REVIEW ARTICLE

Phytopharmacological review of *Xanthium strumarium L.* (Cocklebur)

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Xanthium strumarium L. (Family: Compositae) a medicinal plant commonly found as a weed, is widely distributed in North America, Brazil, China, Malaysia and hotter parts of India. The herb is traditionally used mostly in treating several ailments. Extracts of the whole plant, especially leaves, roots, fruits and seeds have been applied in traditional medicine for the treatment of leucoderma, poisonous bites of insects, epilepsy, salivation, long-standing cases of malaria, rheumatism, tuberculosis, allergic rhinitis, sinitis, urticaria, rheumatoid arthritis, constipation, diarrhoea, leprosy, lumbago, pruritis, bacterial and fungal infections. This comprehensive account provides a botanical description of the plant, its phytochemical constituents and pharmacological activities are reviewed, focussing on antibacterial, antitumour, antitussive, antifungal, antiinflammatory, antinociceptive, hypoglycaemic, antimitotic, antioxidant, antitrypanosomal, CNS depressant activity, diuretic effects, contact dermatitis, insecticidal and herbicidal activities. Most of the pharmacological effects can be explained by the constituents like sesquiterpene lactones, glycoside, phenols, polysterols present in all plant parts. However, future efforts should concentrate more on in vitro and in vivo studies and also on clinical trials in order to confirm traditional wisdom in the light of a rational phytotherapy. Because of its multi-activity, in particular, anti-tumour, anti-cancer activity, so much attention is focussed on the herb. Finally, research needs quantitation of individual constituents and assessment of their pharmacological activities in humans.

Key words: Clinical trials, pharmacological activities, phenols, phytotherapy, sulphated glycoside, *Xanthium strumarium*

INTRODUCTION

Xanthium strumarium L. (Family: Compositae) is a cocklebur or burweed commonly found as a weed in roadsides, rice fields, hedges throughout the tropical parts of India.[1,2] The word "xanthium" is derived from an ancient Greek word "xanthos" meaning yellow and "strumarium" means "cushionlike swelling," with reference to the seedpods which turn from green to yellow as they ripen (later they become deep yellow to brown).[3] It is commonly called chotagokhru due to the shape of its fruit which look likes the cow's toe. In many parts of India, it is known as adhasisi, as this weed is used for the treatment of common disease hemicrania." The genus *Xanthium* includes 25 species, all of American origin. *Xanthium spinosum* Linn. and *X. strumarium* Linn. are used medicinally in Europe, North America and Brazil; *Xanthium canadens* Mill. is used in North America and Brazil and *X. strumarium* Linn. in China, India and Malaysia.[4]

Animals eat young plants which are toxic, and can be poisoned if they consume them in sufficient quantity and die after ingesting this plant. In Western literature, xanthium is not described as a medicinal herb, but is a well-known toxic herb (rated as highly toxic) for grazing animals (e.g. cattle, pigs, horses, poultry).[3] It has been recognised to cause losses in cattles,[5,6] horses, goats, pigs, sheep,[6-8] swine and diminished weight gain in poultry.[9] The plant produces allergic contact dermatitis in susceptible humans. Cocklebur was cultivated as a leafy vegetable in China. Young floral tops and the two leaves below are boiled in water and eaten as a pot-herb in Assam. The herb as such is suspected to be poisonous but the toxic substances are removed by washing and cooking.[10] A highly toxic glycoside, carboxyatractyloside, is present in the seeds and seedlings of cocklebur. The amount of the chemical was measured to be 0.457% in the seeds and 0.12% in the seedling at the two-leaf stage. The poison occurs only in the cotyledons or seed leaves of the seedlings. The toxin readily disappears after germination.[11]

BOTANICAL DESCRIPTION

X. strumarium is an annual herb, up to 1 m in height, with a short, stout, hairy stem and commonly grows in waste places, roadsides and along river banks in warmer parts. Leaves broadly alternate are triangular-ovate or suborbicular, light and bright green in colour in an alternate pattern with irregular lobes and relatively inconspicuous teeth, 5–15 cm long, often three-lobed, with prominent veins, long petiole, scabrous on both sides. Stems are round or slightly ribbed, often speckled

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Received: 23-05-2009; **Accepted:** 26-06-2010; DOI: 10.4103/0973-8258.69154

with purple and have short white hairs scattered across the surface; flower heads are in terminal and axillary racemes, and are white or green; numerous male uppermost, female ovoid, covered with hooked bristles [Figure 1]. Fruits are obovoid, enclosed in the hardened involucre, with two hooked beaks and hooked bristles. Flowering time in India is August-September. This weed is easily dispersed through animals as the fruits have hooked bristles and two strong hooked beaks. It flowers from July to October, and the seeds ripen from August to October. The flowers are monoecious and are pollinated by insects. The plant is self-fertile. The fruits are harvested when ripe and dried for use.[12]

ETHNOPHARMACOLOGICAL ACTIVITY

The herb is used a reputed medicine in Europe, China, Indo-China, Malaysia and America. The whole plant, especially root and fruit, is used as medicine. According to Ayurveda, the plant has cooling, laxative, fattening, anthelmintic, alexiteric, tonic, digestive, antipyretic activities and improves appetite, voice, complexion and memory. It cures leucoderma, biliousness, poisonous bites of insects, epilepsy, salivation and fever. The plant has been reported as fatal to cattle and pigs.[13] It is used by various native American tribes to relieve constipation, diarrhoea and vomiting. Indigenous Chinese applications are as a headache remedy and to assist with cramping and numbness of the limbs, ulcers and sinus problems. The plant is considered to be useful in treating long-standing cases of malaria[14] and is used as an adulterant for *Datura stramonium*.

The leaves and roots are used for their anodyne, antirheumatic, antisyphilitic, appetiser, diaphoretic, diuretic, emollient, laxative and sedative activities. An infusion of the plant has been used in the treatment of rheumatism, diseased kidneys and tuberculosis. It has also been used as a liniment on the armpits to reduce perspiration.[14] The fruits contain a number of medically active compounds including glycosides and phytosterols. They are anodyne, antibacterial, antifungal, antimalarial, antirheumatic, antispasmodic, antitussive, cytotoxic, hypoglycaemic and stomachic. They are used internally in the treatment of allergic rhinitis, sinusitis, urticaria, catarrh, rheumatism, rheumatoid arthritis, constipation, diarrhoea, lumbago, leprosy and pruritis.[15] They are also used externally to treat pruritis and small pox. The ashes are applied to sores on the lips and mucous membrane of the mouth. The root is a bitter tonic and febrifuge.[14] It has historically been used in the treatment of scrofulous tumours and used locally on ulcers, boils and abscesses. [16] The paste of green spiny fruits is used against migraine and the juice of leaves and fruits is believed to be useful for smallpox and the roots are used for cancer.[14] The burs are used in china as a tonic, diuretic and sedative. A decoction of the root has been used in the treatment of high fevers, leucorrhoea and to help a woman expel the afterbirth. A decoction of the seeds has been used in the treatment of bladder complaints. A poultice of the powdered seed has been applied as a salve on open sores. Seeds yield semi-drying edible oil (30–35%) which resembles sunflower oil and is used for treating bladder infections, herpes and erysipelas. The dried leaves are a source of tannin. A yellow dye is obtained from the leaves. The seed powder has been used as blue body paint.[15] The dried plant repels weevils from stored wheat grain. The seed contains an essential oil.[15,17]

Figure 1: *Xanthium strumarium* L.

Cocklebur was cultivated as a leafy vegetable in China. Young floral tops and the two leaves below are boiled in water and eaten as a pot-herb in Assam. The herb as such is suspected to be poisonous but the toxic substances are removed by washing and cooking.[10] Xanthium is defined as a toxic herb in Chinese Pharmacopoeia. Patients taking over 100 g of the fruit may complain of malaise, headache and gastrointestinal disturbance in 12 hours. Other toxic symptoms in humans include dizziness, drowsiness, coma and generalised tonic seizure, appearance of jaundice, hepatomegaly, impairment of liver function, proteinuria, cylindruria, and haematuria. The toxic substance soluble in water is extensively used for the treatment of sinus congestion. It has not been blamed for any harmful effects among Western consumers, and has not been banned by any health department in any country. Yet, it is a herb that should be investigated, as will be done here. Because of its multiactivity, in particular, antitumour, anticancer activity, so much attention is paid towards the herb. Pollens are found to cause asthma, rhinitis and dermatitis in susceptible persons. The herb is suspected of causing allergy only in autumn when it is in the prefruiting stage.[18-21] Xanthium is classified in modern Materia Medicas as either a herb for dispelling wind chill or a herb for dispelling wind damp. Its modern uses are mainly for allergy-type disorders, specifically allergic rhinitis, atopic dermatitis (urticaria), chronic paranasal sinusitis and chronic eczema.[3]

CHEMICAL CONSTITUENTS

The aerial parts of the plant contain a mixture of unidentified alkaloids, which are said to be toxic. Besides alkaloids, the aerial parts of the plant contain sesquiterpene lactones, viz. xanthinin; its stereoisomer, xanthumin, xanthatin (deacetylxanthinin); a toxic principle, a sulphated glycoside: xanthostrumarin, atractyloside, carboxyatractyloside; phytosterols, xanthanol, isoxanthanol, xanthinosin, 4-oxo-bedfordia acid, hydroquinone; xanthanolides;[22-26] caffeoylquinic acids; α and γ-tocopherol;[27] thiazinedione,[28] 4-oxo-1(5),2,11,(13)-xanthatriene-12,8-olide, known as "deacetyl xanthumin" an antifungal compound; linoleic acid. The main toxic compound isolated from the plant has been identified as carboxyatractyloside, a kaurene glycoside previously called xanthostrumarium.[29] In addition to carboxyatractyloside CAT, potentially toxic ingredients include several sesquiterpene lactones (e.g. guaianolides, germacranolides, and elemanolides).[30] [Figure 2]

Aerial parts contain three xanthanolide and xanthane-type sesquiterpenoids, 11α,13-dihydroxanthatin, 4β,5β-epoxyxanthatin-1α,4α-endoperoxide, 1β,4β,4α,5α–diepoxy xanth-11(13)-en-12-oic acid,[31] a dimeric xanthanolide, sesquiterpene lactones,[32] 8-epixanthatin, 2-epixanthumin and 8-epi-xanthatin-5β-epoxide. The phenols isolated are caffeic acid, potassium3-O-caffeoylquinate, 1-O-caffeoyl quinic 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.[33,34] [Figure 2] The toxic principles of the seeds are hydroquinone, choline and a third more toxic unidentified compound. Besides these, the seeds also contain considerable amount of iodine.[10,14]

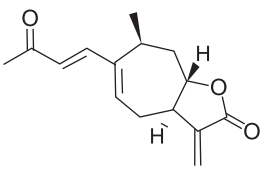
The fruits are rich in vitamin C. Thiazinediones isolated from the fruits are 7-hydroxy methyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside,[35] 2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-11-O-β-D-glucopyranoside, 7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5-dione, 7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]thiazine-3,5-dione-(2-O-caffeoyl)-β-D-glucopyranoside, ferulic acid, formononetin and ononin.[35] [Figure 2] The powdered shell of fruit can be used for making activated carbon. The shells contain 15.9% pentosans and can be used as a raw material for the synthesis of furfural.[36] The young fruit contains glucose, fructose, sucrose, organic acids, phosphatides, potassium nitrate, β-sitosterol, γ-sitosterol, β-D-glucoside of β-sitosterol called strumaroside.[37-39] The total free amino acid content is 1.65%. It includes amino-*n*-butyric acid, arginine, aspartic acid, cystine, glutamic acid, methionine, proline, tryptophan in micromoles per milligram dry weight.[40,41]

The stem oil is characterised by large amounts of monoterpenes (49.4%) and sesquiterpenes (29.1%); the leaf oil is also characterised by higher amounts of monoterpenes (55.8%) than sesquiterpenes (26.4%). The oil is light yellow, odourless and has the same taste as other vegetable oils. Oil contains d-limonene (35.0%), d-carveol (25.0%), α-ionone (10.5%), terpinolene (7.0%), β-caryophyllene (6.0%) and *p*-cymene (5.0%).[42,43] The essential oil obtained by hydrodistillation of the stems and leaves was analysed by gas chromatography (GC) and GC/mass spectrometry (MS). Twenty-two compounds representing 86.4% of the stem oil were identified, among which bornyl acetate (19.5%), limonene (15.0%) and β-selinene (10.1%) were the major ones. The leaf oil of the plant is characterised by higher amount of limonene (24.7%) and borneol (10.6%) among the 28 components comprising 85.2% of the total oil detected. Steam distillation of the essential oil of *X. strumarium* under pressure gave in decreasing amounts: limonene, carveol, terpineolene, β-caryophyllene, *p*-cymene, sabinene, bornyl acetate, β-cubebene and a trace of α-pinene.[8] Sesquiterpenes (germacrene D) constituted the major part of the volatiles in Iran.[17,44] Fatty acid composition of oil includes unsaturated fatty acids like oleic, linoleic, palmitic, stearic, behenic acid and saturated fatty acids include capric, lauric, myristic and palmitic acid.[45]

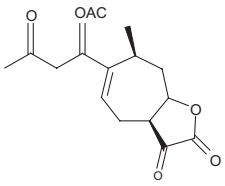
Lipid fraction of the plant is composed of C_{27}–C_{33} *n*-alkanes and C_{28}–C_{32} *n*-alkanols, and the unsaponifiable fraction consists of C_{23}–C_{35} *n*-alkanes and C_{22}–C_{30} *n*-alkanols besides a mixture of β-sitosterol, stigmasterol, campesterol,[46] isohexacosane, chlorobutanol, stearyl alcohol, stromasterol, oleic acid, 3,4-dihydroxycinnamic acid, heptacosanol, oxalic acid, KCl, KNO_3, K_2SO_4 in roots and stems.[14,47] β-selinene, phytol, xanthanodiene, isoalantolactone, 2-hydroxytomentosin, tomentosin, isoguaiene is also present.[48,49]

PHARMACOLOGICAL PROFILE

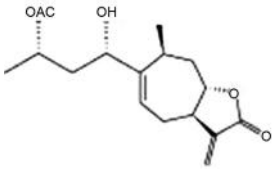
X. strumarium is widely distributed in Zimbabwe where it is often found as a noxious weed in maize fields, along roadsides, wastelands and around cattle kraals. It is known to occur on the sandy river beds in the Matebeland province where it would be accessible to extensively reared pigs and cattle and causes intoxication of these animals. However, because the toxicity of this plant is largely unknown in this country, it has not been implicated for causing livestock losses. The herb has several health-promoting benefits, including antibacterial, antitumour, anticancer, antifungal, anti-inflammatory, antinociceptive, antititussive, hypoglycaemic, antimitotic, antitrypanosomal, antimalarial, diuretic, antioxidant, analgesic, repellent and insecticidal activities.



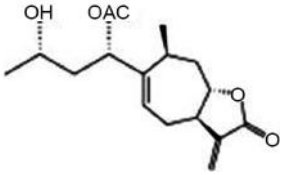
(–)-Xanthatin



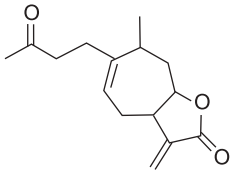
Xanthinin



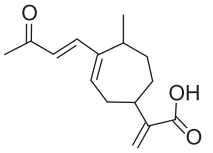
Xanthanol



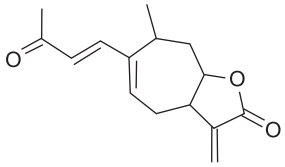
Isoxanthanol



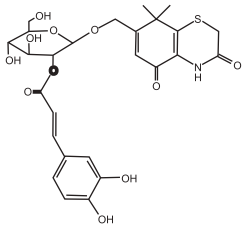
Xanthinosin



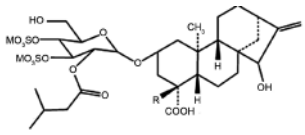
4-Oxo-bedfordia



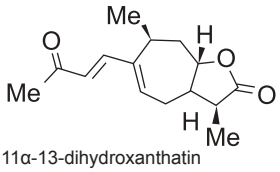
Deacetyl xanthumin



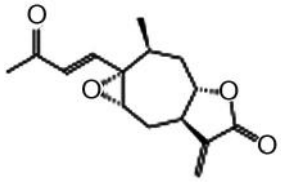
7-Hydroxy-8,8-dimethyl-4,8-dihydro benzol [1,4]thiazine-3,5-dione-(2-O-caffeoyl)-β-D-glucopyranoside



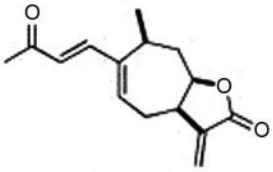
Atractyloside (ATR)
M = H, R = H
Carboxyatractyloside (CATR)
M = H, R = COOH



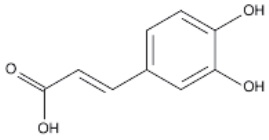
11α-13-dihydroxanthatin



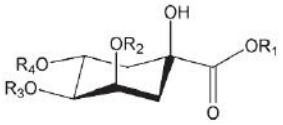
8-epixanthatin-5β-epoxide



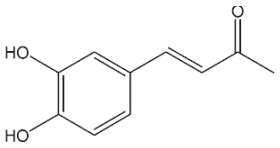
8-epixanthatin



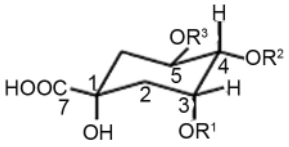
Caffeic acid



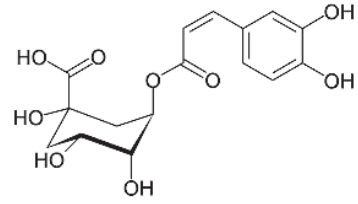
1,3,5-tri-O-caffeoylquinic acid: R_1 = H; R_2 = caffeoyl; R_3 = caffeoyl; R_4 = caffeoyl
1,5-di-O-caffeoylquinic acid: R_1 = H; R_2 = caffeoyl; R_3 = H; R_4 = caffeoyl
3,5-di-O-caffeoylquinicacid: R_1 = H; R_2 = H; R_3 = caffeoyl; R_4 = caffeoyl
Potassium3-O-caffeoylquinate: R_1 = K; R_2 = H; R_3 = caffeoyl; R_4 = H
1-O-caffeoyl quinic acid: R_1 = H; R_2 = caffeoyl; R_3 = H; R_4 =H



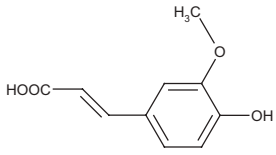
Caffeoyl



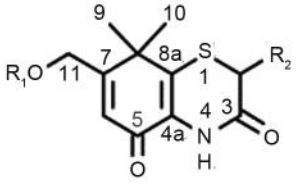
3,4,5-tri-O-caffeoylquinic acid: R_1 = caffeoyl; R_2 = caffeoyl; R_3 = caffeoyl
4,5-di-O-caffeoylquinic acid: R_1 = H; R_2 = caffeoyl; R_3 = caffeoyl
4-O-caffeoylquinic acid: R_1 = H; R_2 = caffeoyl; R_3 = H



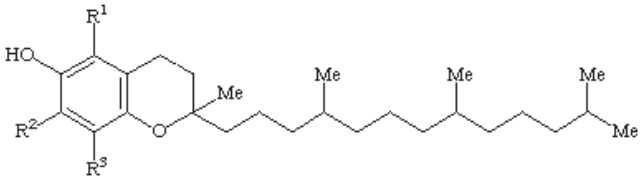
Chlorogenic acid



Ferulic acid



7-hydroxy methyl-8,8-dimethyl-4,8-dihydrobenzol [1,4]
thiazine-3,5-dione-11-O-β-D-glucopyranoside: R_1 = β-D-Glcp; R_2 = H
2-hydroxy-7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzol[1,4]
thiazine-3,5-dione-11-O-β-D-glucopyranoside: R_1 = β-D-Glcp; R_2 = OH
7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzo[1,4] thiazine-3,5-dione: R_1 = H; R_2 = H



α-tocopherol R_1 = R_2 = R_3 = Me
γ-tocopherol R_1 = H; R_2 = R_3 = Me

Figure 2: Structures of phytochemical constituents

Antibacterial, Antitumour and Anticancer Activities

The plant extract exhibited antimicrobial activity against *Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Candida albicans* and *Candida pseudotropicalis*. The activity is due to presence of xanthol.[50] The xanthinin contained in plant acts as a plant growth regulator and has antibacterial activity. Seed yields semi-dry edible oil (30–35%) which resembles sunflower oil and is used in bladder infection, herpes, and erysipelas.[51,52] Two xanthanolide sesquiterpene lactones, 8-epi-xanthatin and 8-epi-xanthatin-5β-epoxide,[1,2] isolated from the leaves demonstrated significant inhibition on the proliferation of cultured human tumour cells, i.e. A549 (non-small cell lung), SK-OV-3 (ovary), SK-MEL-2 (melanoma), XF498 (CNS) and HCT-15 (colon) *in vitro*. They were also found to inhibit the farnesylation process of human lamin-B by farnesyltransferase, in a dose-dependent manner *in vitro*.[46,53,54]

Alcoholic solution of xanthinin in concentration of 0.01–0.1% showed strong antibacterial activity against gram-negative bacteria and fungi.[55] In a study, the antibacterial activity of each extract (ether or ethylacetate under neutral, acidic and alkali conditions) was tested against 16 strains of bacteria, 2 strains of yeast and 2 strains of fungus. The ether neutral extract exhibited the strongest growth inhibition upon the eight strains of gram-positive bacteria, six strains of gram-negative bacteria and *Cryptococcus neoformans*. Fluorescein diacetate (FDA) testing of XE-N and XEA-N showed growth inhibition of the three strains of *Escherichia coli, S. aureus* and *C. albicans* even at 30 ng/ml and with the exception of *Pseudomonas aeruginosa*. The results of antitumour activities of the crude extract and of its purified compounds showed that XE-N-S1 had the best antitumour activity against HeLa cells. In terms of antitumour activity against HepG2 cells, XE-N-S1 and XE-N-S3 were superior; against HT29 cells, XE-N and XE-N-Sl had a good activity; against Saos2, NCI H522, NCI H1703 and Clone M3 cells, XE-N-51 was very active; against LN CAP cells, XE-N-S3 was the best. Comparing the cellular toxicities of various extracts and purified compounds with the existing antitumour agents, XE-A and XEA-A and XEA-B were found to have the lowest toxicity and XE-B had a lower toxicity than etoposide. XE-N-S1 and XE-N-S3 showed higher toxicities than etoposide and the toxicity of XE-A-S3 was higher than that of etoposide and lower than that of cisplatin.[53]

Xanthatin showed the strongest gastric protective activity. In a study, the inhibitory action exerted by this molecule on the lesions induced by 0.6 N HCl and 0.2 N NaOH was highly significant, reducing ulceration in the range of 58–96% at a dose from 12.5 to 100 mg/kg in rats. These results appear to confirm that the presence of a non-hindered 4,5-unsaturated carbonyl group seems to be an essential structural requirement for the gastric cytoprotective activity of these compounds. In order to explore this possibility, a theoretical conformational analysis was performed. The mechanism of protection would involve, at least in part, a nucleophilic attack of the sulfhydryl group from the biological molecules present in the gastric mucosa to electrophilic carbons accessible in suitable Michael acceptors.[56]

Gautam *et al*. tested the plant extract for *in vitro* antimycobacterium activity and found that the ethylacetate extract and MeOH-petroleum ether extract possess significant *in vitro* antimycobacterium activities against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis*. Ethyl acetate extract exhibited 4 mm zones of inhibition at 20 mg/ml in agar-well diffusion assay using streptomycin sulphate (1 mg/ml) as positive control showing 20 mm zones of inhibition.[57] The petroleum ether and methanol extracts exhibited 70 and 12% inhibition, respectively, at 1 mg/ml in radiorespirometry assay using BACTEC system with rifampin (2 μg/ml) and clarithromycin (32 μg/ml) as positive controls.[58]

The plant also possesses anticancer activity. Fouche *et al.* screened the plant extract for *in vitro* anticancer activity against a panel of three human cell lines (breast MCF7, renal TK10 and melanoma UACC62) at the CSIR. The plant extract that exhibited anticancer activity against these three human cell lines was screened by NCI against 60 human cancer cell lines organised into sub-panels representing leukaemia, melanoma, cancer of the lung, colon, kidney, ovary, CNS, breast and prostate.[59]

Antitussive Activity

Mandal *et al.* showed that the extract possesses significant antitussive activity in a dose-dependent manner in mice. The antitussive potential of extract was comparable to that of codeine phosphate (10 mg/kg), a standard drug. The extract at a dose level of 100, 200 mg/kg (p.o.) showed significant inhibition of cough reflex by 39.75 and 65.58%, respectively, during 2 hours of the experiment.[60,61]

Antifungal Activity

The plant has potent antifungal activity against pathogenic as well as non-pathogenic fungi due to the presence of terpenes, d-limonene and d-carveol.[40] The antifungal compound from plant was identified as 4-oxo-1(5),2,11,(13)-xanthatriene-12, 8-olide, known as "deacetyl xanthumin." Fresh sap from *X. strumarium* at 50-fold dilution was highly effective in controlling the disease incidence in pot and field trials. Crude extracts of the plant inhibited mycelial growth and zoospore germination of *Phytophthora drechsleri*, the causal agent of Atractylis rot, *in vitro* at a concentration of 12.5 and 15.6 μg/ml, respectively.[60] The leaf extract of plant may be used as a potent fungitoxicant against the mycelial growth of *Fusarium moniliforme*.[62] Amerjothy *et al*.

studied the hexane, ethylacetate and alcoholic extracts of the leaves for their antimicrobial (antifungal, antibacterial) activities by disc diffusion assay. The antifungal activity was compared with that of fluconazole and nystatin as standards. Hexane extract showed marked inhibition against *C. albicans*, *Aspergillus niger*, *P. aeruginosa* and *S. aureus* at a concentration of 200 μg/disc. Ethylacetate extract showed an inhibition against *A. niger, S. aureus* and *E. coli* at a concentration of 200 μg/disc. Alcoholic extract showed an inhibition only against *S. aureus* at a concentration of 200 μg/disc.[63] The plant possesses significant potency against *C. neoformans* and *Candida* species with low toxicity to brine shrimps. The 4,5-dihydroxyl groups in the quinic acid moiety were necessary for the activity and introduction of a free amino group increased the inhibitory activity against *Aspergillus fumigatus*.[64]

Anti-inflammatory, Antinociceptive and Vasorelaxant Activities

In an investigation, the effects of methanol extract of the semen of *X. strumarium* L. (MEXS) on lipopolysaccharide (LPS)-induced nitric oxide (NO), prostaglandin E_2 (PGE_2) and tumour necrosis factor-α (TNF-α) production in RAW 264.7 cells were evaluated. Data indicate that MEXS is a potent inhibitor of NO, PGE_2 and TNF-α production, which is achieved by inhibition of nuclear factor kappa B (NF-κB) DNA binding activity and the translocation of NF-κB to the nucleus by blocking the degradation of inhibitor of kappa B-α (IκB-α) that is responsible for its anti-inflammatory effects. Further, the anti-inflammatory and antinociceptive activities of MEXS (100, 200 mg/kg/day, p.o.) *in vivo* reduced acute paw oedema induced by carrageenan in rats, and showed analgesic activities in an acetic acid induced abdominal constriction test and hot plate test in mice.[65] Presence of phenolic components like caffeoylquinic acids (3,5- and 4,5-O-dicaffeoylquinic acids) explains the antinociceptive effects.In another investigation, an ethanol extract was fractionated on the basis of polarity. Among the different fractions, the *n*-butanol fraction showed the highest anti-inflammatory activity in the croton-oil–induced ear oedema test and furthermore reduced the number of writhings induced by acetic acid in mice in a dose-dependent manner. This indicates that the *n*-butanol fraction of plant possesses potent analgesic effects which are likely to be mediated by its anti-inflammatory activity.[66] The plant also possesses vasorelaxant activity and relaxes vascular smooth muscle via endothelium-dependent nitric oxide.[67]

Yoon *et al.* isolated xanthatin, xanthinosin, and 4-oxobedfordia acid from *X. strumarium* and revealed them as inhibitors of NO production in LPS-activated microglial BV-2 cells. The α-methylene-γ-lactone ring was identified as the essential moiety for their biological activity. They exerted their activity through the inhibition of I-κB-α degradation, NF-κB activation, and subsequent suppression of iNOS and COX-2 expression. These results imply that plant may be beneficial for the treatment of neuroinflammatory diseases through downregulation of such inflammatory enzymes as iNOS and COX-2.[68,69]

Hypoglycaemic Activity

The plant exhibited potent hypoglycaemic activity in the rat.[56,70] The antihyperglycaemic effect of caffeic acid and phenolic compounds present in the fruit of *X. strumarium* was investigated. After an intravenous injection of caffeic acid into diabetic rats of both streptozotocin-induced and insulin-resistant models, a dose-dependent decrease of plasma glucose was observed. However, a similar effect was not produced in normal rats. An insulin-independent action of caffeic acid can thus be considered. Otherwise, this compound reduced the elevation of plasma glucose level in insulin-resistant rats receiving a glucose challenge test. Also, glucose uptake into the isolated adipocytes was raised by caffeic acid in a concentration-dependent manner. Increase of glucose utilisation by caffeic acid seems to be responsible for the lowering of plasma glucose.[71] Carboxyatractyloside also possesses hypoglycaemic activity.[59]

Cockleburs as such provide a relatively inexpensive source of raw material for worldwide production of a naturally occurring insulin substitute. The main advantage is that the product does not produce its results by causing production of insulin by stimulation of Islets of Lagerhans in the pancreas.[3]

Antimitotic Activity

X. strumarium may possess antimitotic components. In a study, the plant was screened for its antimitotic activity using the microtubule-tubulin system isolated from mammalian tissue. The separated fractions obtained were identified and used for *in vitro* polymerisation studies. The whole as well as partially separated chemical constituents showed effective inhibition of tubulin polymerisation.[72]

Neuropharmacological Activity

Xanthumin showed CNS depressant activity. Rodents treated with the plant extract exhibited alterations in general behaviour patterns, reduction in spontaneous motility, prolongation of pentobarbitone-induced sleep, suppression of exploratory behaviour patterns, and avoidance response.[73,74]

Antitrypanosomal and Antimalarial Activities

In an investigation, the antitrypanosomal activity of crude 50% ethanolic extract of *X. strumarium* leaves was studied *in vitro* and *in vivo*. The extract exhibited trypanocidal activity at all four concentrations tested, i.e. 5, 50, 500 and

1000 μg/ml, *in vitro*. *In vivo* trial revealed that the extract exerted antitrypanosomal effect at dosages of 100, 300 and 1000 mg/kg, intraperitoneally. At 100 and 300 mg/kg doses, the survival period of the *Trypanosoma evansi* infected mice was significantly prolonged. However, the extract was found to be toxic to the animals at 1000 mg/kg dose.[75] Quan *et al.* found that H_2O and MeOH–H_2O extract of the plant has antiplasmodial activity by inhibiting the growth of the chloroquine-resistant *Plasmodium falciparum* strain FCR-3 with EC_{50} values less than 10 μg/ml.[76] The presence of xanthinin explains these effects of the plant.

Contact Dermatitis

The plant is suspected to cause air-borne contact dermatitis. In a study, patch tests with a 15% aqueous extract of air-dried leaves showed a severe positive reaction. The titre of contact hypersensitivity with the plant extract was more than 1:100,000 and for *Parthenium hysterphorus* it was 1:10, indicating a high degree of hypersensitivity to *X. strumarium*. Further tests in 14 other patients revealed a high prevalence of cross sensitivity between the two plants.[77] The antigens in the two plants seem to be very similar.[78,79]

Diuretic Activity

The plant possesses diuretic properties. The study was conducted on 60 *Balb/c* rats and fluid extract of *X. strumarium* 30% were administered. The results obtained with the plant were compared with that of a positive control, such as cyclophosphamide, and a negative control that was administered the alcoholic vehicle used in the extract.[80] Also, another experimental study was carried out in Wistar rats to evaluate the potential diuretic effect of fluid extract in 65% hydroalcoholic solution of *X. strumarium*. Three levels of dose, i.e. 100, 200 and 400 mg/kg of body weight, were used. Results confirm the similarity between diuretic action of extract and that of Furosemide, with a high level of accompanying natriuresis and kaluresis. Results confirmed and supported the safety of the plant because there were no clinical signs evidencing toxicity and deaths with a dose of 2000 mg/kg, which is the limit dose, according to standard used.[81]

In the course of *in vitro* screening for the angiotensin converting enzyme (ACE) inhibitory activity of the various extracts from medicinal plants, *n*-BuOH soluble extract of the seeds of *X. strumarium* was found to exhibit distinct ACE inhibitory activity. Bioassay-guided fractionation and purification of the *n*-BuOH soluble extract of the seeds of plant afforded a new xanthiazone-11-glucopyranoside. The ACE activity was significantly inhibited by the addition of a new xanthiazone-11-glucopyranoside in a dose-dependent manner.

Antioxidant and Hydrophobic Activities

The antioxidant effect of extract fractions from plant on lens protein was estimated by cross-linking assay method. The cross-linking activities of extract fractions (crude, $CHCl_3$, EtAc and H_2O) on lens protein were determined by incorporation with [(14)C]N-formyl-lysine. The results obtained indicate that crude, $CHCl_3$ and EtAc extracts showed approximately 10% of antioxidant effect, whereas H_2O extract showed no effect by cross-linking assay.[82]

The effect of plant fractions on survival of human lens epithelia, HLE B-3 cells, was tested by using cell culture system. H_2O_2-mediated cellular death and its IC_{50}, with approximately 100 μM H_2O_2 were determined by using MTT assay. The HLE B-3 cells pretreated with extract fractions were incubated with 100 μM H_2O_2, and in order to assess the cell viability, the cultures were incubated with MTT solution. Among the fractions, crude fraction, $CHCl_3$ fraction, and EtAc fraction were found to have statistically significant antioxidant activities at concentrations of 500 ng/ml, 1 μg/ml and 100 ng/ml, respectively. Also, the fact that only the fractions extracted with organic solvents had antioxidant activity suggests that the active components from the extract have hydrophobic property.[82]

In another study, various (hexane, ethylacetate, *n*-butanol, water) extracts of *X. strumarium* were screened and their antioxidant activities in a range of lipid peroxidation systems using rat brain homogenates, antihaemolysis assay of red blood cells, and other *in vitro* assays to determine their ability to scavenge superoxide and hydroxide radicals were evaluated. Butanol extract relatively had higher antioxidant activity. It could be related to presence of phenolic compounds such as tannins and flavonoids, and also polyphenols because of their scavenging ability with reactive oxygen species (ROS) and chelating ability with divalent cations due to hydroxyl groups.[83]

Repellent and Insecticidal Effects

The repellent effects of the extracts of *X. strumarium* fruits and leaves diluted with 1/6, 1/8, 1/10 water (w/v) for fruits and 1/6, 1/8 (w/v) for leaves were investigated with randomised plot design and 25 replicates under laboratory conditions. It was found that the insecticidal effect was low, whereas the repellent effect was quite high. On the other hand, the effect of 1/6 concentration of fruit extract against adult and larvae of Colorado Potato Beetle was investigated under field conditions and the repellent effect was confirmed. This effect may appear because of toxic components of the fruits and leaves of *X. strumarium*. Low toxic components were hydroquinone and xanthatin. These components are known as repellent components.[84,85]

Antiallergic Activity

The aqueous extract of dried fruit of *X. strumarium* exerts inhibitory dose-dependent effect on mast cell mediated

allergic reaction. The extract inhibited local immunoglobulin E (IgE) mediated passive cutaneous anaphylactic reaction. When 0.1 mg/ml *Xanthii fructus* was added, the secretion of TNF-α from anti-dinitrophenyl (DNP) IgE antibody-stimulated mast cells was inhibited by 56%. Hence, fruits of the plant may be beneficial in the treatment of various types of allergic or inflammatory diseases.[86]

Phototoxicity of the plants may also be used therapeutically. *In vivo* phototoxicity in mice of seed oil of *X. strumarium* was evaluated for sunburn oedema, formation of sunburn cell, decrease of epidermal langerhans cells and local suppression of contact hypersensitivity by UVA irradiation.[87]

TOXICITY

X. strumarium is poisonous to mammals. It is reported to have medium to strong allergenic effects. The toxic principle is a sulphated glycoside, carboxyatractyloside**,** found in the seeds and during the two-leaf seedling stage.[88] The mature plant is reported as non-toxic, although toxicosis has been reported in cattle which had ingested mature plants with burs despite the general belief that ingestion of burs should be limited by mechanical injury during mastication. CAT is a plant growth inhibitor. It has been hypothesised that it functions in a germinating seed to keep the second seed in the fruit capsule dormant so that its development is delayed until the next year. Cocklebur fruits, the portion used in Chinese herbal medicine, have the risk of high carboxyatractyloside content, particularly in the spines.[3,43,88,89] CAT is water soluble but is not destroyed by boiling (decocting) and probably not washed away by simple rinsing. Rather, removing the prickles appears to be the best way to reduce the toxic component, which is partly accomplished by stir-frying alone.[3]

When ingested in sufficient quantities by animals, it produces hypoglycaemia and hepatic damage; the latter possibly is due to increased vascular permeability in response to severe hypoglycaemia. The mechanism of action has been proposed to be an uncoupling (disruption) of oxidative phosphorylation, a process essential for the cell's energy metabolism and transfer system. In addition to CAT, it contains potential toxic ingredients like several sesquiterpene lactones that can cause vomiting, weakness, tremors, weak pulse, loss of appetite and convulsions in high doses. Marked hypoglycaemia, elevated serum glutamate oxaloacetate transaminase and serum isocitric dehydrogenase concentrations occurred in pigs with acute hepatic necrosis, which had received either cocklebur seedlings, ground bur or carboxyatractyloside xanthatin.[8,30] The plant is a potential cause of sudden death in pigs extensively reared in Zimbabwe, which is revealed by an investigation in which six healthy porkers of the Mukota breed were fed *ad libitum* either crushed burs (fruits) or the two-leaf seedling stage of *X. strumarium* at 2% of body weight. Major clinical signs were depression, vomiting, abdominal pain, weakness, recumbency, paddling convulsions terminating in death from 6 to 96 hours after ingestion. Microscopically, acute hepatic congestion and haemorrhage, centrilobular hepatocyte necrosis, with occasional binucleation together with discoid lysis of skeletal and cardiac muscle fibres were remarkable changes.[13]

Another toxicological study on male rats revealed that metabolism of CAT may have a role in its cytotoxic and lethal effects. Clinical signs of toxicosis, duration of illness, lethality, gross lesions and hepatic and renal histopathological lesions were recorded. The CAT toxicosis has independent lethal and cytotoxic components, which could be partly due to an active metabolite formed by *de novo* synthesised P450–P448-independent haemoprotein, while CAT detoxification may occur partly through haemoprotein-independent, (phenyl butazone) PBZ-inducible enzyme, and partly through a P448-dependent (BNF-inducible) enzyme; and CAT detoxification apparently is not P450- or GSH-dependent.[90,91]

Atractyloside poisoning is an infrequent, but often fatal, form of herbal poisoning, which occurs worldwide, especially in Africa and the Mediterranean regions. The primary mechanism of atractyloside poisoning is known to be inhibition of the mitochondrial ADP transporter. Atractyloside in large amounts gives rise to massive necrosis, but *in vitro* studies have shown that at lower doses the cells progress to apoptosis.[92] Symptoms of poisoning appear in several hours. Gait, gloom, muscle contraction, the spasm, lying down, breath and heart rate it increases, with critical example 12-24 dies being hour reaches.

MISCELLANEOUS

MSMA-resistant (R) and susceptible (S) biotypes of common cocklebur were used to study PSI and PSII activities, and chlorophyll and carotenoid content of MSMA-treated and untreated R and S biotypes. MSMA at 1, 10, and 100 mg/l did not inhibit either PSI or PSII activities. The R biotype had higher PSI and PSII activity than the S biotype with and without MSMA treatments. R biotype leaf discs had higher chlorophyll and carotenoid content than the S biotype after treatment with MSMA; the S biotype cotyledons had higher levels of both pigments as compared to the R biotype cotyledons. MSMA induced a reduction in both pigments in S biotype cotyledons, and in young and mature leaf discs. Results indicate that photosynthetic capability might indirectly be involved in the resistance mechanism and

carotenoids may protect against MSMA toxicity, possibly caused by an induced free radical mechanism.[92,93]

The possible allelopathic and herbicidal effects of ground plant tissues and leaves, flowers and seed extracts of hearleaf of cocklebur on some crops and weeds were studied. Results state that hearleaf cocklebur had no allelopathic effect on seeds of *Daucus carota* L., *Descurania Sophia* L. Webb. Ex Prant, *Abutilon theophrastii* Medik. *and Lepidium sativum* L. However, it inhibited the germination considerably in *Triticum vulgare* L., *Lolium perenne* L. and *Avena sterilis* L. Effect of hearleaf cocklebur on the plants' growth in the pots in post-emergence ranged from 0.00 to 86.66%. The herbicidal effects of hearleaf cocklebur were greater on *A. retroflexus*, *A. sterilis* and *Conium maculatum* L. than on the other plant species used in this study.[34]

To assure the safe use of xanthium, it should be processed by stir-frying, as described in the Pharmacopoeia of the PRC, to eliminate most of the prickles. Water washing of the fruits or decocting is not a satisfactory detoxification method; stir-frying with retention of most of the fruit spikes is not as effective in eliminating the toxic component as when the spikes are removed. There is no evidence that the residual amounts of CAT or other compounds are a threat to human health. Still, as a precaution, the dosage of xanthium should be limited to the range (3–10 g/day) normally recommended in Materia Medica guides, whenever there is prolonged use of the herb, thus allowing a 10-fold margin of safety compared to the dose reported to have caused a significant reaction in a human (100 g). By the combination of correct processing and limiting the dose, the risk should be eliminated. Practitioners who use crude herbs can check the xanthium pods for the condition of the prickles. Manufacturers who produce extracts or powders need to check the pods prior to processing the finished product.[21]

Acetolactate synthase (ALS) was isolated from a field population of cocklebur that developed resistance to the herbicide Scepter following three consecutive years of application. The active ingredient of Scepter, imazaquin, gave an inhibitor concentration required to produce 50% inhibition of the enzyme activity that was more than 300 times greater for the resistant enzyme than for the wild-type cocklebur ALS. [94]

CONCLUSION

Pharmacological studies have generally confirmed the traditional use of extract of whole plant, root, leaves and fruits as an ailment for leucoderma, poisonous bites of insects, epilepsy, salivation, long-standing cases of malaria, rheumatism, tuberculosis, allergic rhinitis, sinitis, urticaria, rheumatoid arthritis, constipation, diarrhoea, leprosy, lumbago, pruritis, and inflections due to bacteria and fungus. Most of the biological effects can be explained by the high amount of xanthatin, xanthanolide sesquiterpene lactones (antibacterial, anticanacer, antitumour), desacetyl xanthumin (antifungal), xanthanol, xanthumin (CNS depressant), thiazinedione, desacetyl xanthumin (antifungal), carboxyatractyloside, caffeic acid derivative (hypoglycaemic) and its quinic acid derivatives (hypoglycaemic, anti-inflammatory, analgesic) and terpenes (antioxidant) present in all plant parts.

The pharmacological studies so far have mostly been performed *in vitro* and *in vivo* with animals. Therefore, clinical studies are urgently needed in order to confirm traditional wisdom in the light of a rational phytotherapy. Even today, plants are the almost exclusive source of drugs for a majority of the world's population. Therefore, it remains a challenge for scientists to provide efficient, safe and cheap medications, especially for rural areas. The plant is widely distributed in North America, Brazil, china, Malaysia and hotter parts of India. Their quantification of individual phytoconstituents as well as pharmacological profile based on *in vitro*, *in vivo* studies and on clinical trials should be further investigated.

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Source of Support: Nil, **Conflict of Interest:** None declared.