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Fl. Medit. 29: 93-102
https://doi.org/10.7320/FlMedit29.093
Version of Record published online on 15 July 2019

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Xanthium strumarium – a potential cheap resource of plant substances for medicinal use

Abstract

Kozuharova, E., Ionkova, I. & Spadaro, V.: *Xanthium strumarium* – a potential cheap resource of plant substances for medicinal use. — Fl. Medit. 29: 93-102. 2019. — ISSN: 1120-4052 printed, 2240-4538 online.

Xanthium strumarium L. (*Asteraceae*) is an annual herb which reproduces solely by seed. So far its centre of origin was considered Central or South America. Recent archeological research revealed that the burs of *X. strumarium* were used in Yuergou site (400–200 cal BC) in the Turpan Basin of northwestern China. This plant adventive to Europe reduces germination of various crops and behaves like and aggressive invasive species. *X. strumarium* is the most frequently recorded plant in the field borders between the crop land and adjacent territories the agricultural areas in Bulgaria.
We aim of this study is to reveal the potential of *X. strumarium* as a cheap source of compounds with valuable pharmacological activities. Here we analyse: 1) the traditional ethnobotanical data from its native habitats; 2) the modern investigations of pharmacological activity and essential secondary compounds.
Traditionally the plant is used as febrifuge drug and an immunostimulant, as a diaphoretic agent and against malaria, as well as dysentry cure, astringent, sedative, analgesic, diuretic, against leucorrhoea and urinary diseases, eczema and skin disease, bleeding, insect bite, to treat boils and pimples, against smallpox and stomach diseases, earache and strumous disease, leprosy, headache, fever, etc.
X. strumarium contains sesquiterpene lactones, thiazinediones, phenolic acids etc. and posses anticancer, antitussive, antifungal, antiinflammatory, antinociceptive, hypoglycaemic, antioxidant, antitrypanosomal, and antidepressant-like activity, diuretic effects, insecticidal and herbicidal activities as well as antitrypanosomal effect. A pharmaceutical application of this plant in the future would reduce its populations and thus would contribute to the biodiversity conservation.

Key words: ethnobotany, pharmacological activity, invasive plants management, sustainable development.

Introduction

Xanthium strumarium L. (common cocklebur) is a coarse, erect, branching, annual herb which reproduces solely by seed (Holm & al. 1991). The geographic distribution of *X.*

strumarium extends from latitude 53°N to 33°S (Holm & al. 1977). It is most often found in the temperate zone, but also occurs in subtropical and Mediterranean climates. Love and Dansereau (1959) identified the centre of origin of *X. strumarium* in Central or South America. The native North American *Xanthium* taxa originally grew along shores and rivers and the fruits were dispersed by water or occasionally by animals (Love & Dansereau 1959). Their hard brown, ovoid fruits covered with hooked spines and with two terminal beaks, readily stick to clothing and fur, and thus are easily spread (CABI 2018).

Interestingly the statement that *X. strumarium* originates from Central or South American (Love & Dansereau 1959) needs a revision. Recently, the burs of *X. strumarium* were discovered at the Yuergou site (400–200 cal BC) in the Turpan Basin of northwestern China. It is interesting that most of these cockleburs were broken with their seeds missing. They were likely opened by humans with a knife. The cockleburs were likely used as a common medicinal resource (Sheng & al. 2018).

X. strumarium tolerates a wide variety of soil types and textures and a soil pH range of 5.2 to 8.0, as well as frequent flooding and saline conditions (Weaver & Lechowicz 1983). This plant occurs in cultivated fields, along beaches, coastal dunes, watercourses, railway embankments, roadsides, field edges, and waste places but is not common in the mountains. It prefers open communities and will disappear if shaded or crowded (Kaul 1971). *X. strumarium* reduces germination of various crops (Gilani & al. 2010; Shajie & Saffari 2007). Adventive (not native) to all continents (Kuzmanov 2012) it is regarded, invasive in UK (CABI, 2018) and potentially invasive in Bulgaria where was the most frequently recorded plant species during a survey in the field borders between the crop land and adjacent territories in representative agricultural areas (Aneva & al. 2018).

We aim of this mini-review is to reveal the potential of *Xanthium strumarium* as cheap source of compounds with valuable pharmacological activities. Here we present data on the: 1) traditional ethnobotanical data from its native habitats; 2) modern investigations of pharmacological activity and essential secondary compounds.

Material and Methods

In 2018 and in 2019, we accessed the Scolar Google, Web of Science and PubMed to identify publications with the search string: "*Xantium strumarium**, "*traditional**", "*compounds**", "*pharmacological**", "*medicinal**", "*toxic**", "*cancer**", "*inflamatory**", "*in vivo**", "*in vitro**"etc.

Ethnobotanical data on traditional medicinal use

Xantium strumarium, has been used for various medicinal purposes. The traditional medicinal applications are summarized in Table 1. Few of the traditional indications are contradictive (decreases perspiration/diaphoretic properties). Similar applications are reported for distantly situated arrears and cultures.

Table 1. Comparison between traditional medicinal applications and modern pharmacological tests of *Xanthium strumarium*.

Traditional medicinal application	Contemporary pharmacological tests
Dysentry [1, 2]	Significant inhibition of *Shigella flexneri* [22]
Stomach diseases [3], diarrhea [21]	No modern pharmacological tests
Dental sourness and toothaches [4, 5, 16]	Analgesic [26]
Astringent, bleeding [6, 9, 17, 18]	No modern pharmacological tests
Small pox [1, 3, 6]	No modern pharmacological tests
Leprosy [7]	No modern pharmacological tests
Tuberculosis [34]	No modern pharmacological tests
Eczema, skin disease, boils and pimples [8-10, 19, 20]	Antibacterial activity against *Bacillus subtilus* and *Staphylococcus aureus* [22]
Chronic malaria [8, 11]	No modern pharmacological tests
Immunostimulant [12]	Immunostimulant [12]
Decreases perspiration [13]	No modern pharmacological tests
Diaphoretic properties [8, 10]	No modern pharmacological tests
Febrifuge [4, 14]	No modern pharmacological tests
Diuretic properties [1, 6, 8, 9] as well as leucorrhoea and urinary diseases [5, 8, 10, 11, 15]	Diuretic properties [23]
Insect bite [9]	No modern pharmacological tests
Earache and strumous disease [4]	No modern pharmacological tests
Sedative [1, 6]	CNS depressant Antidepressant -like activity
To cure total paralysis [34]	No modern pharmacological tests
Headache, analgesic [5, 7]	Analgesic [26]
No anecdotal reports	Anticancer activity, antimitotic [23, 27-32]
No anecdotal reports	Antitussive [23, 24]
No anecdotal reports	Antifungal [23, 24]
No anecdotal reports	Anti-inflammatory [23, 24, 26]
No anecdotal reports	Hypoglycaemic [23, 24]
No anecdotal reports	Antioxidant [23, 24]
No anecdotal reports	Antitrypanosomal [33]

Legend: [1] Arshad & Khan (2000); [2] Gilani & al. (2014); [3] Ullah & al. (2013); [4] Ali & Qaiser (2009); [5] Gilani, & al. (2014); [6] Hussain, & al. (2008); [7] Akhtar & al. (2013); [8] Bhardwaj & (2011); [9] Yadav & al (2015); [10] Manandhar (2003); [11] CABI (2018); [12] Alonso-Castro & al. (2016); [13] Hocking (1956); [14] Speck (1941); [15] Bocek (1984); [16] Fowler (1989); [17] Reagan (1929); [18] Swank (1932); [19] Elmore (1944); [20] Hocking (1956); [21] Curtin (1949); [22] Nasir & Khan (2012); [23] Kamboj & Saluja (2010); [24] Kim & al. (2003); [25] Keya & al. (2018); [26] Han & al. (2007); [27] Roussakis & al. (1994); [28] Saxena & Mondal (1994); [29] Kim & al. (2003); [30] Kim & al. (2005); [31] Ramirez-Erosa & al. (2007); [32] Nibret & al. (2001); [33] Talakal & al. (1995); [34] Romero (1954).

North and Central America

According to the traditional, folk and herbal medicine of native tribes of North and Central America *Xantium strumarium* is used for various health conditions. Navaho used the burs to decrease perspiration (Hocking 1956). Houma used it as febrifuge drug - decoction of root taken for high fever (Speck 1941). Costanoan used it as urinary aid - a decoction of seeds was used for bladder ailments (Bocek 1984). Lakota used *X. strumarium* as a medicine in ceremonies, although detailed information was not reported (Rogers 1980). Paiute, Northern applied it as oral aid - burs rubbed on sore gums to take the pain, poison and blood out (Fowler 1989). Apache, (White Mountain) used roots and leaves as a blood medicine while seeds were ground to make bread (Reagan 1929). Costanoan used to eat seeds in pinole (Bocek 1984). Keres (Western) used a poultice of ground, seed powder on open sores or saddle galls (Swank 1932). Mahuna used *X. strumarium* as an orthopedic aid (for total paralysis) and as a tuberculosis remedy (Romero 1954). Navajo applied *X. strumarium* as a dermatological cure - the plant was used as a liniment for the armpit to remove excessive perspiration (Elmore 1944; Hocking 1956). Pima used the plant against diarrhea as a decoction of burs (Curtin 1949). *X. strumarium* is listed among traditionally used medicinal plants from Mexico, Central America, and the Caribbean with pharmacological evidence of its immunostimulant effects (Alonso-Castro & al. 2016).

India

According to traditional, folk and herbal medicine of the Central Aravalli region of Rajasthan (North West India) *X. strumarium* is credited with powerful diaphoretic properties. The dose of half to one ounce is recommended in chronic malaria, leucorrhoea and urinary diseases. Leaves are used in eczema and leucoderma (Bhardwaj & al. 2011). The use against malaria is particularly emphasised (Bhardwaj & al. 2011; CABI 2018).

According to traditional, folk and herbal medicine of the northern part of Chhattisgarh State of India (Central India) *X. strumarium* is credited with skin disease, bleeding, diuretic, insect bite, urinary problems (Yadav & al. 2015).

Nepal

Fruit paste mixed with other plants is used to treat boils and pimples traditionally Manandhar (2005). In farwest Nepal *X. strumarium* is reported as one of the alien species used in traditional medicines although it is not indicated for the treatment of what health condition (Kunwar & al. 2015).

Pakistan

In Rawal Town, Pakistan is reported as sedative, diuretic, smallpox and dysentry cure Arshad & Khan 2000. In Wana district is reported to have the highest use value of all medicinal plants. Roots, fruit and seeds are demulcent and useful for stomach diseases and smallpox (Ullah & al 2013). It is one of the important medicinal plants of Hattar region in spring season - Whole plant is claimed to have a sedative, astringent, diuretic activity. Root is used in earache, fruit used in smallpox (Hussain & al. 2008). In Chitral valley leaves are chewed for dental sourness. Root is used in earache and strumous disease (Ali & Qaiser 2009). In the region of Swat, North Pakistan - fever, headache, analgesic (Akhtar & al 2013). In Galliat, Ayubia, Kashmir, Bahawalpur and Cholistan (Desert) area - the fruit is used in the cure of dysentery and urinary diseases. It is also useful in toothaches, headaches, and leprosy (Gilani & al. 2014).

China

The fruits (Chinese name 'Cang-Er-Zi') are used as a traditional herbal medicine in China for the treatment of nasal sinusitis, headache, urticaria and arthritis (Pharmacopoeia of P.R. China 2000).

Chemical composition of the plant

Xanthium strumarium contains vast number of metabolites (Fan & al. 2019). They fall into the following groups of compounds: terpenes, flavonoids, phenolic acids (such as: caffeic acid, potassium3-O-caffeoylquinate, 1-O-caffeoylquinic acid, chlorogenic acid, 4-O-caffeoylquinic acid, 1,4-di-O-caffeoylquinic acid, 1,5-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinicacid, 4,5-di-O-caffeoylquinic acid, 1,3,5-tri-O-caffeoylquinic acid, 3,4,5-tri-O-caffeoylquinic acid, and cynarin, Minato & al. 1965; Winters & al. 1969; Malik & al. 1992; Marco & al. 1993; Kamboj & Saluja 2010). Cumarins (Fan & al. 2019) and thiazinediones (Ma & al. 1998; Qin & al. 2006 Fan & al. 2019) are reported from *X. strumarium*. The plant also contains sesquiterpene lactones (Malik & al. 1992; Marco & al. 1993; Kim & al. 2003). i.e. xanthinin, xanthatin (deacetylxanthinin), xanthanol, isoxanthanol, xanthinosin, xanthanolides, deacetylxanthumin, etc.

Chemical studies on the composition of the stem oil differed two main groups of compounds: monoterpenes (49.4%) and sesquiterpenes (29.1%). The leaf oil has similar composition: monoterpenes (55.8%) and sesquiterpenes (26.4%). The major components in both oils were identified as: limonene (35.0%), carveol (25.0%), α-ionone (10.5%), β-caryophyllene (6.0%) and p-cymene (5.0%) (Kamboj & Saluja 2010).

Many researchers claim importance to more phytochemical groups for the pharmacological action of the herb, but the findings are inconsistent within the sources (Kamboj & Saluja 2010). Apart from the etheric oil, sesquiterpenes and phenolics form the main pharmacologically active principles of the species. Also the sesquiterpene lactones (Fig. 1) should not be neglected (Roussakis & al. 1994; Saxena & Mondal 1994; Schmidt 1999, Kim & al. 2003; Nibret & al. 2011, Ghantous & al 2013, Amorim & al 2013, Piloto-Ferrer & al. 2019).

Toxicity

The data about toxicity are somewhat contradictive. The plant was traditionally considered toxic. During the famines of the 1950's in China, their seeds were collected and consumed by the farmers of Northeast China. Thirty-five people suffered from alimentary toxicosis, and seven individuals were killed (Shen 2005). It has been reported as fatal to cattle and pigs (Masvingwe & Mavenyengwa 1998). The chloroform and hexane soluble fractions of root extract were tested in Wistar rats and the toxicity determination was done according to the Organization for Economic Cooperation and Development guidelines. The study indicates that acute and subacute administration did not produce any toxicity to rats as evident from weight change, mortality, and limited biochemical and histopathological analysis. Hence, the extracts are considered as unclassified and are found to be safe (Aranjani & al. 2012). However kaurene glycosides that are present in extract obtained with 75% aqueous ethanol by infiltration induce hepatotoxicity in mice by way of its induction of oxidative stress as lipid peroxidation in liver, which merited further studies. Therefore, these toxic constituents explain, at least in part, the hepatotoxicity of *X. strumarium* L. (Wang & al. 2011). The presence of sesquiterpene lactones is also a hazard for toxicity (Kamboj & Saluja 2010). Sesquiterpene lactones are potent pharmacologically active principles (e.g. artemisinin and its derivatives are in use as first-line antimalarials and parthenolide, have recently reached cancer clinical trials). However, the toxicological profile of these compounds must be thoroughly characterized, since the same properties that make these compounds useful medicines can also cause severe toxicity (Schmidt 1999, Ghantous & al 2013, Amorim & al. 2013).

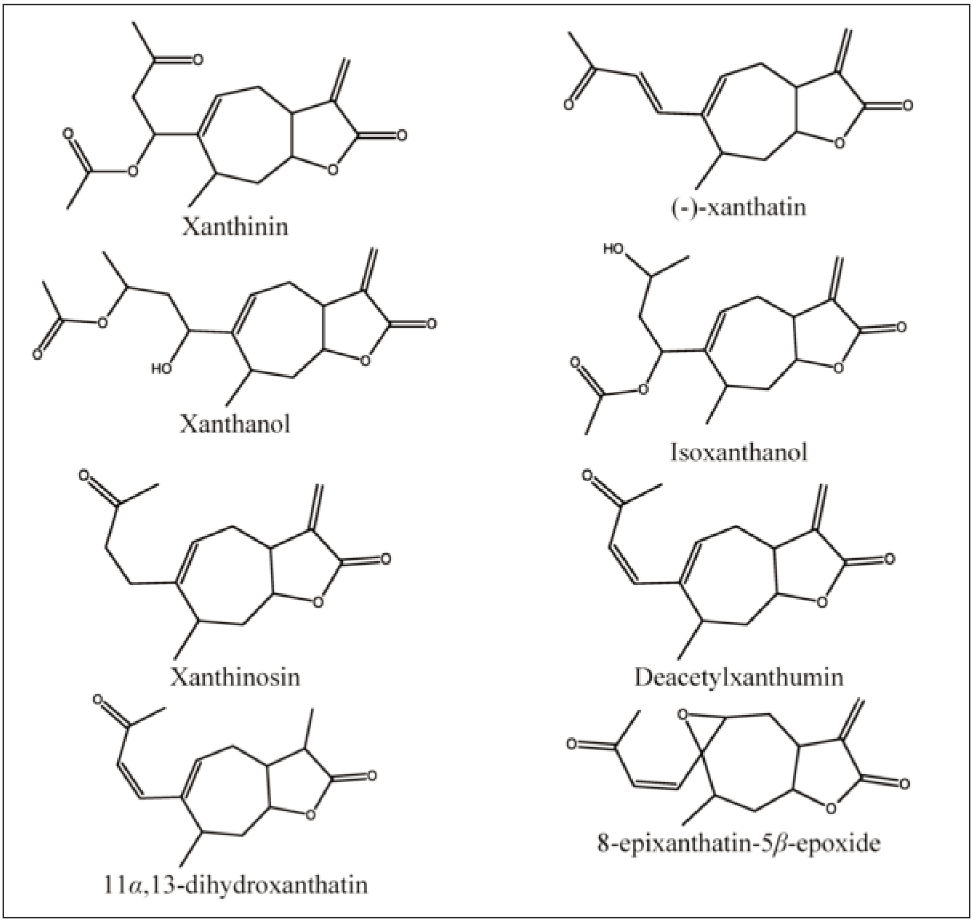

Fig. 1. Sesqiuterpene lactones in *Xanthium strumarium*.

Contemporary pharmacological investigations

Due to the presence of sesquiterpene lactones is related the potential anticancer activity (Roussakis & al. 1994; Saxena & Mondal 1994; Kim & al. 2003; Nibret & al. 2011, Piloto-Ferrer & al. 2019). For instance xanthatin and xanthinosin are two sesquiterpene lactones isolated from the burs which showed moderate to high *in vitro* cytotoxic activity in the human cancer cell lines WiDr ATCC (colon), MDA-MB-231 ATCC (breast), and NCI-417 (lung). Xanthatin and xanthinosin were purified as the result of a multi-screening bioassay-guided study of wild plant species of the family Asteraceae, collected from various sites in Saskatchewan, Canada (Ramirez-Erosa & al. 2007). Also the In vitro results show that X. strumarium, mediated by xanthatins, induces G2/M arrest and impair anaphase entrance. This leads to a significant induction of apoptotic and necrotic in CT26WT cells, demonstrating their significant anti-proliferative activity through interfering with the mitotic apparatus (Piloto-Ferrer & al. 2019).

The western herbalism practice to treat yellow diarrhea, caused by various species of Shigella with *Xanthium strumarium* was tested. Results obtained indicate that chloroform fraction from *X. strumarium* showed significant activity against *Shigella flexneri* (19 mm zone of inhibition). The same fraction revealed good antibacterial activity against *Bacillus subtilus* and *Staphylococcus aureus*, the main causative agents for skin related disorders (Nasir & Khan 2012).

The plant showed antitussive, antifungal, antiinflammatory, antinociceptive, hypoglycaemic, antimitotic, antioxidant, CNS depressant activity, diuretic effects, contact dermatitis, insecticidal and herbicidal activities (Kamboj & Saluja 2010) as well as antitrypanosomal effect (Talakal & al. 1995).

Quite interesting is the antidepressant-like activity of *X. strumarium.* The experimental data clearly demonstrate that the methanolic extract of *X. strumarium* posses antidepressant-like activity in the animal model. Administration of MEXS extract of 50, 100, and 200mg/kg significantly (p< 0.001) decreased the immobility periods of mice when compared to the control group (0.9% normal saline water), indicating significant antidepressant-like activity. The positive control imipramine hydrochloride (30mg/kg) also showed similar effect as MEXS (Keya & al. 2018).

Conclusions

Xanthium strumarium deserves further investigations as it has valuable pharmacological activities. Many of the traditional applications are confirmed with modern pharmacological tests but there are more ethnobotanical data that are still not tested. Also the data collected and analyzed in 2010 concerning the pharmacological activity (Kamboj & Saluja 2010) are extended and enriched later on (Nibret & al. 2011; Nasir & Khan 2012; Keya & al. 2018). As *X. strumarium* posses character of invasive plant species and being most often recorded weed in the agricultural lands (Aneva & al. 2018), it offers lavishly plant substance resources. Additionally a pharmaceutical application of this plant in the future would reduce its populations and thus would contribute to the biodiversity conservation.

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