Review

Traditional Uses, Botany, Phytochemistry, Pharmacology, Pharmacokinetics and Toxicology of Xanthium strumarium L.: A Review

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Received: 28 December 2018; Accepted: 16 January 2019; Published: 19 January 2019

Abstract: Xanthium strumarium L. (Asteraceae) is a common and well-known traditional Chinese herbal medicine usually named Cang-Er-Zi, and has been used for thousands of years in China. The purpose of this paper is to summarize the progress of modern research, and provide a systematic review on the traditional usages, botany, phytochemistry, pharmacology, pharmacokinetics, and toxicology of the X. strumarium. Moreover, an in-depth discussion of some valuable issues and possible development for future research on this plant is also given. X. strumarium, as a traditional herbal medicine, has been extensively applied to treat many diseases, such as rhinitis, nasal sinusitis, headache, gastric ulcer, urticaria, rheumatism bacterial, fungal infections and arthritis. Up to now, more than 170 chemical constituents have been isolated and identified from X. strumarium, including sesquiterpenoids, phenols, glycoside, alkaloids, fatty acid and others [4]. In addition, increasing evidence has indicated that X. strumarium possesses a wide spectrum of pharmacological activities including anti-allergic rhinitis (AR) effects, anti-tumor effects, anti-inflammatory and analgesic effects, insecticide and antiparasitic effects, antioxidant effects, antibacterial and antifungal effects, antidiabetic effects, antilipidemic effects and antiviral effects. However, further research should focus on investigating bioactive compounds and demonstrate the mechanism of its detoxification, and more reasonable quality control standards for X. strumarium should also be established.

Keywords: Xanthium strumarium L.; traditional usages; botany; phytochemistry; pharmacology; pharmacokinetics; toxicology

1. Introduction

Since 1963, the fruits of Xanthium strumarium L. have been listed in the Pharmacopoeia of the People’s Republic of China (CH.P.), and currently over 60 formulas containing the fruits of X. strumarium have been applied for treating various diseases, including rhinitis, nasal sinusitis, headache, gastric ulcer, urticarial, rheumatism, bacterial and fungal infections, and arthritis [1–3]. So far, many studies have been devoted to the pharmacological and phytochemical studies of X. strumarium, and more than 170 chemical compounds have been isolated and identified from this plant, including sesquiterpene lactones, phenols, glycoside, alkaloids, fatty acid and others [4]. In addition, increasing evidence has indicated that X. strumarium possesses a wide spectrum of pharmacological activities including...
analgesic and anti-inflammatory, antioxidant, hypoglycemic, anti-cancer, antibacterial and antifungal, anti-trypanosomal, anti-tussive activities, and effects on nervous and digestive systems, as well as other effects [1]. Nowadays, the fruits of *X. strumarium* remains a common Traditional Chinese Medicine (TCM) listed in the C.H.P, and atractyloside and chlorogenic acid are used as the quality indicator agents for evaluating quality of the fruits of *X. strumarium* [5].

In this paper, we systematically summarize the traditional uses, botany, phytochemistry, pharmacology, pharmacokinetics as well as the safety aspects of *X. strumarium*, hoping that it could propel the research forward for applying the medicinal values of this plant completely. Moreover, potential research directions and emphasis on *Xanthium strumarium* L. are discussed as well.

2. Traditional Usages

*X. strumarium* has a long history for utilization as a medicinal plant in China due to its extensive biological and pharmacological activities. In particular, the fruit is the predominant medicinal part of *X. strumarium*, and is one of the most common used herbal medicines to treat rhinitis and headache for thousands years [6]. Before clinical use, the fruits of *X. strumarium* are often processed by stir-baking to a yellowish color, which aims to reduce toxicity and enhance efficacy. The first record of the pharmacological effects of this plant can be traced back to ShenNong BenCaoJing, which is the earliest monograph of TCM during the Eastern Han dynasty. In this monograph, it was used for the treatment of anemofrigid headache and rheumatic arthralgia. Then, in Mingyi Bielu which is another known TCM monograph, *X. strumarium* was recorded as an effective herbal medicine with the function of curing gonyalgalia. In Yaoxinglun, *X. strumarium* was described as an agent for treating hepatic heat and eye diseases. Subsequently, another famous monograph, Xinxiu Bencao, described *X. strumarium* with improving eyesight, antiepileptic and anti-inflammatory properties. Besides, *X. strumarium* was also listed in some other classical monographs of materia medica in China, such as Bencao Shiyi, Bencao Mengquan, Depei Bencao, Caomu Bianfang, Tianbao Bencao and others.

Currently, the fruits of *X. strumarium* have become an important traditional Chinese medicine commonly used in clinic for the treatment of nasal diseases (including acute and chronic rhinitis, allergic rhinitis (AR), nasosinusitis, and nasal obstruction), itching diseases, and painful diseases. In order to meet clinical needs better, various forms of formulas are developed, such as pills, tablets, granules, oral liquid, powders and others (Table 1). Furthermore, in India, *X. strumarium*, commonly known as Chotagokhru or Chotadhatura, are usually used to cure leucoderma, poisonous bites of insects, epilepsy, and biliousness [7]. In addition, several North American Indian tribes and Zuni tribes apply this plant to relieve constipation, diarrhoea and vomiting [1]. Besides, *X. strumarium* is also reported as a folk herbal medicine in Bangladesh for the treatment of urinary disorder, ear infection, diabetic, and gastric disorder [8].

Apart from clinical application, its potential capacity as a biodiesel feedstock has been proven. *X. strumarium* has very strong environmental adaptability and thus has numerous wild resources. The seed has a high oil content (42.34%) which gives potential annual output of 100,000 tons just in China [9]. Furthermore, the research in Pakistan also found the prospects of non-edible seed oils for use as biodiesel to solve the serious energy crisis [10].

**Table 1.** The traditional and clinical uses of *Xanthium strumarium* in China.

| Preparation Name | Main Compositions | Traditional and Clinical Uses | References |
|------------------|-------------------|------------------------------|------------|
| Li Bi Tablets    | Xanthii Fructus, Scutellariae Radix, Magnoliae Flos, Menthae Haplocalycis Herba, Angelicae Dahuricae Radix, Asar Radix Et Rhizoma, Taraxaci Herba | Curing common cold with nasal obstruction, nasosinusitis, turbid nasal discharge | “Chinese Pharmacopoeia (2010)” a |
| Shuang Xin Bi Dou Yan Ke Li | Xanthii Fructus, Magnoliae Flos, Angelicae Dahuricae Radix, Asar Radix Et Rhizoma, Lonicerae Japonicae Flos, Lonicerae Japonicae Caulis, Taraxaci Herba, Glycyrrhizae Radix Et Rhizoma, Platycodonis Radix, Chrysanthemi Flos, Scutellariae Radix, Paoniae Radix Rubra, Coicis Semen, Rehmanniae Radix | Treating nasosinusitis | “Guo Jia Zhong Cheng Yao Biao Zun” b |
| Preparation Name | Main Compositions | Traditional and Clinical Uses | References |
|------------------|-------------------|------------------------------|------------|
| Xiao Er Bi Yan Tablets | Xanthii Fructus, Ligustici Rhizoma Et Radix, Saposhnikoviae Radix, Angelicae Dahuricae Radix, Polygony Tintori Foliu, Taraxaci Herba, Cnicifugae Rhizoma, Glycyrrhizae Radix Et Rhizoma | Curing chronic rhinitis of child | “Zhong Yao Cheng Fang Zhi Ji” c |
| Yu Yuan Wan | Xanthii Fructus, Scutellariae Radix, Gardeniae Fructus, Schrophulariae Radix, Magnoliae Flos, Ophiopogonis Radix, Lycii Cortex, Paonae Radix Rubra, Forsythiae Fructus, Angelicae Dahuricae Radix, Menthae Haplocalyx Herba, Schizonepetae Herba, Glycyrrhizae Radix Et Rhizoma, Platycodonis Radix | Treating redness and swelling of the nostrils, swelling and pain in throat | “Zhong Yao Cheng Fang Zhi Ji” c |
| Yi Xuan Ning Jiao Nang | Xanthii Fructus, Chrysanthemi Flos, Arisaema Cum Bile, Scutellariae Radix, Bambusae Caulyis in Taenias, Ostreae Concha, Crataege Fructus, Citri Reticulatae Pericarpium, Paonae Radix Alba Poria, Lycii Fructus | Treating hyperactivity of liver-yang, vertigo due to deficiency of Qi and blood | “Xin Yao Zhuan Zheng Biao Zhum” d |
| Qing Re Zhi Ke Li | Xanthii Fructus, Scutellariae Radix, Fritillariae Thunbergii Bulbus, Paridis Rhizoma, Commelinae Herba, Anemarrhenae Rhizoma, Gypsum Fibrosum, Citri Reticulatae Pericarpium, Auranti Fructus, Armeniacae Semen Amarum, Platycodonis Radix | Curing cough, phlegm, fever, pharyngalgia, thirst, chest tightness, dry stool, yellow urine due to pulmonary retention of phlegmoperiyxia; acute bronchitis, acute exacerbation of chronic bronchitis | “Xin Yao Zhuan Zheng Biao Zhum” d |
| Di Tong Bi Yan Liquid | Xanthii Fructus, Taraxaci Herba, Asari Radix Et Rhizoma, Scutellariae Radix, Ephedrae Radix, Acori Tatarinowii Rhizoma, Angelicae Dahuricae Radix, Magnoliae Flos | Curing common cold with nasal obstruction, chronic rhinitis, allergic rhinitis, nasosinusitis | “Zhong Yao Cheng Fang Zhi Ji” c |
| Di Tong Bi Yan Liquid Pen Wu Ji | Xanthii Fructus, Scutellariae Radix, Taraxaci Herba, Ephedrae Radix, Magnoliae Flos, Angelicae Dahuricae Radix, Asari Radix Et Rhizoma, Acori Tatarinowii Rhizoma | Curing common cold with nasal obstruction, chronic rhinitis, allergic rhinitis, nasosinusitis | “Xin Yao Zhuan Zheng Biao Zhum” d |
| Fu Yang Chong Ji | Xanthii Fructus, Chuanxiong Rhizoma, Carthami Flos, Kochiae Fructus | Treating pruritus, eczema, urticaria | “Zhong Yao Cheng Fang Zhi Ji” c |
| Dan Xiang Bi Yan Tablets | Xanthii Fructus, Pogostemonis Herba, Angelicae Dahuricae Radix, Centipedi Herba, Schizonepetae Herba, Lonicerae Japonicae Flos, Chrysanthemi Indici Flos | Curing chronic simple rhinitis, allergic rhinitis, acute and chronic rhinitis, and nasosinusitis | “Zhong Yao Cheng Fang Zhi Ji” c |
| Nao Ning Tablets | Xanthii Fructus, Polygona Rhizoma, Epimedi Foliu, Ophiopogonis Radix, Ginseng Radix Et Rhizoma Rubra, Polygalae Radix, Ziziphi Spinose Semen, Schisandrae Chinensis Fructus, Lycii Fructus, Cervi Cornus Pantotrichum, Testudinis Carapax Et Plastrum, Poria, Jujubae Fructus, Rehmanniae Radix Praeparata, Cervi Cornus Colla | Curing neurasthenia, forgetfulness and insomnia, dizziness and palpitation, weariness of body, weak heat and spontaneous perspiration, impotence and spermatorrhea | “Zhong Yao Cheng Fang Zhi Ji” c |
| Nao Ning Su Tablets | Xanthii Fructus, Polygona Rhizoma, Lycii Fructus, Poria, Epimedi Foliu, Polygalae Radix, Jujubae Fructus, Schisandrae Chinensis Fructus, Ziziphi Spinose Semen, Ophiopogonis Radix, Testudinis Carapax Et Plastrum, Cervi Cornus Pantotrichum, Cervi Cornus Colla, Rehmanniae Radix Praeparata, Ginseng Radix Et Rhizoma | Curing neurasthenia, forgetfulness and insomnia, dizziness and palpitation, weariness of body, weak heat and spontaneous perspiration, impotence and spermatorrhea | “Zhong Yao Cheng Fang Zhi Ji” c |
| Qin Zhi Bi Yan Tang Jiang | Xanthii Fructus, Scutellariae Radix, Angelicae Dahuricae Radix, Ephedrae Herba, Magnoliae Flos, Centipedi Herba, Menthae Haplocalyx Herba | Treating acute rhinitis | “Chinese Pharmacopoeia (2015)” a |
| Cang Yi Di Bi You | Xanthii Fructus, Angelicae Dahuricae Radix, Borneolum Syntheticum | Curing nasosinusitis, nasal obstruction and runny nose | “Zhong Yao Cheng Fang Zhi Ji” c |
| Cang Xin Qi Wu Ji | Xanthii Fructus, Magnoliae Flos, Asari Radix Et Rhizoma, Angelicae Dahuricae Radix, Copidis Rhizoma | Curing nasal obstruction, rhinocenesus, sneeze, allergic rhinitis, acute and chronic rhinitis | “Guo Jia Zhong Cheng Yao Biao Zhum” b |
| Xin Yi Bi Yan Pills | Xanthii Fructus, Magnoliae Flos, Menthae Haplocalyx Herba, Perillae Foliu, Glycyrrhizae Radix Et Rhizoma, Pogostemonis Herba, Centipedi Herba, Satidis Radix, Angelicae Dahuricae Radix, Saposhnikoviae Radix, Houttuyniae Herba, Chrysantheni Flos | Treating allergic rhinitis, chronic rhinitis, nervous headache, cold and rhinorrhea, nasal obstruction | “Zhong Yao Cheng Fang Zhi Ji” c |
| Xin Qin Chong Ji | Xanthii Fructus, Asari Radix Et Rhizoma, Scutellariae Radix, Schizonepetae Herba, Saposhnikoviae Radix, Angelicae Dahuricae Radix, Astragli Radix, Atractylodis Macrocephalae Rhizoma, Cinnamomi Ramulus, Acori Tatarinowii Rhizoma | Curing allergic rhinitis due to deficiency of lung qi | “Zhong Yao Cheng Fang Zhi Ji” c |
| Preparation Name | Main Compositions | Traditional and Clinical Uses | References |
|------------------|-------------------|-------------------------------|------------|
| Xin Qin Tablets  | Xanthii Fructus, Asari Radix Et Rhizoma, Scutellariae Radix, Schizonepetae Herba, Saposhnikoviae Radix, Angelicae Dahuricae Radix, Astragali Radix, Atractylodis Macrocephalae Rhizoma, Cinnamomum Ramulus | Curing allergic rhinitis, deficiency of lung qi, exogenous pathogenic wind | “Xin Yao Zhuan Zheng Biao Zhun” d |
| Xin Qin Ke Li    | Xanthii Fructus, Asari Radix Et Rhizoma, Scutellariae Radix, Schizonepetae Herba, Saposhnikoviae Radix, Angelicae Dahuricae Radix, Astragali Radix, Atractylodis Macrocephalae Rhizoma, Cinnamomum Ramulus, Acori Tatarinovii Rhizoma | Curing rhinocnesmus, sneeze, rhinorrhea, cold, allergic rhinitis | “Chinese Pharmacopoeia (2010)” a |
| Tong Qiao Bi Yan Tablets | Xanthii Fructus, Saposhnikoviae Radix, Astragali Radix, Magnoliae Flos, Atractylodis Macrocephalae Rhizoma, Menthae Haplocalycis Herba | Curing nasal obstruction, rhinorrhea, rhinocnesmus, forehead headache, chronic rhinitis, allergic rhinitis, nasosinusitis | “Chinese Pharmacopoeia (2010)” a |
| Tong Qiao Bi Yan Jiao Nang | Xanthii Fructus, Saposhnikoviae Radix, Astragali Radix, Magnoliae Flos, Atractylodis Macrocephalae Rhizoma, Menthae Haplocalycis Herba | Curing nasal obstruction, rhinorrhea, rhinocnesmus, forehead headache, chronic rhinitis, allergic rhinitis, nasosinusitis | “Xin Yao Zhuan Zheng Biao Zhun” d |
| Tong Qiao Bi Yan Ke Li | Xanthii Fructus, Astragali Radix, Magnoliae Flos, Atractylodis Macrocephalae Rhizoma, Menthae Haplocalycis Herba | Curing nasal obstruction, rhinorrhea, rhinocnesmus, forehead headache, chronic rhinitis, allergic rhinitis, nasosinusitis | “Chinese Pharmacopoeia (2015)” a |
| Fang Zhi Bi Yan Tablets | Xanthii Fructus, Chrysanthemi Indici Flos, Centipedeae Herba, Angelicae Dahuricae Radix, Saposhnikoviae Radix, Xanthii Fructus, Astragali Radix, Ephedrae Herba, Paeoniae Radix Alba, Arisaema Cum Bile, Glycyrrhize Radix Et Rhizoma, Tribuli Fructus | Curing sneeze, nasal obstruction, headache, allergic rhinitis, nasosinusitis | “Zhong Yao Cheng Fang Zhi Ji” c |
| Bi Yan Qing Du Ji | Xanthii Fructus, Chrysanthemi Indici Flos, Paridis Rhizoma, Zanthoxyli Radix, Prunellae Spica, Gentianae Radix Et Rhizoma, Codonopsis Radix | Treating chronic inflammation of nasopharynx, swelling and pain in throat | “Zhong Yao Cheng Fang Zhi Ji” c |
| Bi Yan Qing Du Ke Li | Xanthii Fructus, Chrysanthemi Indici Flos, Paridis Rhizoma, Zanthoxyli Radix, Prunellae Spica, Gentianae Radix Et Rhizoma, Codonopsis Radix | Treating chronic inflammation of nasopharynx | “Chinese Pharmacopoeia (2015)” a |
| Bi Yuan Pills | Xanthii Fructus, Magnoliae Flos, Lonicerae Japonicae Flos, Rubiae Radix Et Rhizoma, Chrysanthemi Indici Flos | Curing nasal obstruction, nasosinusitis, ventilation lack, rhinorrhea, anosmia, headache, pain of superciliary ridge | “Chinese Pharmacopoeia (2010)” a |
| Bi Yuan He Ji | Xanthii Fructus, Magnoliae Flos, Lonicerae Japonicae Flos, Rubiae Radix Et Rhizoma, Chrysanthemi Indici Flos | Curing nasal obstruction, nasosinusitis, ventilation lack, rhinorrhea, anosmia, headache, pain of superciliary ridge | “Xin Yao Zhuan Zheng Biao Zhun” d |
| Bi Yuan Tablets | Xanthii Fructus, Magnoliae Flos, Lonicerae Japonicae Flos, Rubiae Radix Et Rhizoma, Chrysanthemi Indici Flos | Curing chronic rhinitis, nasosinusitis | “Zhong Yao Cheng Fang Zhi Ji” c |
| Bi Yuan Shu Kou Fu Ye | Xanthii Fructus, Magnoliae Flos, Menthae Haplocalycis Herba, Angelicae Dahuricae Radix, Scutellariae Radix, Gardeniae Fructus, Bupleuri Radis, Asari Radix Et Rhizoma, Chuanxiong Rhizoma, Astragali Radix, Clematidis Armandii Caulis, Platycodonis Radix, Poria | Curing rhinitis, nasosinusitis | “Chinese Pharmacopoeia (2010)” a |
| Bi Yuan Shu Jiao Nang | Xanthii Fructus, Magnoliae Flos, Menthae Haplocalycis Herba, Angelicae Dahuricae Radix, Scutellariae Radix, Gardeniae Fructus, Bupleuri Radis, Asari Radix Et Rhizoma, Chuanxiong Rhizoma, Astragali Radix, Clematidis Armandii Caulis, Platycodonis Radix, Poria | Curing rhinitis, nasosinusitis | “Chinese Pharmacopoeia (2010)” a |
| Bi Yuan Tong Qiao Ke Li | Xanthii Fructus, Magnoliae Flos, Angelicae Dahuricae Radix, Menthae Haplocalycis Herba, Ligustici Rhizoma Et Radix, Scutellariae Radix, Forsythiae Fructus, Chrysanthemi Indici Flos, Trichosanthis Radix, Paeoniae Radix Alba, Artemisiae Salviae Miltiorrhizae Radix Et Rhizoma, Poria, Glycyrrhize Radix Et Rhizoma | Curing acute nasosinusitis, nasal obstruction, headache, fever | “Chinese Pharmacopoeia (2015)” a |
| Bi Yan Ling Pills | Xanthii Fructus, Magnoliae Flos, Angelicae Dahuricae Radix, Asari Radix Et Rhizoma, Scutellariae Radix, Fritillariae Cirrhosae Bulbus, Sojaee Semen Praeparatum | Curing nasosinusitis, nasal obstruction, chronic rhinitis | “Zhong Yao Cheng Fang Zhi Ji” c |
| Bi Yan Ling Tablets | Xanthii Fructus, Magnoliae Flos, Angelicae Dahuricae Radix, Asari Radix Et Rhizoma, Scutellariae Radix, Fritillariae Cirrhosae Bulbus, Sojaee Semen Praeparatum | Treating chronic nasosinusitis, rhinitis, nasal obstruction and headache, anosmia | “Zhong Yao Cheng Fang Zhi Ji” c |
The capitula are discoid, whose female (proximal) or functionally male (distal) are in racemiform enclosed in the hardened involucre, with two hooked beaks and hooked bristles [11,12]. Male capitula are saucer-shaped, 3–5 mm in diameter. The achenes are black, fusiform, obovoid, and both surfaces are hirtellous or strigose, usually with gland-dotted, margin entire or toothed. The capitula are discoid, whose female (proximal) or functionally male (distal) are in racemiform enclosed in the hardened involucre, with two hooked beaks and hooked bristles [11,12]. Male capitula are saucer-shaped, 3–5 mm in diameter. The achenes are black, fusiform, obovoid, and both surfaces are hirtellous or strigose, usually with gland-dotted, margin entire or toothed.

### 3. Botany

_Xanthium_, belonging to the Asteraceae family, is a taxonomically complex genus, which includes more than 20 species in the world and three species and one varietas in China [8]. _Xanthium strumarium_ L. (Figure 1) is an annual herb approximately 20–90 cm in height, its stems are erect, branched, often speckled with purple and have short white hairs scattered across the surface. Leaves are green, cauline, mostly alternate (proximal 2–6 sometimes opposite) with petiole, which are 5–20 cm long and 4–16 cm wide; the shape of blades are lanceolate, linear, ovate, orbicular-deltate, or suborbicular, and both surfaces are hirtellous or strigose, usually with gland-dotted, margin entire or toothed. The capitula are discoid, whose female (proximal) or functionally male (distal) are in racemiform to spiciform arrays or borne singly (in axils). The female capitula are elliptic, 2–5 mm in diameter; Male capitula are saucer-shaped, 3–5 mm in diameter. The achenes are black, fusiform, obovoid, enclosed in the hardened involucre, with two hooked beaks and hooked bristles [11,12].

![Figure 1. Xanthium strumarium L. A–D represent the whole plants (A), leaves (B), inflorescence (C) and fruits (D) of X. strumarium L.](image)
This plant is widely distributed all over the world, including Russia, Iran, India, North Korea and Japan. It is native to China and widely distributed in the area of Northeast China, Southwest China, North China, East China and South China. It often grows in plains, hills, mountains and wilderness roadsides. The flowering time ranges from July to August, and fruiting stage lasts from September to October in China [1].

4. Phytochemistry

So far, many phytochemical studies of *X. strumarium* have been conducted, and more than 170 compounds have been isolated and identified from this plant. Among them, sesquiterpenes and phenylpropanoids are the most abundant and major bioactive constituents in *X. strumarium*, and are considered as the characteristic constituents of this plant. In addition to the chemical constituents found in fruits, constituents in other parts of *X. strumarium* were also comprehensively reported, including leaves, roots and stems, etc. In this section, the identified compounds are listed in the following table and the corresponding structures are also comprehensively presented. (Table 2, Figures 2–12).

### Table 2. Chemical constituents isolated from *X. strumarium*.

| Classification | No. | Chemical Component | Part of Plant | Reference |
|----------------|-----|--------------------|---------------|-----------|
|                 | 1   | sibirolide A       | Fruits        | [13]      |
|                 | 2   | sibirolide B       | Fruits        | [13]      |
|                 | 3   | norxanthantolide A | Fruits        | [13]      |
|                 | 4   | norxanthantolide B | Fruits        | [13]      |
|                 | 5   | norxanthantolide C | Fruits        | [13]      |
|                 | 6   | norxanthantolide D | Fruits        | [13]      |
|                 | 7   | norxanthantolide E | Fruits        | [13]      |
|                 | 8   | norxanthantolide F | Fruits        | [13]      |
|                 | 9   | 1β-hydroxy-5α-chloro-8-epi-xanthatin | Aerial parts | [14]      |
|                 | 10  | 11α,13-dihydro-8-epi-xanthatin | Aerial parts | [14]      |
|                 | 11  | xanthinin          | Leaves        | [15]      |
|                 | 12  | xanthumin          | Leaves        | [15]      |
|                 | 13  | xanthanol          | Leaves        | [15]      |
|                 | 14  | xanthanol Acetate  | Leaves        | [15]      |
|                 | 15  | iso xanthanol      | Leaves        | [15]      |
|                 | 16  | xanthumanol        | Leaves        | [16]      |
|                 | 17  | deacetoxylxanthumin| Leaves        | [16]      |
|                 | 18  | xanthatin          | Leaves        | [16]      |
|                 | 19  | xanthinosin        | Leaves        | [16]      |
|                 | 20  | tomentosin         | Leaves        | [17]      |
|                 | 21  | 8-epi-tomentosin   | Leaves        | [17]      |
|                 | 22  | 11α,13-dihydroxanthuminol | Leaves | [18]      |
|                 | 23  | desacetylxantholin  | Leaves        | [18]      |
|                 | 24  | (2E,4E,1'S,5'S,6'R)-dihydrophaseic acid | Fruits | [19]      |
|                 | 25  | 8-epi-xanthatin    | Aerial parts  | [20]      |
|                 | 26  | 2-hydroxy xanthinosin | Aerial parts | [21]      |
|                 | 27  | lasidiol p-methoxybenzoate | Leaves | [18]      |
|                 | 28  | 1β, 4β, 4α,5α-diepoxyxanth-11(13)-en-12-oic acid | Aerial parts | [22]      |
|                 | 29  | 11α,13-dihydroxanthatin | Aerial parts | [22]      |
|                 | 30  | 4β,5β-epoxyxanth-11(13)-en-12-oic acid | Aerial parts | [22]      |
|                 | 31  | 4-epi-xanthanol    | Aerial parts  | [22]      |
|                 | 32  | 4-epi-isoxanthanol  | Aerial parts  | [22]      |
|                 | 33  | 4-oxo-bedfordia acid | Aerial parts | [22]      |
|                 | 34  | 2-hydroxytomentosin | Aerial parts | [20]      |
|                 | 35  | 2-hydroxytomentosin-1β,5β-epoxide | Aerial parts | [20]      |
|                 | 36  | xantholin          | Aerial parts  | [21]      |
|                 | 37  | 6β,9β-dihydroxy-8-epi-xanthatin | Leaves | [21]      |
|                 | 38  | irusoniolide       | Aerial parts  | [21]      |
|                 | 39  | (35S,5R,6R,7E)-5,6-epoxy-3-hydroxy-7-megastigmen-9-one | Fruits | [14]      |
|                 | 40  | pungiolide E       | Aerial parts  | [25]      |
|                 | 41  | pungiolide A       | Aerial parts  | [25]      |
|                 | 42  | pungiolide D       | Aerial parts  | [25]      |
|                 | 43  | 5-azuleneacetic acid | Aerial parts | [21]      |
|                 | 44  | dihydrophaseic acid sodium salt 4’-O-β-D-glucopyranoside | Fruits | [26]      |
|                 | 45  | (35S,5R,6R,7E,9β)-megastigman-7ene-3,5,6,9-tetrol-3-O-β-D-glucopyranoside | Aerial parts | [27]      |

| Classification | No. | Chemical Component | Part of Plant | Reference |
|----------------|-----|--------------------|---------------|-----------|
| Triterpenoids  | 46  | betulinic acid     | Roots         | [28]      |
|                 | 47  | betulin            | Roots         | [28]      |
|                 | 48  | erythrodiol        | Roots         | [28]      |
|                 | 49  | lup-20(29)-en-3β-ol | Aerial parts | [27]      |
| No.  | Classification | Chemical Component | Part of Plant | Reference |
|-----|----------------|-------------------|--------------|-----------|
| 50  | Triterpenoids   | lupenyl acetate   | Aerial parts | [29]      |
| 51  | Triterpenoids   | lupeol acetate    | Whole plants | [30]      |
| 52  | Triterpenoids   | β-amyrin          | Aerial parts | [31]      |
| 53  | Triterpenoids   | oleanolic acid    | Aerial parts | [31]      |
| 54  | Triterpenoids   | α-amyrin          | Leaves       | [32]      |
| 55  | Phenylpropenoids| 1,3,5-tri-O-cafeoylquinic acid | Fruits | [33] |
| 56  | Phenylpropenoids| 3,5-di-O-cafeoylquinic acid | Fruits | [33] |
| 57  | Phenylpropenoids| neochlorogenic acid | Fruits | [34] |
| 58  | Phenylpropenoids| 1,3-di-O-cafeoylquinic acid | Fruits | [34] |
| 59  | Phenylpropenoids| methyl-3,5-di-O-cafeoylquinic acid | Fruits | [34] |
| 60  | Phenylpropenoids| chlorogenic acid   | Fruits       | [35]      |
| 61  | Phenylpropenoids| 1,4-di-O-cafeoylquinic acid | Fruits | [35] |
| 62  | Phenylpropenoids| 4,5-di-O-cafeoylquinic acid | Fruits | [35] |
| 63  | Phenylpropenoids| 5-O-cafeoylquinic acid | Fruits | [35] |
| 64  | Phenylpropenoids| 1,5-di-O-cafeoylquinic acid | Fruits | [36] |
| 65  | Phenylpropenoids| 3,4-di-O-cafeoylquinic acid | Fruits | [37] |
| 66  | Phenylpropenoids| 3,5-di-O-cafeoylquinic acid | Fruits | [37] |
| 67  | Phenylpropenoids| 1,4-di-O-cafeoylquinic acid | Fruits | [37] |
| 68  | Phenylpropenoids| 4,5-di-O-cafeoylquinic acid | Fruits | [37] |
| 69  | Phenylpropenoids| 5-O-cafeoylquinic acid | Fruits | [37] |
| 70  | Phenylpropenoids| xanthiazone-(2-O-cafeoyl)-β-D-glucopyranoside | Whole plants | [44] |
| 71  | Phenylpropenoids| rel-(2α,3β,5β)-7-O-methylcedrusin | Fruits | [42] |
| 72  | Phenylpropenoids| caffeic acid choline ester | Fruits | [46] |
| 73  | Phenylpropenoids| 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one | Fruits | [41] |
| 74  | Phenylpropenoids| 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one | Fruits | [41] |
| 75  | Phenylpropenoids| 1,3-propanediol | Fruits | [42] |
| 76  | Phenylpropenoids| 1,5,2R,1,2,6,7-8,9,10-dehydrodiconiferyl alcohol | Fruits | [42] |
| 77  | Phenylpropenoids| 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one | Fruits | [42] |
| 78  | Phenylpropenoids| 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one | Fruits | [42] |
| 79  | Phenylpropenoids| 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-propan-1-one | Fruits | [42] |
| 80  | Phenylpropenoids| xanthiunonic B | Fruits | [40] |
| 81  | Phenylpropenoids| xanthiunonic C | Fruits | [40] |
| 82  | Phenylpropenoids| xanthiunonic D | Fruits | [40] |
| 83  | Phenylpropenoids| xanthiunonic E | Fruits | [40] |
| 84  | Phenylpropenoids| xanthiunonic F | Fruits | [40] |
| 85  | Phenylpropenoids| xanthiunonic G | Fruits | [40] |
| 86  | Phenylpropenoids| xanthiunonic H | Fruits | [40] |
| 87  | Phenylpropenoids| xanthiunonic I | Fruits | [40] |
| 88  | Phenylpropenoids| xanthiunonic J | Fruits | [40] |
| 89  | Phenylpropenoids| xanthiunonic K | Fruits | [40] |
| 90  | Phenylpropenoids| xanthiunonic L | Fruits | [40] |
| 91  | Phenylpropenoids| xanthiunonic M | Fruits | [40] |
| 92  | Phenylpropenoids| xanthiunonic N | Fruits | [40] |
| 93  | Phenylpropenoids| xanthiunonic O | Fruits | [40] |
| 94  | Phenylpropenoids| xanthiunonic P | Fruits | [40] |
| 95  | Phenylpropenoids| xanthiunonic Q | Fruits | [40] |
| 96  | Phenylpropenoids| xanthiunonic R | Fruits | [40] |
| 97  | Phenylpropenoids| xanthiunonic S | Fruits | [40] |
| 98  | Phenylpropenoids| xanthiunonic T | Fruits | [40] |
| 99  | Phenylpropenoids| xanthiunonic U | Fruits | [40] |
| 100 | Phenylpropenoids| xanthiunonic V | Fruits | [40] |
| 101 | Phenylpropenoids| xanthiunonic W | Fruits | [40] |
| 102 | Phenylpropenoids| xanthiunonic X | Fruits | [40] |
| 103 | Phenylpropenoids| xanthiunonic Y | Fruits | [40] |
| 104 | Phenylpropenoids| xanthiunonic Z | Fruits | [40] |
| 105 | Phenylpropenoids| xanthiunonic A | Fruits | [40] |
| 106 | Phenylpropenoids| xanthiunonic B | Fruits | [40] |
| 107 | Phenylpropenoids| xanthiunonic C | Fruits | [40] |
| 108 | Phenylpropenoids| xanthiunonic D | Fruits | [40] |
| 109 | Phenylpropenoids| xanthiunonic E | Fruits | [40] |
| 110 | Phenylpropenoids| xanthiunonic F | Fruits | [40] |
| 111 | Phenylpropenoids| xanthiunonic G | Fruits | [40] |
| 112 | Phenylpropenoids| xanthiunonic H | Fruits | [40] |
Table 2. Cont.

| Classification | No. | Chemical Component | Part of Plant | Reference |
|----------------|-----|--------------------|---------------|-----------|
| Lignanoids     | 113 | 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxypropyl)-2-methoxy]-phenoxo-1,3-propanediol | Fruits | [48] |
|                | 115 | syringaresinol      | Roots         | [39] |
|                | 116 | fructusol A         | Fruits        | [42] |
|                | 117 | balanophonin        | Fruits        | [24] |
|                | 118 | 4-exominoaresinol   | Roots         | [28] |
|                | 119 | pinosinol           | Fruits        | [24] |
| Coumarins      | 120 | jatrocin B          | Roots         | [39] |
|                | 121 | clemsisomin A       | Roots         | [39] |
|                | 122 | clemsisomin C       | Roots         | [39] |
|                | 123 | scopoletin          | Roots         | [39] |
| Coumarins      | 124 | stigmast-4-en-β-ol-3-one | Roots     | [39] |
|                | 125 | β-sitostene         | Roots         | [39] |
|                | 126 | β-sitosterol        | Fruits, Leaves | [39] |
|                | 127 | daucosterol         | Roots         | [39] |
|                | 128 | 5α,8α-epidioxy-2E-ergosta-6,22-dien-3β-ol | Roots | [39] |
|                | 129 | 6β-hydroxy-stigmaster-4,22-dien-3-one | Roots | [28] |
|                | 130 | 6β-hydroxy-stigmaster-4-en-3-one | Roots | [28] |
|                | 131 | 3-oxo-∆4,6-sitostene | Roots     | [28] |
| Steroids       | 132 | β-daucosterol       | Roots         | [28] |
|                | 133 | β-stigmastereol     | Roots         | [28] |
|                | 134 | 7-ketoestisterol     | Roots         | [28] |
|                | 135 | stigmastereol       | Aerial parts  | [31] |
|                | 136 | β-sitosterol-3-O-β-D-glucopyranoside | Aerial parts | [31] |
|                | 137 | ergosterol          | Whole plants  | [30] |
|                | 138 | taraxasteryl acetate | Whole plants | [30] |
|                | 139 | 7α-hydroxy-β-sitosterol (stigmast-5-ene-3β,7α-diol) | Fruits | [24] |
|                | 140 | stigmast-4-ene-3β,6α-diol | Fruits     | [24] |
|                | 141 | 14-methyl-12,13-dehydro-sitosterol-heptadecanone | Leaves   | [32] |
| Glycosides     | 142 | atрактиloside       | Fruits        | [49] |
|                | 143 | carboxyatraktloside | Burns         | [50] |
|                | 144 | 3β-norpinan-2-one-3-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside | Fruits | [41] |
|                | 145 | 8-O-β-D-glucopyranoside | Fruits     | [41] |
|                | 146 | 8-O-β-D-glucopyranoside | Fruits     | [41] |
|                | 147 | 7-[β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl]oxymethyl]-8,9-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione | Fruits | [41] |
|                | 148 | 3′,4′-didesulfated-atрактиloside | Fruits     | [46] |
|                | 149 | 2-methyl-3-buten-2-ol-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside | Fruits | [51] |
|                | 150 | everlastoside C     | Fruits        | [51] |
| Flavonoids     | 151 | ononin              | Fruits        | [43] |
|                | 152 | quercetin           | Fruits        | [37] |
|                | 153 | allopialtin         | Fruits        | [37] |
|                | 154 | patuletin-3-glucuronide | Fruits     | [34] |
| Flavonoids     | 155 | quercetin-3-O-glucuronide | Fruits     | [34] |
|                | 156 | formononemin        | Fruits        | [43] |
| Thiazides      | 157 | xanthiazone         | Fruits        | [36] |
|                | 158 | 2-hydroxy-xanthiazone | Fruits     | [42] |
|                | 159 | 11-O-β-D-glucopyranoside | Fruits     | [43] |
|                | 160 | 2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside | Fruits | [43] |
|                | 161 | 7-Hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione-(2-O-cafeiny)-β-D-glucopyranoside | Fruits | [52] |
| Anthraquinones & naphthoquinones | 162 | xanthaldehyde | Fruits | [53] |
|                | 163 | chrysophanic acid   | Fruits        | [54] |
|                | 164 | emodin              | Fruits        | [54] |
|                | 165 | aloe emodin         | Fruits        | [54] |
|                | 166 | 5-hydroxy-3,6-dimethoxy-7-methyl-1,4-napthalenedione | Roots       | [28] |
| Other compounds | 167 | 5-methyluracil      | Roots         | [39] |
|                | 168 | uracil              | Roots         | [39] |
|                | 169 | sibiricumthionol    | Fruits        | [19] |
|                | 170 | indole-3-carbaldehyde | Fruits     | [45] |
|                | 171 | N-(1′-D-deoxyxylitolyl)-6,7-dimethyl-1,4-dihydro-2,3-quinoxalinedione | Fruits | [38] |
|                | 172 | nonadecanoic acid   | Roots         | [39] |
|                | 173 | hexadecanoic acid   | Leaves        | [32] |
4.1. Sesquiterpenoids and Triterpenoids

Sesquiterpenoids have many important biological functions and physiological activities, which are abundant in *X. strumarium*. Sesquiterpene lactones, the main characteristic components of plants in the Asteraceae family, exhibit strong activities with anti-microbial, antiviral, anti-tumor and anti-inflammation [55,56]. The predominant sesquiterpene lactones are the guaiane type and seco-guaiane type, of which xanthanolides are the important active constituent. In 2015, eight sesquiterpenes were isolated from the fruits of *X. strumarium*, including sibirolide A (1), sibirolide B (2) and norxanthanolide A–F (3–8) [13]. In addition, 1β-hydroxyl-5α-chloro-8-epi-xanthatin (9) and 11α, 13-dihydro-8-epi-xanthatin (10) were isolated from the aerial parts of *X. strumarium* [14]. Moreover, xanthinin (11), xanthumin (12), xanthanol (13), xanthanol acetate (14), iso-xanthanol (13), xanthumanol (16), de-acetoxyxanthumin (17), xanthatin (18), xanthinosin (19), tomentosin (20) were isolated from the leaves of *X. strumarium* [15,16]. Furthermore, other sesquiterpenoids were isolated and identified from the fruits, leaves and aerial parts of *X. strumarium*, including 8-epi-tomentosin (21) [17], 11α,13-dihydroxanthuminol (22), desacetyl xanthanol (23) [18], (2E,4E,1'S,2'R,4'S,6'R)-dihydrophaseic acid (24) [19], 8-epi-xanthatin (25) [20], 2-hydroxy xanthinosin (26) [21], lasidiol p-methoxybenzoate (27) [18], 1β,4β, 4α,5α-diepoxyxanth-11(13)-en-12-oic acid (28), 11α,13-dihydroxanthatin (29), 4β, 5β-epoxyxanthatin-1α,4α-endoperoxide (30), 4-epi-xantholin (31), 4-epi-isoxantholin (32), 4-oxo-bedfordia acid (33) [22], 2-hydroxytomentosin (34), 2-hydroxytomentosin-1β,5β-epoxide (35) [20], xanthnon (36) [21], 6β,9β-dihydroxy-8-epi-xanthatin (37) [25], inusoniolide (38) [21], (3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmene-9-one (39) [24], pungiolide E (40), pungiolide A (41), pungiolide D (42) [25], 5-azuleneacetic acid sodium salt 4’-O-β-D-glucopyranoside (44) [26], (3S,5R,6R,7E,9S)-megastigman-7ene-3,5,6,9-tetrol-3-O-β-D-glucopyranoside (45) [27].

Triterpenoids are another important kind of biomolecule found in *X. strumarium*. Nine triterpenoids including betulinic acid (46), botulin (47), erythrodiol (48) [28], lup-20(29)-en-3β-ol (49) [27], lupenyl acetate (50) [29], lupeol acetate (51) [30], β-amyrin (52), oleanolic acid (53) [31] and α-amyrin (54) [32] are reported from this plant. The chemical structures of these sesquiterpenoids and triterpenoids isolated from *X. strumarium* are shown in Figures 2 and 3.
β,5β-epoxide (35) [20], xanthnon (36) [21], 6β,9β-dihydroxy-8-epi-xanthatin (37) [25], inusoniolide (38) [21], (3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmene-9-one (39) [24], pungiolide E (40), pungiolide A (41), pungiolide D (42) [25], 5-azuleneacetic acid (43) [21], dihydrophaseic acid sodium salt 4'-O-β-D-glucopyranoside (44) [26], (3S,5R,6R,7E,9S)-megastigman-7ene-3,5,6,9-tetrol-3-O-β-D-glucopyranoside (45) [27].

Triterpenoids are another important kind of biomolecule found in X. strumarium. Nine triterpenoids including betulinic acid (46), botulin (47), erythrodiol (48) [28], lup-20(29)-en-3β-ol (49) [27], lupenyl acetate (50) [29], lupeol acetate (51) [30], β-amyrin (52), oleanolic acid (53) [31] and α-amyrin (54) [32] are reported from this plant. The chemical structures of these sesquiterpenoids and triterpenoids isolated from X. strumarium are shown in Figures 2 and 3.

Figure 2. Cont.
Figure 2. Chemical structures of the sesquiterpenoids in X. strumarium.
Phenylpropanoids are also important active constituents found in *X. strumarium*. To date, 45 phenylpropanoids have been reported in this plant. Phenolic acids, mainly chlorogenic acid, are considered to be the main anti-inflammatory and analgesic active ingredients and the highest content of organic acids [57]. The phenolic acids in *X. strumarium* contain caffeic acid, ferulic acid, and protocatechuic acid, etc. However, studies have shown that factors such as origin, harvesting time, processing time and temperature have obvious effects on the content of phenolic acid in *X. strumarium* [58]. Thirteen caffeoylquinic acids (CQA) derivatives were isolated from *X. strumarium*, including 1,3,5-tri-(4’-hydroxy-3’-methoxy)-1,3-propanediol (75), (4’)-hydroxy-3’-methoxy)-1,3-propanediol (72) [19], isovanillic acid ([36]), protocatechuic acid ([83]) [19], isovanillic acid ([84]) [30], 7-(4-hydroxy-3-methoxyphenyl)-1-phenyleth-4-en-3-one ([85]) [28], xanthiazone-(2-O-cafeoyl)-β-D-glucopyranoside ([86]) [44], rel-(2α,3β)-7-O-methylcedrusin ([87]) [42], caffeic acid choline ester ([88]) [38], icariside
D1 (89) [45], 3-methoxy-4-hydroxy-transcinnamaldehyde (90) [24], methylchlorogenate (91) [46], icariside F2 (92), arbutin (93), coniferine (94) [45], 3-hydroxy-1-(4-hydroxy-phenyl)-propan-1-one (95) [47], ω-hydroxypropioguaiacone (96) [45], caffeic acid ethyl ester (97) [19], 4-hydroxy-3-methoxycinnamaldehyde (98) [37], p-hydroxybenzaldehyde (99) [24], The chemical structures of these phenylpropenoids isolated from X. strumarium are shown in Figure 4.
4.3. Lignanoids and Coumarins

In recent years, some studies found that *X. strumarium* contain lignanoids and coumarins, moreover, 21 lignanoids and four coumarins have been discovered in this plant and are displayed in Figures 5 and 6. In 2017, xanthiumnolic B (100) was found from the fruits of *X. strumarium* and its anti-inflammatory activity has been demonstrated [40]. Later, 14 lignanoids were also isolated from the fruits of *X. strumarium*, including (-)-1-O-β-D-glucopyranosyl-2-{2-methoxy-4-[1-(E)-propen-3-ol]phenoxyl} -propane-3-ol (101), leptolepisol D (102), dihydrodehydrodiconiferyl alcohol (103), chushizisin E (104), (-)-(2R)-1-O-β-D-glucopyranosyl-2-{2-methoxy-4-[Eformylvinyl]phenoxyl}propane-3-ol (105), (-)-7R,8S-dehydrodiconiferyl alcohol (106), (-)-simulanol (107), 2-(4-hydroxy-3-methoxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-1-propanol (108), diospyrosin (109), dehydrodiconiferyl alcohol (110), balanophonin A (111), threo-dihydroxydehydrodiconiferyl alcohol (112), 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxypropyl)-2-methoxy]-phenoxy-1,3-propandiol (113), 7R,8S-dihydrodehydrodiconiferyl alcohol 4-O-β-D-glucopyranoside (114) [48]. Furthermore, syringaresinol (115) [39], fructusol A (116) [42], balanophonin (117) [24], 4-oxopinoresinol (118) [28], pinoresinol (119) [24] were identified from the plant.

In 2011, Kan et al. isolated four coumarins from the roots of *X. strumarium* for the first time, including scopoletin (120), Jatrocin B (121), cleomiscosin A (122), cleomiscosin C (123) [39].
Figure 5. Chemical structures of the lignanoids in *X. strumarium*.

Figure 6. Chemical structures of the coumarins in *X. strumarium*. 
4.4. Steroids

A few studies have been conducted investigating the steroids in *X. strumarium*. In 2010, $\beta$-sitostenone (124), $\beta$-sitosterol (125), daucosterol (126), stigmast-4-en-$\beta$-ol-3-one (127), and 5$\alpha$-$\delta$-epidioxy-22E-ergosta-6,22-dien-3$\beta$-ol (128) were isolated from *X. strumarium* [39]. Furthermore, Chen et al. found 6$\beta$-hydroxy-stigmast-4,22-dien-3-one (129), 6$\beta$-hydroxy-stigmast-4-en-3-one (130), 3-oxo-$\Delta$4,5-sitostenone (131), $\beta$-daucosterol (132), $\beta$-stigmasterol (133) and 7-ketositosterol (134) from the roots of *X. strumarium* [28].

Lately, stigmasterol (135), $\beta$-sitosterol-3-O-$\beta$-D-glucopyranoside (136) [31], ergosterol (137), taraxasteryl acetate (138) [30], 7$\alpha$-hydroxy-$\beta$-sitosterol(stigmast-5-ene-3$\beta$,7$\alpha$-diol) (139), stigmast-4-ene-3$\beta$,6$\alpha$-diol (140) [24] and 14-methyl-12,13-dehydro-sitosterol-heptadecenate (141) [32] were isolated and identified in *X. strumarium*. The chemical structures of these steroids isolated from *X. strumarium* are shown in Figure 7.

![Figure 7. Chemical structures of the steroids in X. strumarium.](image-url)
4.5. Glycosides

In 1962, Song et al. isolated a toxic glycoside component named AA2 from the fruits of X. strumarium, which has been authenticated as atractyloside (142) by Wang in 1983 [49,59]. Subsequently, John et al. found another toxic ingredient known as carboxyatractyloside (143) in 1975 [50]. Research showed that the content of atractyloside in X. strumarium could be reduced after stir-flying, and its toxicity could be reduced. [60] Lately, seven other glycosides were separated from the fruits of X. strumarium, such as 3β-norpinan-2-one 3-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (144), (6Z)-3-hydroxymethyl-7-methylocta-1,6-dien-3-ol 8-O-β-D-glucopyranoside (145), (6E)-3-hydroxymethyl-7-methylocta-1,6-dien-3-ol 8-O-β-D-glucopyranoside (146), 7-[(β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl)oxyethyl]-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione (147) [41], 3′,4′-dedisulphated-tractyloside (148) [46], 2-methyl-3-buten-2-ol-phated-tractylosideimethy-D-glucopyranoside (149), everlastoside C (150) [51], and all glycosides are displayed in Figure 8.

4.6. Flavonoids

Flavonoids are common chemical components in plants all over the world. Six flavonoids including ononin (151) [43], quercetin (152), allopatauletin (153) [37], patuletin-3-glucuronide (154), quercetin-3-O-glucuronide (155) [34], formononetin (156) [43] have been isolated from this plant and are presented in Figure 9.
4.7. Thiazides

To this day, six thiazides from *X. strumarium* have been reported. In 1997, xanthiazone (157) was isolated from the aqueous acetone extract of the fruits [36]. Furthermore, 2-hydroxy-xanthiazone (158) [42], 7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]-thiazine-3,5-dione-11-O-β-D-glucopyranoside (159), 2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside (160) [43], 7-Hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-(2-O-cafeoyl)-β-D-glucopyranoside (161) [52], and xanthialdehyde (162) [53] were identified from this plant (Figure 10).

![Chemical structures of the Thiazides in X. strumarium.](image1)

A few studies have been focused on anthraquinones in *X. strumarium*. In one report in 2005, Huang et al. found chrysophanic acid (163), emodin (164) and aloe emodin (165) in the fruits of *X. strumarium* [54]. Then, the 5-hydroxy-3,6-dimethoxy-7-methyl-1,4-naphthalenedione (166), a new naphthoquinone, was isolated from the roots of *X. strumarium* [28] (Figure 11).

![Chemical structures of the anthraquinones and naphthoquinones in X. strumarium.](image2)
4.8. Other Compounds

Apart from these major types of phytochemical compounds mentioned above, there are some other chemical ingredients isolated from X. strumarium, including 5-methyluracil (167), uracil (168) [39], sibiricumthionol (169) [19], indole-3-carbaldehyde (170) [45], N-(1’-D-deoxyxylitolyl)-6,7-dimethyl-1,4-dihydro-2,3-quinoxalinedione (171) [38], nonadecanoic acid (172) [39], hexadecanoic acid (173) [32] (Figure 12).

5. Pharmacology

5.1. Anti-AR Effect

X. strumarium is a traditional medicine widely used in the treatment of nasal diseases, especially allergic rhinitis (AR). In modern pharmacological study, the mechanism of X. strumarium in treating AR has been studied extensively. In 2003, it was reported that WEX inhibited compound 48/80 (C48/80)-induced systemic anaphylaxis in mice (0.01 to 1 g/kg, p.o.), and the mechanism may be related to the inhibition of histamine and TNF-α released from rat peritoneal mast cells (RPMC) [61,62]. In 2008, Zhao et al. found that WEX (0.25–1 mg/mL) can modulate the human mast cell-mediated and peripheral blood mononuclear cell (PBMNC)-mediated inflammatory and immunological reactions which induced by pro-inflammatory cytokines including interleukin (IL)-4, IL-6, IL-8, GM-CSF and TNF-α [63]. Furthermore, the MEX is found to possess the inhibitory effect on the activation of C48/80 stimulated mast cells, and the mechanism was correlated to inhibit Ca²⁺ uptake and histamine release, and increase cAMP in RPMC [64]. In addition, in 2014, Peng et al. demonstrated that the caffeoylxanthiazonoside (CXT) (5, 10, 20 mg/kg, p.o.) isolated from the fruits of X. strumarium was helpful to alleviate the nasal symptoms of ovalbumin (OVA) induced AR rats via anti-allergic, down-regulating IgE, anti-inflammatory and analgesic properties [65].

5.2. Anti-Tumor Effect

Anti-tumor effects are also regarded as primary pharmacological properties of X. strumarium, and have been extensively investigated in lung cancer, breast cancer, cervical cancer, colon cancer, liver cancer, meningioma, and leukemia.

Tao et al. studied the inhibitory effect of xanthatin (1-40 μM), an active agent in X. strumarium, against lung cancer cells (Cell lines of A549, H1975, H1299, H1650 and HCC827) and its potential mechanisms [66,67]. It found that xanthatin could downregulate the STAT3, GSK3β and β-catenin, moreover, xanthatin could also trigger Chk1-mediated DNA damage and destabilize Cdc25C via lysosomal degradation [66–68]. In 1995, Ahn et al. isolated three cytotoxic compounds from the leaves of X. strumarium, among them, xanthatin and 8-epi-xanthatin possessed obvious anti-tumor activity on A549 cells with IC₅₀ (half maximal inhibitory concentration) values of 1.3 and 1.1 μg/mL, respectively [17]. Later, in 2002, it was reported that 1,8-epi-xanthatin epoxide has notable anti-tumor
effect against A549 cells with IC\textsubscript{50} value of 3.0 \textmu M [69]. Furthermore, Wang et al. and Ferrer et al. reported that 8-epi-xanthatin-1α,5α-epoxide, 1β-hydroxyl-5α-chloro-8-epi-xanthatin and EEXA can inhibit the proliferation of A549 cells (IC\textsubscript{50} = 9.5 \textmu M, 20.7 \textmu M and 52.2 \textmu g/mL, respectively) [25,70].

In 2007, by using CellTiter 96 assay in vitro, Ramiréz-Erosa et al. found that xanthatin and xanthinosin, two sesquiterpene lactones isolated from the burs of X. strumarium, obviously restrain the proliferation of breast cancer MDA-MB-231 cells with the IC\textsubscript{50} values of 13.9 and 4.8 \textmu g/mL, respectively [71]. Furthermore, Takeda et al. studied the mechanism of xanthatin against breast cancer MDA-MB-231 cells in 2011, and the results indicated that xanthatin (5–25 \textmu M) inhibits cell growth via inducing caspase independent cell death which were irrelevant with FTase inhibition [72]. In addition, xanthatin (2.5–10 \textmu M) can also up-regulate GADD45γ tumor suppressor gene, and induce the prolonged expression of c-Fos via N-acetyl-l-cysteine-sensitive mechanism [73,74]. In 2016, the anti-tumor activity of EEXA on MFC7 cells was reported as well, with an IC\textsubscript{50} value of 70.6 \textmu g/mL [70].

In 2015, Vaishnav et al. demonstrated that WEX with a concentration of 12.5–50 \textmu g/mL were able to induce death in HeLa cervical cancer cells by altering the antioxidant levels [75]. Recently, Liu et al. revealed that xanthatin (5–20 \textmu M) targeted the selenocysteine (Sec) residue of thioredoxin reductase (TrxR) and inhibited the enzyme activity irreversibly [76]. Meanwhile, the inhibition of TrxR by xanthatin promoted oxidative stress-mediated apoptosis of HeLa cells.

In 1995, Ahn et al. reported that xanthatin and 8-epi-xanthatin were remarkably cytotoxic to colon cancer HCT-15 cells with ED\textsubscript{50} (median effective dose) values of 1.1 and 0.1 \textmu g/mL, respectively [17]. Later, in 2007, Ramírez-Erosa et al. (2007) found that xanthatin (IC\textsubscript{50} = 6.15 \textmu g/mL) and xanthinosin (IC\textsubscript{50} = 6.15 \textmu g/mL) possessed the function of inhibiting WiDr cells growth [71]. Furthermore, eremophil-1(10),11(13)-dien-12,8β-olide, 8-epi-xanthatin-1β,5β-epoxide and tomentosin were isolated from the aerial parts of X. strumarium, and their anti-tumor activities on BGC-823 cells and KE-97 cells were also determined. The related results showed that the IC\textsubscript{50} values of three compounds on BGC-823 cells are 13.22, 2.43, and 4.54 \textmu M, respectively. Similarly, IC\textsubscript{50} values of three compounds on BGC-823 cells are 4.41, 1.44, and 3.47 \textmu M, respectively [77]. Moreover, Zhang et al. reported that xanthatin (3.9–18.6 \textmu M) inhibited the proliferation of MKN-45 cells by inducing G2/M cell cycle arrest and apoptosis [78]. Later, in 2015, Karmakar et al. found that xanthinosin (8 \textmu M) and lasidiol p-methoxybenzoate (16 \textmu M) potentiate both extrinsic and intrinsic TRAIL-mediated apoptosis pathways and also decreased the level of cell survival protein Bcl-2 in AGS cells [20]. Simultaneously, fructusnoid C (IC\textsubscript{50} = 7.6 \textmu M) also reported to exhibit cytotoxic effects on AGS cells [79]. EEXA and CFEEXA have been identified as the active ingredients against the growth of CT26 cells with IC\textsubscript{50} values of 58.9 and 25.3 \textmu g/mL, respectively [70].

Furthermore, the anti-tumor effects of X. strumarium on liver cancers have also been reported in recent years. In 2013, Wang et al. found that the 1β-hydroxyl-5α-chloro-8-epi-xanthatin possessed significant in vitro cytotoxicity with an IC\textsubscript{50} value of 5.1 \textmu M against SNU387 cells [25]. Later, in 2017, the cytotoxic effects of MEX and EAFMEX on HepG2 cells were verified as LC\textsubscript{50} (Lethal Concentration 50) values of 112.9 and 68.739 \textmu g/mL [80]. Furthermore, Liu et al. demonstrated that xanthatin (5–40 \textmu M) can induce HepG2 cells apoptosis by inhibiting thioredoxin reductase and eliciting oxidative stress [76].

Additionally, an investigation in 1995 indicated that Xanthatin and 8-epi-xanthatin both have cytotoxic effects on SK-MEL-2 cells with ED\textsubscript{50} values 0.5 and 0.2 \textmu g/mL, respectively [17]. In 2012, the EEEXS showed notable inhibitory activity on Mel-Ab cells through downregulation of tyrosinase via GSK3β phosphorylation at concentrations of 1–50 \textmu g/mL [81]. Later, in 2013, Li et al. reported the anti-tumor effects of xanthatin both in vitro and in vivo. Previous results showed that xanthatin (2.5–40 \textmu M) possess a remarkable anti-proliferative effect against B16-F10 cells, and the related mechanism probably associated with activation of Wnt/β-catenin pathway as well as inhibition of angiogenesis. Meanwhile, the in vivo evidence in mice (xanthatin, 0.1–0.4 mg/10 g, i.p.) also verified the results mentioned above [82].
In 1994, DFEEXA was reported to be toxic to leukemia P-388 cells with an IC\(_{50}\) value of 1.64 µg/mL [83]. In addition, results of Nibret et al. showed that xanthatin has significant cytotoxic on HL-60 cells in 2011 [84]. Another report in 2017 reported that both MEX and EAFMEX have inhibitory effects on Jurkat cells, and EAFMEX showed higher toxicity to Jurkat cells when compared to MEX [80]. Besides, in 1995, Ahn et al. found that xanthatin and 8-epi-xanthatin have cytotoxic effects on CNS carcinoma XF-498 cells, and the ED\(_{50}\) values were 1.7 and 1.3 µg/mL, respectively [17]. In 2013, Pan et al. reported that WEX can cause significant cytotoxic effects on arcoma S180 cells in vivo (S180 cells bearing mice, 5–20 g/kg) [85]. The in vitro anti-proliferative activity of CEXR and MEXR on laryngeal cancer HEP-2 cells were implemented at doses of 12.5–100 µg/mL, and the two extracts of X. strumarium showed potent cytotoxic activities against the HEP-2 cells [86].

5.3. Anti-Inflammatory and Analgesic Effects

In 2004, it was reported that WEX (10, 100 and 1000 µg/mL) inhibited inflammatory responses in Lipopolysaccharide (LPS)-stimulated mouse peritoneal macrophages via decreasing IFN-\(\gamma\), LPS-induced NO production and TNF-\(\alpha\) production in a dose dependent manner [87]. Furthermore, in 2005, Kim et al. evaluated the anti-inflammatory and anti-nociceptive activities of MEX both in vitro and in vivo, it showed that the MEX (30, 60 and 90 mg/mL) can down-regulate the production of NO, PGE\(_2\) and TNF-\(\alpha\), and MEX treatment (100 and 200 mg/kg/day, p.o.) clearly reduced carrageenan induced hind paw edema in rats [88]. In addition, MEX (100 and 200 mg/kg/day, p.o.) significantly reduced the amount of writhing induced by acetic acid, and increased jumping response latency in a hot plate test. Later, in 2008, xanthatin and xanthinosin were reported to inhibit LPS-induced inducible nitric oxide synthase and cyclooxygenase-2 (COX-2) expression in microglial BV-2 cells with IC\(_{50}\) values of 0.47 and 11.2 µM, respectively [89]. By using LPS inhibition assay and animal model of inflammation (carrageenan induced hind paw edema), the MEXL (100, 200 and 400 mg/kg) showed obvious anti-inflammatory activity both in vitro (IC\(_{50}\) = 87 µg/mL) and in vivo [90]. A report in 2015 showed that MEXR (50–400 µg/mL) can suppress inflammatory responses via the inhibition of nuclear factor-\(\kappa\)B (NF-\(\kappa\)B) and signal transducer and activator of transcription 3 (STAT3) in LPS-induced murine macrophages [91]. Moreover, the WEX was found to restrain LPS-induced inflammatory responses through suppressing NF-\(\kappa\)B activation, inhibiting JNK/p38 MAPK phosphorylation, and enhancing HO-1 expression in macrophages [92]. In 2016, Hossen et al. demonstrated that the inhibitory effect of MEX on the inflammatory disease possibly related to signaling inhibition of MAPK and AP-1 [93]. In another study, Hossen et al. found the potential anti-inflammatory activity of MEXA on LPS-treated macrophages and an HCl/EtOH-induced mouse model of gastritis by inhibiting PDK1 kinase activity and blocking signaling to its downstream transcription factor, NF-\(\kappa\)B [94]. Later, in 2017, Jiang et al. found a new phenylpropanoid derivative named Xanthiumnolic E isolated from X. strumarium, which has notable inhibitory effect on LPS-induced nitric oxide (NO) production with IC\(_{50}\) value of 8.73 µM [26].

Additionally, X. strumarium was confirmed to inhibit some other kinds of inflammatory and painful diseases. In 2011, Huang et al. suggested that WEX inhibited the development of paw edema induced by carrageenan, and exhibited inhibitory activity on acetic acid effect and reduced the formalin effect at the late-phase (0.1, 0.5 and 1.0 g/kg, p.o.) [95]. In addition, the NFEEX at doses of 0.5, 0.75 and 1.0 mg/ear showed strong anti-inflammatory activity in the croton-oil-induced ear edema test, and reduced the amount of writhing induced by acetic acid in mice in a dose-dependent manner (100, 200 and 400 mg/kg) [96]. A report in 2011 demonstrated the anti-inflammatory activity of xanthatin by inhibiting both PGE\(_2\) synthesis and 5-lipoxygenase activity at doses of 100 and 97 mg/mL, respectively [84]. Furthermore, Park et al. first explained the anti-inflammatory mechanism of EEX, which inhibited TNF-\(\alpha\)/IFN-\(\gamma\)-induced expression of Th2 chemokines (TARC and MDC) by blocking the activation of the NF-\(\kappa\)B, STAT1 and ERK-MAPK pathways in HaCaT keratinocytes [97]. The hot plate test, acetic acid induced writhing test and formalin test were applied to evaluate the analgesic
activity of EEX, and it showed significant analgesic activity at concentrations of 250 and 500 mg/kg body weight [98].

5.4. Insecticide and Antiparasitic Effects

In 1995, Talakal et al. reported that EEXL possess anti-plasmodial activity against *Trypanosoma evansi* both in vitro and in vivo. The EEXL exhibited trypanocidal activity at all the four tested doses at 5, 50, 500 and 1000 µg/mL in vitro, and it can significantly prolong the survival period of the *T. evansi* infected mice at concentrations of 100, 300 and 1000 mg/kg [99]. In 2011, xanthatin was demonstrated to be the dominating insecticidal active compound against *Trypanosoma brucei brucei* with an IC₅₀ value of 2.63mg/mL and a selectivity index of 20 [84]. In addition, Go¨kce et al. showed that MEX exhibited both ingestion toxicity and ovicidal activity to *Paralobesia viteana* with an LC₅₀ of 11.02% (w/w) [100]. In 2012, by using schizont inhibition assay, the anti-plasmodial activity of EEXL against *Plasmodium berghei* was assessed, and it showed significant activity (IC₅₀ = 4 µg/mL) and high selectivity index in vitro [101]. Later, in 2014, Roy et al. found that WEXL had distinct insecticidal properties against *Callosobruchus chinensis* with strong toxicity, repellent properties, inhibited fecundity and adult emergence of the insects at 1%, 2% and 4% concentrations [102]. Moreover, it is reported that EEX revealed anti-nematode activity against *Meloidogyne javanica* in inhibiting egg hatching and inducing mortality among second stage juveniles (J2s) [103]. Furthermore, the effect of MEX on the mortality rates of *Aedes caspius* and *Culex pipiens* were investigated, and the results revealed that the LC₅₀ values of MEX were found to be 531.07 and 502.32 µg/mL against *A. caspius* and *C. pipiens*, respectively [80].

5.5. Antioxidant Effect

In 2010, it was reported that CEXR and MEXR showed significant free radical scavenging activity by 1,1-diphenyl-2-picrylhydrazyl (DPPH) method with LC₅₀ values of 10.28 and 40.40 µg/mL, respectively [86]. After administration of PEEXW (250 and 500 mg/kg, p.o., for 20 days), the contents of superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase significantly increased in rats’ brain [104]. Later, in 2011, Huang et al. found that WEXL had distinct antioxidant properties against *Callisosbruchus chinensis* with strong toxicity, repellent properties, inhibited fecundity and adult emergence of the insects at 1%, 2% and 4% concentrations [102]. Moreover, it is reported that EEX revealed anti-nematode activity against *Meloidogyne javanica* in inhibiting egg hatching and inducing mortality among second stage juveniles (J2s) [103]. Furthermore, the effect of MEX on the mortality rates of *Aedes caspius* and *Culex pipiens* were investigated, and the results revealed that the LC₅₀ values of MEX were found to be 531.07 and 502.32 µg/mL against *A. caspius* and *C. pipiens*, respectively [80].
5.6. Antibacterial and Antifungal Effects

In 1983, Mehta et al. reported that the WEXFT possessed antimicrobial properties against *Vibrio cholera* [109]. Later, a study in 1997 revealed that the xanthatin isolated from the leaves of *X. strumarium* had notable potent activities against *Staphylococcus epidermidis*, *Bacillus cereus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Salmonella typhi* with minimum inhibitory concentration (MIC) values of 31.3, 62.5, 31.3, 125 and 125 µg/mL, respectively [110]. In addition, it is reported that MEXL (500 and 100 mg/mL) exhibited strong activity against *K. pneumoniae*, *Proteus vulgaris*, *P. aeruginosa*, *Pseudomonas putida*, *Salmonella typhimurium*, *B. cereus*, *Bacillus subtilis* and *S. epidermidis* [111]. In 2015, Chen et al. also reported that *β*-sitosterol and *β*-daucosterol isolated from the *X. strumarium* have significant inhibitory effects against *Escherichia coli*, with MIC values of 0.17 and 0.35 mg/mL, respectively [112]. By using the disc diffusion method, Devkota et al. determined the antibacterial activity of MEXL and WEXL, and results showed that the two extracts inhibited growth towards *K. pneumoniae*, *Proteus mirabilis*, *E. coli*, *B. subtilis*, *Enterococcus faecalis* and *Staphylococcus aureus* at concentrations of 50, 100, 150, 200 and 250 mg/mL [113]. Moreover, Sharifi-Rad et al. revealed that EOXL can significantly suppress the growth of *S. aureus*, *B. subtilis*, *K. pneumoniae* and *P. aeruginosa* with MIC values of 0.5, 1.3, 4.8 and 20.5 µg/mL, respectively; additionally, EOXL (30, 60 and 120 mg/mL) also exhibited obvious antibacterial activity against Shiga toxin-producing *Escherichia coli* [114,115]. Furthermore, Wang et al. revealed that WEX possessed antibacterial potentials against *S. aureus* and *E. coli* with MIC values of 31.25 and 7.81 mg/mL, respectively [116]. Using the disk diffusion, the antibacterial activity of EOXF on *Rathayibacter toxicus* and *Pyricularia oryzae* was evaluated, and the MIC values were 25 and 12.5 µg/mL, respectively [108].

Similar to the antibacterial potentials, the antifungal activities of *X. strumarium* were also deeply investigated. In the year of 2002, Kim et al. found an antifungal constituent from *X. strumarium*, which was named deacetylxanthomin. It can inhibit mycelial growth and zoospore germination of *Phytophthora drechsleri* with a MIC value of 12.5 µg/mL [117]. In 2011, Yanar et al. used radial growth technique to test the antifungal activities of MEX against *Phytophthora infestans*, and the MEX showed the lowest MIC value of 2.0% w/v which was lower than the standard fungicide (Metalaxyl 4% + Mancuzeb 64%, MIC value was 2.5%, w/v) [118]. Later, in 2015, Sharifi-Rad et al. investigated the antifungal ability of EOXL on *Candida albicans* and *Aspergillus niger*, and the MIC values were 55.2 and 34.3 µg/mL, respectively [114]. In vitro, using the disk diffusion method, the EOXL exhibited strong inhibition against *Pyricularia oryzae* and *Fusarium oxysporum* with MIC values of 12.5 and 50 µg/mL, respectively [108]. Furthermore, the EOXL showed remarkable growth inhibition of a wide spectrum of fungal strains, such as *A. niger*, *Aspergillus flavus*, *F. oxysporum*, *Fusarium solani*, *Alternaria alternata* and *Penicillium digitatum* with both MIC and MBC (minimum bactericidal concentration) values of 8 µg/mL [119].

5.7. Antidiabetic Effect

In 1974, Kupiecki et al. found that the WEX (15 and 30 mg/kg, i.p.) exhibited potent hypoglycemic activity in normal rats in a dose-dependent manner [120]. In 2000, the antidiabetic effect of caffeic acid isolated from *X. strumarium* was investigated on both streptozotocin-induced and insulin-resistant rat models. The results showed that caffeic acid (0.5–3.0 mg/kg, i.v.) can decrease the plasma glucose level via increasing the glucose utilization [121]. In 2011, Narendiran et al. found that MEXS at the doses of 100 and 200 mg/kg (p.o., for 30 days) had remarkable diabetic activity in normal-glycemic and streptazocin induced hyperglycemic rats [105]. A report in 2013 demonstrated that the methyl-3,5-di-O-cafeoylquinate showed strong ability to counteract diabetic complications via competitive inhibition of aldose reductase (AR) and galactitol formation in rat lenses [47]. In addition, it is reported that the CFMEXL exhibited notable inhibitory activity on α-glucosidase enzyme with the IC\textsubscript{50} value of 72 µg/mL. [122]. Similarly, another study found that MEX also had a strong α-glucosidase inhibitory effect with IC\textsubscript{50} value of 15.25 µg/mL [28].
5.8. Antilipidemic Effect

Recently, investigations into the antilipidemic effects of *X. strumarium* have been conducted. In 2011, the CEXR and EEXR were evaluated for anti-lipidemic activity in Triton WR-1339 induced hyperlipidemia in Swiss albino rats. The results showed that CEXR and EEXR (200 and 400 mg/kg p.o.) can significantly decrease the contents of plasma cholesterol, TG, LDL, and VLDL and increase plasma HDL levels, which was possibly related to their significant antioxidant activity [106]. Later, in 2016, Li et al. found that WEX (570 and 1140 mg/kg, p.o., for 6 weeks) could improve the synthesis of fatty acid and TG, thus decreased the circulating free fatty acid (FFA) levels, indicating that WEX is involved in solving the abnormality of FFA in the circulation, which is executed by promoting the storage of the excess fat, rather than the elimination of added fat [123]. Furthermore, after treatment with WEX (3.7 and 11.11 g/kg, p.o., for 4 weeks), the blood glucose, TC, TG, LDLC levels decreased and HDLC levels increased in diabetic mice [124].

5.9. Antiviral Activity

In 2009, it was reported that the WEX (0.01, 0.1 and 1.0 g/kg, i.g., for 10 days) possessed antiviral activity against duck hepatitis B virus, and it can delay pathological changes [125]. In addition, five compounds were isolated from the fruits of *X. strumarium*, and their antiviral abilities were also evaluated. The results indicated that norxanthantolide F, 2-desoxy-6-epi-parthemollin, xanthatin, threo-guaiaacylglycerol-8′-vanillic acid ether and caffeic acid ethyl ester exhibited notable activity against influenza A virus with IC₅₀ values of 6.4, 8.6, 8.4, 8.4 and 3.7 µM, respectively by a cytopathic effect (CPE) inhibition method [13].

5.10. Other Pharmacological Effects

Apart from the pharmacological effects displayed above, *X. strumarium* also possesses some other activities. In 2016, the CXT (10, 20, and 40 mg/kg, i.p.) isolated from fruits of *X. strumarium* showed significant anti-septic activity in animal models of Cecal ligation and puncture (CLP) operation. Meanwhile, the CXT can increase survival rates of septic mice induced by CLP and decrease TNF-α and IL-6 levels induced by LPS in serum of mice [126]. After treatment with WEX (570 and 1140 mg/kg p.o., for 6 weeks), the glucose tolerance and insulin sensitivity improved, meanwhile, lipogenesis increases and lipid oxidation decreased in the liver of high-fat diet rats [127]. In 2014, Lin et al. demonstrated that the EEX (75 and 300 mg/kg, p.o.) can significantly inhibit paw swelling and arthritic score and increase body weight loss and decrease the thymus index in animal model of rheumatoid arthritis induced by Complete Freund’s Adjuvant (CFA) [128]. Moreover, the overproduction of TNF-α and IL-1β was notably suppressed in the serum of all EEX-treated rats. The anti-pyretic activity of MEXW (200 and 400 mg/kg, p.o.) was estimated on yeast induced hyperpyrexia, and it showed significant reduction in elevated body temperature [129]. Using Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) induced seizures models, the anticonvulsant activity of PEEXW was tested, and results showed that PEEXW can reduce the mean duration of extensor phase and delay onset of myoclonic spasm and clonic convulsion of treated groups at doses of 250 and 500 mg/kg [130]. In 2016, Panigrah et al. explored the antiulithiatic effect of HEEXB, and showed that HEEXB can restore the impairment induced by ethylene glycol including hyperoxaluria, crystalluria, hypocalciuria, polyurea, raised serum urea, creatinine, erythrocytic lipid peroxidise and nitric oxide, kidney calcium content as well as crystal deposition. The mechanism may be related to inhibition of various pathways involved in renal calcium oxalate formation, antioxidant property and down regulation of matrix glycoprotein, osteopontin (OPN) [131]. A report in 2012 indicated the antiulcer effect of EEXL in pylorus ligation induced gastric ulcers, and its gastro-protective mechanism may be due to DNA repair, free radical scavenging and down regulation of oxidativenitrosative stress along with cytokines [132]. In an in vivo study, with the CXT treatment (10, 20 and 40 mg/kg, p.o.), the cardiac hypertrophy reduced and
fractional shortening (FS), ejection fraction (EF), cardiac output (CO) and heart rate (HR) reversed via suppressing the expression of pro-inflammatory cytokines and the NF-κB signaling pathway [133].

5.11. Summary of Pharmacologic Effects

In conclusion, *X. strumarium* has a wide range of pharmacological effects including anti-AR effects, anti-tumor effects, anti-inflammatory and analgesic effects, insecticide and antiparasitic effects, antioxidant effects, antibacterial and antifungal effects, antidiabetic effects, antilipidemic effects, and antiviral effects. (Table 3). It is noteworthy that the research areas of modern pharmacy primarily focus on chemical components and extracts, which indicated the promising potential of *X. strumarium* for treating disease. Nevertheless, the chemical constituents and corresponding pharmacological effects of *X. strumarium* are not systematically sorted out and analyzed. Therefore, it is necessary to investigate the pharmacological activity, structure-activity relationship and mechanism of *X. strumarium* both in vitro and in vivo experiments in the future.

Table 3. Pharmacological effects of *X. strumarium*.

| Effects                      | Detail                                                                 | Extracts/Compounds | Concentration/Dose | In Vivo/In vitro | Reference |
|------------------------------|------------------------------------------------------------------------|--------------------|--------------------|------------------|-----------|
| **Anti-AR effects**          | Inhibiting C 48/80-induced systemic anaphylaxis                         | WEX                | Mice, 0.01–1 g/kg (p.o.) | in vivo          | [61,62]   |
|                             | Inhibiting histamine and TNF-α released from RPMC                      | WEX                | RPMC, 0.01–1 mg/mL  | in vitro         | [63]      |
|                             | Modulating the HMC-1- and PBMNC-mediated inflammatory and immunological reactions | WEX                | HMC-1, PBMNC, 0.25–1 mg/mL | in vitro         | [63]      |
|                             | Inhibiting histamine and cAMP released from RPMC                       | MEX                | RPMC, 20–500 µg/mL  | in vitro         | [64]      |
|                             | Ameliorate the nasal symptoms of OVA induced AR rats via anti-allergic, down-regulating IgE; anti-inflammatory and analgesic properties | CXT                | Rats, 5, 10, 20 mg/kg (p.o.) | in vivo         | [65]      |
| **Lung cancer**              | Growth inhibition by suppression of STAT3, GSK3β and β-catenin          | xanthatin          | Cell lines of A549, H1975, H1299, H1650 & HCC827, 1–40 µM | in vitro         | [66–68]   |
|                             | Triggering Chk1-mediated DNA damage and destabilization of Gdc25C via lysosomal degradation | xanthatin          | xanthatin           |                  |           |
|                             | Cytotoxic effects on A549 cell                                         | xanthatin          | IC<sub>50</sub> = 1.1 µg/mL in vitro | [17]    |
|                             | 8-epi-xanthatin IC<sub>50</sub> = 3.0 µM in vitro                   | 8-epi-xanthatin    | IC<sub>50</sub> = 3.0 µM in vitro | [69]      |
|                             | 8-epi-xanthatin epoxide IC<sub>50</sub> = 1.3 µg/mL in vitro         | 8-epi-xanthatin    | IC<sub>50</sub> = 1.3 µg/mL in vitro | [17]      |
|                             | 8-epi-xanthatin-1α, 5α-epoxide IC<sub>50</sub> = 9.5 µM in vitro    | 8-epi-xanthatin    | IC<sub>50</sub> = 9.5 µM in vitro | [25]      |
|                             | 1β-hydroxy-5α-chloro-8-epi-xanthatin IC<sub>50</sub> = 20.7 µM in vitro | EEXA               | IC<sub>50</sub> = 20.7 µM in vitro | [25]      |
|                             | 1β-hydroxy-5α-chloro-8-epi-xanthatin-1α, 5α-epoxide IC<sub>50</sub> = 52.2 µg/mL in vitro | EEXA               | IC<sub>50</sub> = 52.2 µg/mL in vitro | [70]      |
| **Anti-tumor effects**       | Cytotoxic effects on MDA-MB-231 cells                                  | xanthatin          | IC<sub>50</sub> = 13.9 µg/mL in vitro | [71]      |
|                             | Cytotoxic effects on MDA-MB-231 cells                                  | xanthinosin        | IC<sub>50</sub> = 4.8 µg/mL in vitro | [71]      |
|                             | Inhibiting cell growth via inducing caspase dependent cell death       | xanthatin          | MDA-MB-231 cells, 5–25 µM in vitro | [72]      |
| **Breast cancer**            | Cytotoxic effects on MDA-MB-231 cells                                  | xanthatin          | IC<sub>50</sub> = 13.9 µg/mL in vitro | [71]      |
|                             | Cytotoxic effects on MDA-MB-231 cells                                  | xanthinosin        | IC<sub>50</sub> = 4.8 µg/mL in vitro | [71]      |
|                             | Inhibiting cell growth via inducing caspase dependent cell death       | xanthatin          | MDA-MB-231 cells, 5–25 µM in vitro | [72]      |
### Table 3. Cont.

| Effects | Detail | Extracts/Compounds | Concentration/Dose | In Vivo/In vitro | Reference |
|---------|--------|--------------------|--------------------|------------------|-----------|
| **Anti-tumor effects** | Up-regulating GADD45γ tumor suppressor gene; inducing the prolonged expression of c-Fos via N-acetyl-l-cysteine-sensitive mechanism | xanthatin | MDA-MB-231 cells, 2.5–10 µM | in vitro | [73,74] |
| Cytotoxic effects on MFC7 cells | | EEXA | IC50 = 70.6 µg/mL | in vitro | [70] |
| **Colon cancer** | Altering the antioxidant levels | WEX | Hela cells, 12.5–50 µg/mL | in vitro | [75] |
| Cytotoxic effects on MFC7 cells | | EEXA | IC50 = 70.6 µg/mL | in vitro | [70] |
| Cervical cancer | Promoting apoptosis via inhibiting thioreodoxin reductase and eliciting oxidative stress | xanthatin | Hela cells, 5–20 µM | in vitro | [76] |
| Colon cancer | Cytotoxic effects on HCT-15 cells | xanthatin | ED50 = 1.1 µg/mL | in vitro | [17] |
| Cytotoxic effects on WiDr cells | 8-epi-xanthatin | IC50 = 6.15 µg/mL | in vitro | [71] |
| Cytotoxic effects on BGC-823 cells | xanthinosis | IC50 = 2.65 µg/mL | in vitro | [71] |
| | xeremophil-1(10),11(13)-diene-12,8β-olide | IC50 = 13.22 µM | in vitro | [77] |
| | 8-epi-xanthatin-1β,5β-epoxide | IC50 = 2.43 µM | in vitro | [77] |
| | tomentosin | IC50 = 4.54 µM | in vitro | [77] |
| | xeremophil-1(10),11(13)-diene-12,8β-olide | IC50 = 4.41 µM | in vitro | [77] |
| | 8-epi-xanthatin-1β,5β-epoxide | IC50 = 1.44 µM | in vitro | [77] |
| | tomentosin | IC50 = 3.47 µM | in vitro | [77] |
| Cytotoxic effects on KE-97 cells | xanthatin | MRN-45 Cells, 3.9–18.6 µM | in vitro | [75] |
| | xanthinosis | AGS cells, 8 µM | in vitro | [18] |
| | lasidiol | p-methoxybenzoate | AGS cells, 16 µM | in vitro | [18] |
| | protein Bcl-2 | EEXA | IC50 = 58.9 µg/mL | in vitro | [70] |
| | Cytotoxic effects on CT26 cells | xanthatin | HepG2 cells, 5–40 µM | in vitro | [76] |
| Liver cancer | Cytotoxic effects on SNU387 cells | 1β-hydroxy-1α-chloro-8-epi-xanthatin | IC50 = 5.1 µM | in vitro | [25] |
| Cytotoxic effects on HepG2 cells | MEX | LC50 = 112.9 µg/mL | in vitro | [80] |
| | EAFMEX | LC50 = 68.7 µg/mL | in vitro | [80] |
| Induction of apoptosis via inhibiting thioreodoxin reductase and eliciting oxidative stress | xanthatin | HepG2 cells, 5–40 µM | in vitro | [76] |
| Meningioma | Cytotoxic effects on SK-MEL-2 cells | xanthatin | ED50 = 0.5 µg/mL | in vitro | [17] |
| | 8-epi-xanthatin | ED50 = 0.2 µg/mL | in vitro | [17] |
| | EEXS | Mel-Ab cells, 1–50 µg/mL | in vitro | [81] |
| | Inhibiting cell proliferation associated with activation of Wnt/β-catenin pathway and inhibition of angiogenesis | xanthatin | B16-F10 cells, 2.5–40µM | in vitro | [82] |
| Leukemia | Cytotoxic effects on P-388 cells | DFEEXA | IC50 = 1.64 µg/mL | in vitro | [83] |
| | xanthatin | IC50 = 52.50 µg/mL | in vitro | [84] |
| Cytotoxic effects on HL-60 cells | MEX | LC50 = 50.18 µg/mL | in vitro | [80] |
| | EAFMEX | LC50 = 48.73 µg/mL | in vitro | [80] |
| Meningioma | Cytotoxic effects on SK-MEL-2 cells | xanthatin | ED50 = 0.5 µg/mL | in vitro | [17] |
| | 8-epi-xanthatin | ED50 = 0.2 µg/mL | in vitro | [17] |
| | EEXS | Mel-Ab cells, 1–50 µg/mL | in vitro | [81] |
| | Inhibiting cell proliferation associated with activation of Wnt/β-catenin pathway and inhibition of angiogenesis | xanthatin | B16-F10 cells, 2.5–40µM | in vitro | [82] |
| | Cytotoxic effects on P-388 cells | DFEEXA | IC50 = 1.64 µg/mL | in vitro | [83] |
| | xanthatin | IC50 = 52.50 µg/mL | in vitro | [84] |
| | Cytotoxic effects on HL-60 cells | MEX | LC50 = 50.18 µg/mL | in vitro | [80] |
| | EAFMEX | LC50 = 48.73 µg/mL | in vitro | [80] |
| Leukemia | Cytotoxic effects on P-388 cells | DFEEXA | IC50 = 1.64 µg/mL | in vitro | [83] |
| | xanthatin | IC50 = 52.50 µg/mL | in vitro | [84] |
| | Cytotoxic effects on HL-60 cells | MEX | LC50 = 50.18 µg/mL | in vitro | [80] |
| | EAFMEX | LC50 = 48.73 µg/mL | in vitro | [80] |
| | Cytotoxic effects on MFC7 cells | EEXA | IC50 = 70.6 µg/mL | in vitro | [70] |
Table 3. Cont.

| Effects                          | Detail                                                                 | Extracts/Compounds | Concentration/Dose | In Vivo/ In vitro | Reference |
|---------------------------------|------------------------------------------------------------------------|--------------------|--------------------|-------------------|-----------|
| **Anti-inflammatory**           |                                                                        |                    |                    |                   |           |
| Inhibiting LPS-stimulated       | WEX                                                                    | 10, 100 and 1000   | In vitro           | [87]              |           |
| inflammatory                    | MEX                                                                    | µg/mL              |                    |                   |           |
|                                 | xanthatin and xanthinosin                                             | 30, 60 and 90      | in vitro           | [88]              |           |
|                                 |                                                                        | mg/mL              |                    |                   |           |
|                                 |                                                                        | 11.2 µM            | in vitro           | [89]              |           |
| Inhibiting LPS-stimulated       | MEXL                                                                   | IC₅₀ = 87 µg/mL     | in vitro           | [90]              |           |
| inflammatory                    | MEXR                                                                   | 50–400 µg/mL       | in vitro           | [91]              |           |
|                                 | WEX                                                                    | 0.5, 1 and 2       | in vitro           | [92]              |           |
|                                 | MEX                                                                    | mg/mL              |                    |                   |           |
|                                 | MEXA                                                                   | 0–300 µg/mL        | in vitro           | [93]              |           |
|                                 | xanthiumnolic E                                                        | IC₅₀ = 8.73 µM      | in vitro           | [26]              |           |
|                                 |                                                                        |                    |                    |                   |           |
| Inhibiting carrageenan induced  | MEX                                                                    | 100, 200 mg/kg/d   | in vivo            | [88]              |           |
| hind paw edema                  | WEX                                                                    | (p.o.)             |                    |                   |           |
|                                 |                                                                        | 0.1, 0.5 and 1.0   | in vitro           | [95]              |           |
|                                |                                                                        | g/kg, (p.o.)       |                    |                   |           |
|                                 |                                                                        | 100, 200 and 400    |                    |                   |           |
|                                 |                                                                        | mg/kg body weight. |                    |                   |           |
| **Anti-inflammatory and analgesic effects** |                                                                        |                    |                    |                   |           |
| Inhibiting croton-oil-induced   | MEXL                                                                   | 100, 200 mg/kg/d   | in vivo           | [90]              |           |
| ear edema                       | MEX                                                                    | (p.o.)             |                    |                   |           |
|                                 | NFEEX                                                                  | Mice, 0.5, 0.75 and| in vivo           | [96]              |           |
|                                 |                                                                        | 1.0 mg/ear         |                    |                   |           |
|                                 | xanthatin                                                              | 100 and 97 mg/mL,  | in vitro           | [84]              |           |
|                                 |                                                                        | respectively       |                    |                   |           |
|                                 | EEX                                                                    | 10 µg/mL           | in vitro           | [97]              |           |
| **Analgesic effect**            |                                                                        |                    |                    |                   |           |
| Ameliorating HCl/EtOH-induced   | MEXA                                                                   | 50 and 200 mg/kg   | in vivo           | [94]              |           |
| gastritis lesions               |                                                                        | (p.o.)             |                    |                   |           |
| Analgesic effect on acetic acid | MEX                                                                    | 100, 200 mg/kg/d   | in vivo           | [88]              |           |
| induced abdominal constriction   |                                                                        | (p.o.)             |                    |                   |           |
| test and a hot plate test       |                                                                        |                    |                    |                   |           |
| Reducing the number of writhings | NFEEX                                                                  | Mice, 100,200 and   | in vivo           | [96]              |           |
| induced by acetic acid           |                                                                        | 400 mg/kg body     |                    |                   |           |
| wt.                              |                                                                        | weight.            |                    |                   |           |
| Analgesic effect on writhing    | WXF                                                                    | 0.1, 0.5 and 1.0   | in vivo           | [95]              |           |
| and formalin tests              |                                                                        | g/kg, (p.o.)       |                    |                   |           |
| Analgesic effect on hot plate   | EEX                                                                    | 250 and 500 mg/kg  | in vivo           | [98]              |           |
| test, acetic acid induced       |                                                                        | (p.o.)             |                    |                   |           |
| writhing and formalin test      |                                                                        | body weight.       |                    |                   |           |
| **Insecticide and antiparasitic effects** |                                                                        |                    |                    |                   |           |
| Antiplasmodial activity against | EEXL                                                                   | 5, 50, 500 and 1000| in vitro           | [99]              |           |
| T. evansi                       |                                                                        | µg/mL              |                    |                   |           |
| Insecticidal effects against    | xanthatin                                                              | IC₅₀ = 2.63 µg/mL   | in vitro           | [84]              |           |
| T. b. brucei                    |                                                                        | LC₅₀ = 11.02 (w/w) |                    | [100]             |           |
| Anti-insect effects towards P.  | EEXL                                                                   | IC₅₀ = 4 µg/mL      | in vitro           | [101]             |           |
| vitacea                         |                                                                        | 1%, 2% and 4%      |                    |                   |           |
| Insecticide and antiparasitic   |                                                                        | concentration      |                    |                   |           |
| effects                         |                                                                        |                    |                    |                   |           |
| Anti-nematode activity against  | EEXL                                                                   | LC₅₀ = 531.07 and   | in vitro           | [103]             |           |
| M. javanica                     |                                                                        | 3% and 12%         |                    |                   |           |
| Insecticidal effects against A. |                                                                        | concentration      |                    |                   |           |
| caspius, C. pipiens             | MEX                                                                    | 502.32 µg/mL,      | in vitro           | [80]              |           |
|                                 |                                                                        | respectively       |                    |                   |           |
Table 3. Cont.

| Effects | Detail | Concentration/Dose | In Vivo/In vitro | Reference |
|---------|--------|--------------------|------------------|-----------|
| **Antioxidant effects** | | | | |
| Scavenging DPPH | CEXR and MEXR | IC\(_{50}\) = 10.28 and 40.40 \(\mu\)g/mL | in vitro | [86] |
| | WEX | 0.05-0.2 mg/mL | in vitro | [95] |
| | EEXR and CEXR | IC\(_{50}\) = 29.81 and 24.85 \(\mu\)g/mL | in vitro | [106] |
| | EEXL | IC\(_{50}\) = 85 \(\mu\)g/mL | in vitro | [107] |
| | hexadecanoic acid, \(\alpha\)-amyrin, 14-methyl-12,13-dehydro-sitosterol-heptadecenate | IC\(_{50}\) = 106.4, 64.16 and 76.18 \(\mu\)g/mL | in vitro | [32] |
| Scavenging DPPH | EOX | 138.87 \(\mu\)g/mL | in vitro | [108] |
| | MEX | Not mentioned | in vitro | | |
| | EEXR and CEXR | IC\(_{50}\) = 395.20 and 418.30 \(\mu\)g/mL | in vitro | [106] |
| | EEXL | IC\(_{50}\) = 72 \(\mu\)g/mL | in vitro | [107] |
| | WEX | 0.05-0.2 mg/mL | in vitro | [95] |
| | WEX | 0.05-0.2 mg/mL | in vitro | [95] |
| | EEXL | IC\(_{50}\) = 9.23 \(\mu\)g/mL | in vivo | [105] |
| | EEXL | IC\(_{50}\) = 62 \(\mu\)g/mL | in vivo | [107] |
| | PEEXW | body weight (p.o. for 20 days) | in vivo | [104] |
| | WEX | 250 and 500 mg/kg | in vitro | [95] |
| | WEX | 100 and 200 mg/kg (p.o., for 10 days) | in vivo | [105] |
| | EEXR and CEXR | IC\(_{50}\) = 495.30 and 418.30 \(\mu\)g/mL | in vitro | [106] |
| | EEXL | IC\(_{50}\) = 62 \(\mu\)g/mL | in vitro | [107] |
| | MEXS | β-sitosterol and β-daucosterol | MIC = 0.17 and 0.35 \(\mu\)g/mL | in vitro | [112] |
| | MEX | 50, 100, 150, 200, and 250 \(\mu\)g/mL, respectively | in vitro | [113] |
| | MEXL | 50 and 100 \(\mu\)g/mL | in vitro | [111] |
| | WEX | 0.05-0.2 mg/mL | in vitro | [95] |
| | WEX | 0.05-0.2 mg/mL | in vitro | [95] |
| | MEX | 25, 50 and 50 \(\mu\)g/mL, respectively | in vitro | [108] |
| | MEXL | 50 \(\mu\)g/mL | in vitro | [113] |
| FRAP antioxidant activity | MEX | Not mentioned | in vitro | [28] |

**Antibacterial and antifungal effects**

| Effects | Detail | Concentration/Dose | In Vivo/In vitro | Reference |
|---------|--------|--------------------|------------------|-----------|
| Antibacterial | Inhibitory effects against \(V\). cholerae \(V\). cereus, \(K\). pneumoniae, \(P\). aeruginosa and \(S\). typhimurium, \(B\). cereus, \(B\). subtilis, \(S\). epidermidis | Xanthatin | Not mentioned | MIC = 31.3, 62.5, 125 and 125 \(\mu\)g/mL | in vitro | [109] |
| | Inhibitory effects against \(P\). vulgaris, \(P\). aeruginosa, \(P\). putida, \(S\). typhimurium, \(B\). cereus, \(B\). subtilis, \(S\). epidermidis | MEX | 500 and 100 \(\mu\)g/mL | in vitro | [111] |
| | Inhibitory effects against \(E\). coli | β-sitosterol and \(\beta\)-daucosterol | MIC = 0.17 and 0.35 \(\mu\)g/mL, respectively | in vitro | [112] |
| | Inhibitory effects towards \(K\). pneumonia, \(P\). mirabilis, \(E\). coli, \(B\). subtilis, \(E\). faecalis, \(S\). aureus, \(B\). subtilis, \(K\). pneumonia, \(P\). aeruginosa | MEXL | 30, 60 and 120 \(\mu\)g/mL | in vitro | [115] |
| | Inhibitory effects against \(S\). aureus and \(E\). coli | MEX | MIC = 31.25 and 7.81 mg/mL, respectively | in vitro | [116] |
| | Inhibitory effects against \(R\). toxicus, \(S\). aureus and \(F\). oxysporum | MEX | MIC = 25, 50 and 25 \(\mu\)g/mL, respectively | in vitro | [108] |
| | Inhibitory effects against \(A\). flavus, \(F\). oxysporum, \(F\). solani, \(A\). alternata and \(P\). digitatum | MEX | MIC = 8 \(\mu\)g/mL and MFC = 8 \(\mu\)g/mL | in vitro | [109] |
| Antibacterial and antifungal effects | Inhibitory effects against \(P\). dreckleri, \(P\). infestans and \(A\). niger | Xanthathin and \(\alpha\)-amyrin | Not mentioned | MIC = 2.0% w/v, respectively | in vitro | [117] |
| | Inhibitory effects against \(P\). oryzae and \(F\). oxysporum | \(\alpha\)-amyrin | 30, 60 and 120 \(\mu\)g/mL | in vitro | [115] |
| | Inhibitory effects against \(A\). niger, \(A\). flavus, \(F\). oxysporum, \(F\). solani, \(A\). alternata and \(P\). digitatum | \(\alpha\)-amyrin | MFC = 8 \(\mu\)g/mL | in vitro | [108] |
### Table 3. Cont.

| Effects                | Detail                                                                 | Extracts/Compounds | Concentration/ Dose | In Vivo/ In vitro | Reference |
|------------------------|------------------------------------------------------------------------|--------------------|---------------------|-------------------|-----------|
| **Antidiabetic effects** | Exhibiting potent hypoglycemic activity                               | WEX                | 15 and 30 mg/kg (i.p.) | in vivo           | [120]     |
|                        | Decreasing the plasma glucose in diabetic rats                         | caffeic acid       | 0.5–3 mg/kg (i.v.)   | in vivo           | [121]     |
|                        | Decreasing the blood glucose and HbA1C level and increase the level of insulin | MEXS               | 100 and 200 mg/kg (p.o., for 30 days) | in vivo | [105]     |
|                        | Inhibitory effect against rAR and rhAR                                 | methyl-3,5-di-O-caffeoylquinate | IC₅₀ = 0.30 and 0.67 μM, respectively | in vivo | [47]      |
|                        | Inhibitory effect against α-glucosidase                               | CFMEXL             | IC₅₀ = 72 μg/mL.     | in vitro          | [122]     |
|                        | Inhibitory effect against α-glucosidase                               | MEX                 | IC₅₀ = 15.25 mg/mL.  | in vivo           | [28]      |
| **Antilipidemic effects** | Decreasing plasma cholesterol, triglyceride, LDL, and VLDL and increasing plasma HDL levels | CEXR and EEXR      | 200 and 400 mg/kg (p.o.) | in vivo | [106]     |
|                        | Improving lipid homeostasis                                           | WEX                | 570 and 1140 mg/kg (p.o., for 6 weeks) | in vivo | [123]     |
|                        | Decreasing blood glucose, TC, TG, LDLC levels and increasing HDLC levels. | WEX                | 3.7 and 11.11 g/kg (p.o., for 4 weeks) | in vivo | [124]     |
| **Antiviral activity** | Antiviral activity against duck hepatitis B virus                      | WEX                | 0.01, 0.1 and 1 g/kg (i.g., for 10 days) | in vivo | [125]     |
|                        | Antiviral activity against Influenza A virus                          | nornaxanthotiolde F | IC₅₀ = 6.4 μM         | in vitro          | [13]      |
|                        | Antiviral activity against Influenza A virus                          | 2-desoxy-6-epi-parthenolliol | IC₅₀ = 8.6 μM         | in vitro          | [13]      |
|                        | Antiviral activity against Influenza A virus                          | xanthatin          | IC₅₀ = 8.4 μM         | in vitro          | [13]      |
|                        | Antiviral activity against Influenza A virus                          | threo-guaiacylglycerol-8'-vanillic acid ether | IC₅₀ = 8.4 μM         | in vitro          | [13]      |
|                        | Antiviral activity against Influenza A virus                          | caffeic acid ethyl ester | IC₅₀ = 3.7 μM         | in vitro          | [13]      |
| **Other pharmacological effects** | Anti-septic activity                                                  | CXT                | 10, 20 and 40 mg/kg (i.p.) | in vivo | [126]     |
|                        | Attenuating hepatic steatosis                                         | WEX                | 570 and 1140 mg/kg (p.o., for 6 weeks) | in vivo | [127]     |
|                        | Anti-arthritis effect                                                 | EEX                | 75 and 300 mg/kg (p.o.) | in vivo | [128]     |
| **Other pharmacological effects** | Anti-pyretic activity                                                 | MEXW               | 200 and 400 mg/kg (p.o.) | in vivo | [129]     |
|                        | Anti-epileptic activity                                               | PEEXW              | 250 and 500 mg/kg (p.o., for 20 days) | in vivo | [130]     |
|                        | Antiurolithiatic effect                                               | HEEXB              | 500 mg/kg (p.o.)      | in vivo           | [131]     |
|                        | Antiulcer effect                                                     | EEXL               | 200 and 400 mg/kg (p.o.) | in vivo | [132]     |
|                        | Cardioprotective effect                                              | CXT                | 10, 20 and 40 mg/kg (p.o.) | in vivo | [133]     |

### 6. Pharmacokinetics

Up to now, there are few reports on the pharmacokinetics of the extracts or monomers of *X. strumarium*. Previous pharmacokinetics studies of *X. strumarium* mainly focused on its active compounds including xanthatin, cryptochlorogenic acid, and toxic ingredient such as atractyloside. In 2014, a sensitive, specific and rapid ultra-high performance liquid chromatography (UHPLC) tandem mass spectrometry (UHPLC-MS/MS) method was applied to research pharmacokinetic properties of xanthatin in rat plasma. After intravenous injection of xanthatin at a dose of 2.4 mg/200 g, 4.8 mg/200 g and 9.6 mg/200 g, respectively. The t_{1/2} of three concentrations were found to be 108.58 ± 32.82, 123.50 ± 66.69, and 181.71 ± 148.26 min, respectively; and the peak plasma concentration (C_{max}) values were 418.72 ± 137.51, 904.89 ± 193.53, and 1773.46 ± 1733.10 ng/mL, respectively. As the dose increased, the AUC₀–t and AUC₀–∞ were gradually enlarged, and the AUC₀–t of three doses were 14,340.20 ± 7122.41, 32,149.52 ± 11,259.44, and 49,524.28 ± 28,520.88 ng h/mL, respectively; furthermore, the AUC₀–∞ of three levels are 15,538.97 ± 7733.12, 36,431.22 ± 14,498.16, and 61,885.45 ± 30,704.80 ng h/mL, respectively. In addition, the total body CL were 0.13 ± 0.14, 0.17 ± 0.11, 0.22 ± 0.13 mL/min and V_d were 46.85 ± 20.19, 159.99 ± 30.49, and 208.22 ± 85.97 mL of three concentrations [134].
After intragastric administration of the atractyloside at doses of 11.4, 22.8, and 45.6 mg/kg, the peak time (T\textsubscript{max}) values were determined to be 0.38, 1.85, 0.27 h, respectively, the t\textsubscript{1/2} were 13.64, 9.62, 8.61 h, respectively, and the peak plasma concentration (C\textsubscript{max}) values were 41.98, 24.61, 263.40 µg/mL, respectively. In addition, the area under the concentration-time curve (AUC) was also determined, and the AUC\textsubscript{0–t} was 132.70, 222.90, and 345.20 µg h/L. The results showed that the toxicokinetic behavior of atractyloside in rats was non-linear within the experimental dose range [135].

Furthermore, Shen et al. studied the pharmacokinetics of neochlorogenic acid and cryptochlorogenic acid in X. strumarium and its processed products after intragastric administration in rats. The results showed that the T\textsubscript{max} of neochlorogenic acid and cryptochlorogenic acid in processed fruits of X. strumarium were 2.94 ± 0.18, and 3.00 ± 0.46 h, respectively; the t\textsubscript{1/2} of neochlorogenic acid and cryptochlorogenic acid in processed fruits of X. strumarium were 2.35 ± 1.11, 1.97 ± 0.66 h. Moreover, the T\textsubscript{max} of neochlorogenic acid and cryptochlorogenic acid in raw fruits of X. strumarium were 3.75 ± 0.46, 2.75 ± 0.27 h, and the t\textsubscript{1/2} of neochlorogenic acid and cryptochlorogenic acid in raw fruits of X. strumarium were 1.70 ± 0.61, 2.12 ± 0.68 h. The neochlorogenic acid in fruits of X. strumarium, after being processed, takes effect quickly and lasts for a long time, while the cryptochlorogenic acid takes effect slowly and has a short action time [136].

7. Toxicity

In 1990, it was reported that X. strumarium has medium to strong allergenic effects and is poisonous to mammals, and atractyloside and carboxyatractyloside are considered to be the major toxic compounds [137]. X. strumarium is prudently ranked into the medium grade with less toxicity in the Shennong Bencao Jing, a monograph of materia medica. Some other Chinese materia medicas also record that X. strumarium possessed mild toxicity, such as Bencao Pinhui Jingyao, Bencao Huiyan. Thus, it is obvious that the ancient Chinese people have had a clear understanding of the toxicity of X. strumarium for a long time [138].

In recent years, many investigations have indicated the toxic effects and related mechanisms of the extracts and monomers of X. strumarium (Table 4). In 2005, Li et al. found that the median lethal concentration (LD\textsubscript{50}) value of the WEX in mice was 201.14 g/kg (i.g., crude herbs mass equal) [139]. In addition, a report in 2012 suggested that the LD\textsubscript{50} value of the WEX in mice was 167.60 g/kg (crude herbs mass equal, i.g.), however the LD\textsubscript{50} value was 194.15 g/kg (i.g., crude herb mass equivalent) in Fu’s research report [140,141]. These changes can be attributed to the toxicity of X. strumarium which varied with the processing method, genetic characteristics and growing conditions [138]. Furthermore, the LD\textsubscript{50} value of the EEX in mice was 275.41 g/kg (crude herbs mass equal, i.g.), which was higher than WEX [140]. Another study showed that the carboxyatractyloside (10–100 mg, i.v.) can induce death in swine [142].

Recently, animal experiments and clinical studies on X. strumarium showed that hepatotoxicity is the main toxicity. In 2011, Wang et al. demonstrated that kaurene glycosides including atractyloside (50–200 mg/kg, i.p.) and carboxyatractyloside (50–150 mg/kg, i.p.) induced hepatotoxicity in mice by way of its induction of oxidative stress as lipid peroxidation in liver [143]. Besides, the chief mechanism of atractyloside poisoning is deemed to be inhibition of the mitochondrial ADP transporter [144]. Furthermore, the WFEEX and NFEEX (0.06, 0.3, 0.7 g/kg, i.g., for 28 days), which have marked hepatotoxicity to rats, can cause pathological changes, such as enlarged hepatic cell space, karyolysis, and inflammatory cell infiltration [145]. Moreover, it has been reported that WEX (21.0 g/kg i.g., for 28 days) significantly increased the content of ALT, AST in mice serum and decreased weight loss [146]. In addition, a study in 2014 found that WEX (7.5, 15.0 and 30.0 g/kg, i.g., for 5 days) can increased the serum ALT, AST, ALP, TBIL levels and the contents of LDL/vLDL, β-HB, glutamate, choline, acetate, glucose in male rats [147]. Finally, in 2018, Zeng et al. indicated that the contents of GLDH, α-GST increased and miRNA-122 decreased after administered WEX (16.7 g/kg i.g., for 7 days), which can be used as sensitive biomarkers for studying the regularity of hepatotoxicity of X. strumarium [148]. Apart from hepatotoxicity, Mandal et al. studied the neurotoxicity of the MEXA
in mice and results show that MEXA (100, 200, 300 mg/kg) can obviously depress the action of central nervous system [149].

### Table 4. Toxicities and side effects of X. strumarium.

| Extracts/Compounds | Animal/Subjects | LD50/Toxic Dose Range | Toxic Reactions | Reference |
|--------------------|----------------|-----------------------|-----------------|-----------|
| WEX                | mice           | LD50 = 201.14 g/kg (i.g., crude herb mass equivalent) | Death | [139] |
| WEX                | mice           | LD50 = 167.60 g/kg (i.g., crude herb mass equivalent) | Death | [140] |
| EEX                | mice           | LD50 = 275.41 g/kg (i.g., crude herb mass equivalent) | Death | [140] |
| WEX                | mice           | LD50 = 194.15g/kg (i.g., crude herb mass equivalent) | Death | [141] |
| carboxyatractyloside | swine         | 10–100 mg (i.v.)  | Death | [142] |
| atractyloside      | mice           | 50–200 mg/kg (i.p.) | Increasing contents of ALT, AST, ALP, MDA in mice serum | [143] |
| carboxyatractyloside | mice         | 50–150 mg/kg (i.p.) | Increasing contents of ALT, AST, ALP, MDA in mice serum | [143] |
| NFEEX              | mice           | 0.06, 0.3, 0.7 g/kg (i.g., for 28 days) | Weight loss, enlarged hepatic cell space, karyolysis and inflammatory cell infiltration | [145] |
| WFEEX              | mice           | 0.06, 0.3, 0.7 g/kg (i.g., for 28 days) | Weight loss, enlarged hepatic cell space, karyolysis, and inflammatory cell infiltration | [145] |
| WEX                | mice           | 21.0 g/kg (i.g., for 28 days) | Weight loss and increase of ALT, AST in mice serum | [146] |
| WEX                | mice           | 7.5, 15.0 and 30.0 g/kg (i.g., for 5 days) | Increasing contents of VLDL/LDL, β-HB, glutamate, choline, acetate, glucose in serum | [147] |
| WEX                | mice           | 16.7 g/kg (i.g., for 7 days) | Increasing contents of GLDH, α-GST and decreasing miRNA-122 | [148] |
| MEXA               | mice           | 100, 200, 300 mg/kg | Depressing the action of central nervous system | [149] |
| atractyloside      | hepatocytes    | 0.01–0.05 g/L        | Reducing cell viability and intracellular GSH content | [150] |
| atractyloside, carboxyatractyloside | L-02 cells, BRL cells | 100 μmol/L for 48 h | Inhibiting cell proliferation, improving LDH activity | [147] |
| WEX                | HK-2 cells    | 100 μg/mL            | Inhibiting cell proliferation | [151] |
| HEEXA              | CHO cells     | 25–100 μg/mL         | Inducing DNA damage | [152] |
| EFEEX              | CHO cells     | IC50 = 231.1 μg/ml   | Decreasing viability of cell | [153] |
| WEX                | fatfish       | 15 μg/mL             | Decreasing hatch rate | [154] |

Many other studies have demonstrated that different medicinal parts and extraction parts are also cytotoxic to normal cells including hepatocytes, nephrocytes, ovary cells, etc. The cell inhibition ability of atractyloside on rat hepatocytes was investigated, and the results demonstrated that atractyloside (0.01–0.05 g/L) induced dose-dependent hepatotoxicity according to obvious decreases of cell viability, intracellular glutathione (GSH) content and albumin secretion [150]. Furthermore, atractyloside and carboxyatractyloside was reported to improve LDH activity and inhibit cell proliferation at the concentration of 100 μmol/L [147]. In 2013, Yu et al. indicated that WEX at concentrations 100 μg/mL can inhibit growth of HK-2 cells [151]. Moreover, HEXA (25–100 μg/mL) also causes in vitro DNA damage at cytotoxic concentrations through sister chromatid exchanges, chromosome aberrations, and comet assay, meanwhile, it also shows significant reduction in CHO cell viability [152]. In 2016, Su et al. compared the cytotoxicities of the components with different polarities, and study indicated that EAFEEX (IC50 = 231.1 μg/mL) was the most toxic part [153].

In recent years, few investigations have focused on the toxic effects of X. strumarium on reproduction. In 2014, it was reported that the WEX possessed reproductive toxicity to zebrafish embryos, including decreases in hatch rate, and increases in mortality rate, heart rate and swimming speed [154].

### 8. Future Perspectives and Conclusions

In summary, X. strumarium, which possesses anti-AR effects, anti-inflammatory and analgesic effects and anti-tumor effects, has been widely applied to clinical practice in many countries. In the
meantime, many modern studies on *X. strumarium* were also carried out, and its pharmacological activities and chemical compositions have been preliminarily investigated. Nevertheless, how to find out the mechanism of pharmacological activities and its related compounds, develop clinical efficacy of *X. strumarium* and ensure medication safety are still extremely crucial now.

First, the chemical compounds and pharmacological activity studies of *X. strumarium* mainly focused on its fruits, but there are few investigations on the roots, leaves, stems and other parts of *X. strumarium*. In order to enlarge the source domain of the active compounds and maximize the plant utilization rate, it is very critical for researchers to conduct a comprehensive evaluation of other parts of this plant. Second, the fruits of *X. strumarium* are officially recognized as *Cang-Er-Zi* in the Chinese Pharmacopoeia (2015 Edition), but many other *Xanthium* species such as *X. mongolicum* Kitag, *Xanthium spinosum* L. and *Xanthium canadens* Mill were used as *X. strumarium* alternatives in many areas of China. Therefore, the physical properties, chemical compositions and pharmacological activities should be used to identify and differentiate the different varieties, and it is important to guarantee the safety and efficacy with these herbs to ensure its suitability for clinical use. Third, in China, *X. strumarium* is commonly used after processing in clinical medicine, but the mechanism of its detoxification still needs further study. The degree of processing depends mainly on the subjective experience of people, and it is difficult to ensure the consistency of the quality of Chinese Medicine. Thus, the intelligent sensory technology combined with artificial intelligence technology, such as machine vision, electronic nose and electronic tongue can be applied to standardize processing methods. Fourth, on the basis of current research progress in vivo and in vitro, many active compounds of *X. strumarium* have been found and identified, which are probably developed into effective drugs. Among them, xanthatin possessed strong anticancer activity against many kinds of tumors, which means that it has the potential to become an anticancer drug in the future. However, systematic investigations on pharmacokinetics, target-organ toxicity and clinical research of xanthatin will help to develop its bioactive constituents as novel drugs. Fifth, traditional Chinese medicine has the characteristics of multi-component, multi-target and multi-channel, and a single component cannot completely reveal its pharmacological activity. Recently, quality marker (Q-Markers) technologies have started to contribute to scientifically interpreting the correlation degree of effectiveness-material basis-quality control of significant components in traditional Chinese Medicine. For *X. strumarium*, Q-Markers technologies are able to clarify its possible action, toxicity mechanism and symbolic components, and it is helpful to establish the whole quality control and quality traceability system of *X. strumarium*.

**Author Contributions:** Conceptualization, W.P. and C.W.; writing—original draft preparation, W.F., L.F., C.P., Q.Z., L.W., LL., J.W.; writing—review and editing, W.P. and D.Z.; funding acquisition, W.P. and C.W.

**Funding:** This work was funded by the China Postdoctoral Science Foundation (no. 2018M631071); Innovative Research Team of Chinese Medicine Discipline in Chengdu University of Traditional Chinese Medicine (no.030041007) and Sichuan Science and Technology Project (no.2018Y0435).

**Conflicts of Interest:** The authors declare no conflict of interest.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| WEX          | water extracts of fruit of *Xanthium strumarium* |
| MEX          | methanol extracts of fruits of *X. strumarium* |
| EEXA         | ethanol extracts of aerial parts of *X. strumarium* |
| EEXS         | ethanol extracts of stems of *X. strumarium* |
| WFEEX        | water fraction of ethanol extracts of fruits of *X. strumarium* |
| NFEEX        | n-butanol fraction of ethanol extracts of fruits of *X. strumarium* |
| MEXA         | methanol extracts of aerial parts of *X. strumarium* |
| HEXA         | hydroalcoholic extracts of aerial parts of *X. strumarium* |
| EAFEEX       | ethylacetate fraction of ethanol extracts of fruits of *X. strumarium* |
| CFEEEXA      | chloroform fraction of ethanol extracts of aerial parts of *X. strumarium* |
| CEXR         | chloroform extracts of roots of *X. strumarium* |
MEXR methanol extracts of roots of *X. strumarium*
EAFMEX ethylacetate fraction of methanol extracts of fruits of *X. strumarium*
DFEXA dichloromethane fraction of ethanol extracts of aerial parts of *X. strumarium*
EEX ethanol extracts of fruits of *X. strumarium*
WEXL water extracts of leaves of *X. strumarium*
EEXL ethanol extracts of leaves of *X. strumarium*
PEEXW petroleum ether extracts of whole plant of *X. strumarium*
MEXL methanol extracts of leaves of *X. strumarium*
EEXR ethanol extracts of roots of *X. strumarium*
EOX essential oil of fruits of *X. strumarium*
EOXL essential oil of leaves of *X. strumarium*
WEXFT water extract of flowering twigs of *X. strumarium*
CFMEXL chloroform fraction of methanol extracts of leaves of *X. strumarium*
MEXS methanol extracts of stems of *X. strumarium*
HEEXB hydro-ethanol extracts of burs of *X. strumarium*
EFEEX ethylacetate fraction of ethanol extracts of *X. strumarium*

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