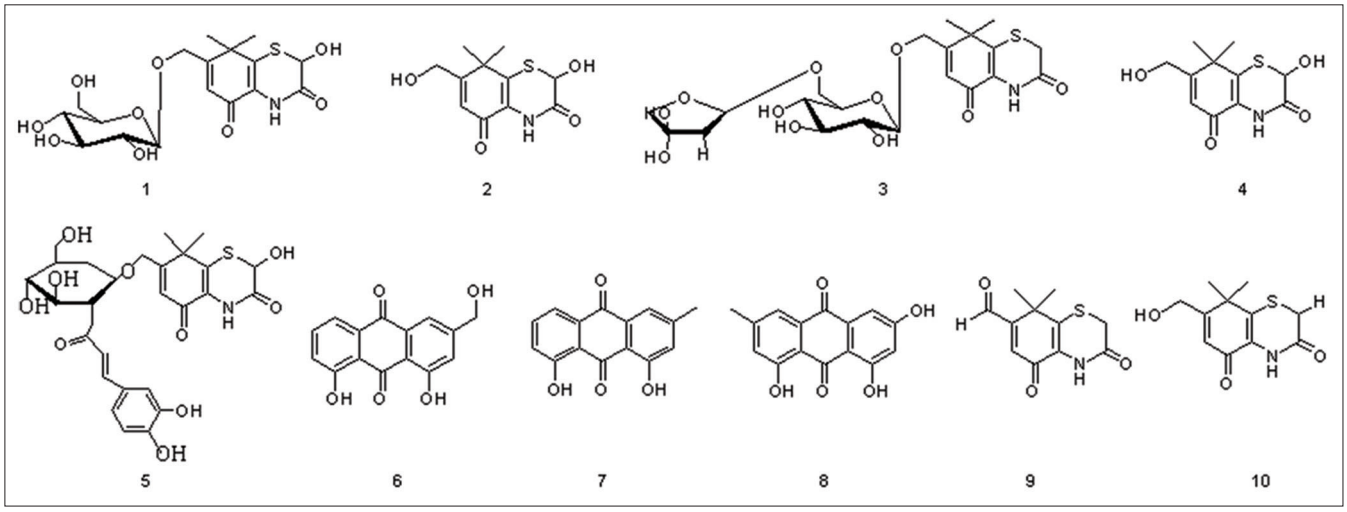

Figure 6: Chemical structure of thiazides reported from *Xanthii Fructus*

Because processing can reduce the toxicity of XF, clinical use generally involves processed products of XF.[23] In the Liu and Song dynasties of the southern and northern dynasties of China, XF was steamed with *Polygonatum sibiricum* (Thunder Lord). The Tang Dynasty employed a method of burning ashes. In the Song Dynasty of China, methods such as burning ashes, stir-frying (Shenghuifang), stir-frying incense to stab (certificate type), and baking (First aid) are recorded. In the Ming Dynasty of China, stir-fry and steaming were commonly used, such as pastry (Puji formula), micro stir-fry (medicine), steaming with *P. sibiricum* juice (introduction), single steaming (Dafa), stir-fry to remove thorns, and wine mix steaming (Chengya). The Qing Dynasty of China used methods such as stir-frying and smashing (the law), and stir-frying, stir-frying with wine (Materia Medica). Presently, XF processing technology is generally divided into net and frying processes.[99] The cleaning process refers to the removal of cockle thorns and impurities. Common methods for the frying process include the clear frying method and the blanching method.[102] During this process, the blanching method is generally selected.[103-106] The optimal way to prepare XF to reduce its toxicity is to fry it and then grind the spines. For clinical use, it must be fried until brown to reduce toxicity.[107]

The chemical composition and pharmacological action of XF also change substantially before and after processing.

For phenolic acid, the content of total phenolic acid in XF was significantly different with different processing temperatures and times, and the content ranged from 7.99 to 9.69 mg/g. The contents of new chlorogenic acid, chlorogenic acid, 1,5-dicaffeinic acid, and total phenolic acid in the decoction of XF after frying increased with increasing preparation temperature.[108,109]

For volatile and fatty oils, the content of fatty oil was significantly higher than that of crude oil, but the physical constant changed little, and the specific gravity and acid values decreased slightly upon processing. Woody *et al*. (2013) qualitatively analyzed the changes in volatile oil and fat oil before and after processing of XF by GC-MS. The volatile oil in the raw products of XF included 18 chemical constituents, and the volatile oil in the fried products of XF included 13 chemical constituents. Four components of XF were identified in raw and fried fat oil. The results showed that the chemical composition of volatile oil was different before and after processing, while the composition of fat oil was not changed.[110]

For water-soluble glycosides and mixed protein, Han (2014) found that the rate of XF seed protein extraction had significantly reduced after frying.[111] Duorui *et al*. (2013) found that the content of hydroxy atractylodes decreased to 10% after XF was fried to yellow. During the frying process, hydroxy atractylodes were converted to atractylodes, and no carboxyl atractylodes were present after XF was fried to char. Moreover, atractylodes increased at temperatures of 140°C–260°C and decreased at temperatures above 260°C.

In 2008, Chen Daihong showed that processing could increase the analgesic effect and reduce drug toxicity.[43] In 2012, Wu Hui compared differences in the toxicity of toxic parts before and after frying by means of an acute toxicity pharmacological test in mice, and showed that the fried products of xanthium have reduced toxicity.[56] Zhao *et al*. showed that a water decoction and fatty oil emulsion of XF were more effective than the raw products against *S. aureus* and *Pneumococcus*.[112] In 2016, the anti-inflammatory effects of raw XF seed products were found to exceed those of fried products, and the effects of processed drugs on blood glucose lowering were better than those of raw products.[43] There was no significant difference between raw and fried xanthium in terms of blood glucose lowering.[113]

XF presents reduced toxicity after stir-frying. Therefore, XF should be used for medicinal purposes after stir-frying, but the temperature should be controlled strictly to prevent the loss of efficacy.

Future Perspectives and Conclusions

XF has been used for years in China as a drug to treat sinusitis. To date, national and international scientists have isolated 100 chemical components from XF. The pharmacological activities of its chemical components have mainly focused on phenylpropanoids and sesquiterpenoids, while studies on lignanoids and thiazides are relatively rare. In addition, the decreased toxicity of XF before and after processing may be related to changes in the chemical composition; however, experimental evidence to support this is lacking. In this article, the chemical components of XF are summarized, which is expected to be helpful for the research and development of new drugs, especially in terms of its pharmacodynamics and structure–activity relationship.

In terms of pharmacology, XF is often used in the clinical treatment of allergic diseases, suggesting that it may have immunosuppressive and anti-allergy effects; however, there has been no reasonable explanation to explain its clinical efficacy. Network pharmacology is commonly used to analyze the mechanism of action of XF, and may represent a suitable method for studies on its mechanism of action. At the same time, researchers should perform further *in vitro* and *in vivo* experiments to elucidate the full therapeutic potential of XF.

With the development of natural medicinal chemistry, more attention must be paid to TCM. XF contains abundant medicinal plant resources and is widely distributed in China. In this article, the chemical components, analytical methods, pharmacological effects, clinical application, toxicity, and processing technology of XF are systematically reviewed, and some issues that need to be overcome are discussed, in order to provide a direction for the future study of XF.

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Availability of data and materials

All reported or analyzed data in this review were extracted from published articles.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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