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Review

Nutriology, pharmacology and cardiovascular effects of *Xanthium sibiricum*

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Summary. *Xanthium sibiricum* is an annual herb of Family *Asteraceae* and *Xanthium L*. This herb has high nutritive values due to its large content of proteins, fats, sugars, calcium, and iron. Traditional medicine have revealed that *Xanthium sibiricum* is effective for the treatment of infection, inflammation, cancer, and pain, *etc*. The food therapy of *Xanthium sibiricum* has shown curative effects for mastitis and tinea capitis. The chemical constituents of *Xanthium sibiricum* with pharmacological activities are mainly sesquiterpene lactones, volatile oils, phenolic acids, and water-soluble glycosides, that can be isolated fromthe plant, fruit, Siberian cocklebur borers (an insect larva, like a silkworm, parasitized in the stem of *Xanthium Sibiricum Patr. et Widd* [*X. strum-atium non L.*]), flower, and root. The fruits of *Xanthium sibiricum* have extensive prospect in clinical applications as for its hypoglycemic, anti-allergy, anti-bacterial, anti-inflammatory, analgesic, and anti-tumor effects. The cardiovascular effects of *Xanthium sibiricum* lie in anti-hyertensive, anti-coagulation, and anti-oxidant properties. However, *Xanthium sibiricum* may impair the hepatocytes, nephrocytes and myocytes and the coagulation system. It may even lead to death. To avoid using untreated prescriptions and unprocessed herbs may ensure the effective and safety use of *Xanthium sibiricum*.

Key words: Nutritive value; pharmacology; *Xanthium*.

Introduction

Xanthium sibiricum is an annual herb of Family *Asteraceae* and *Xanthium L.*, with 25 species distributed worldwide, native to the Americas and eastern Asia (1). The plant is mainly distributed in flatlands, mountains, wildernesses, roadsides, and grasslands. The whole plants, especially the fruits, are the widely used medicinal parts (Figure 1) (2). The fruits are hard in texture, with a slight odor and a bit bitter taste, but they were found to be poisonous. Nevertheless, many aspects of *Xanthium sibiricum* are to be answered in the subject of nutriology, pharmacology, and toxicology. This article aims to present an overview of this plant in terms of the above aspects.

Chemical Components

Xanthium sibiricum has a complex chemical composition. The chemical components isolated from *Xanthium sibiricum* are mainly sesquiterpene lactones and water-soluble glycosides.

The sesquiterpene lactones are its characteristic components, which have a bitter taste, and is attributed to its pharmaceutical activity. In the past decades, the sesquiterpene lactones that were isolated from the plant of *Xanthium sibiricum* were quite heterogeneous. Cumanda et al. (3) isolated five sesquiterpene lactones from the plant of *Xanthium sibiricum*, which were lasidiol pmethoxybenzoate, guaianolide ziniolide, 1α,13-dihydro-8-epoxy Chloropropanyl Xanthine, and two species of *Xanthium* derivatives. Zhang et

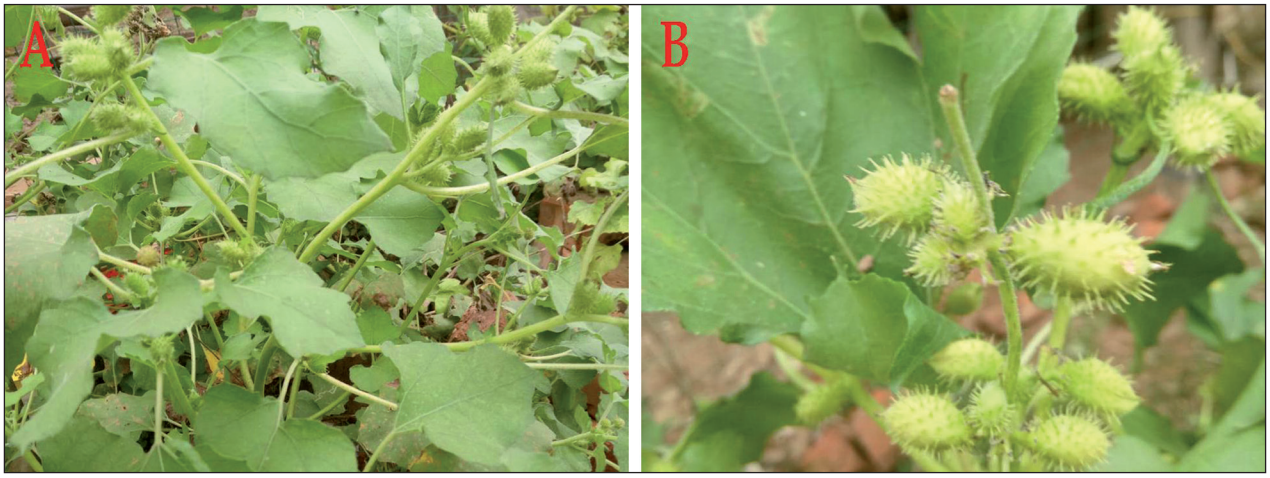

Figure 1. *Xanthium sibiricum*: (A) Plant; and (B) Fruits.

al. (4) isolated two sesquiterpene lactones from the stems of *Xanthium sibiricum*, namely sibiricoides A and sibiriolides B. Kovács et al. (5) isolated four sesquiterpene lactones, xanthatin, 2-hydroxyxanthinosin, 4-epiisoxanthanol, and 4-epixanthanol from the stems of *Xanthium sibiricum*.

Macleod et al. (6) found that the water-soluble glycosides of *Xanthium* may be the main toxic substances. Mahmoud et al. (7) identified two new water-soluble glycosides, xanthiside and thiazinedione glucoside, from a variant of *Xanthium sibiricum*, and studied their structures by spectroscopic techniques. Qin et al. (8) identified a new glycoside from the fruits of *Xanthium strumarium*, whose structure was elucidated by some spectral methods. Ruan and Li (9) detected that *Xanthium sibiricum* contains two important water-soluble glycosides, atractyloside and carboxyatractyloside. The authors proposed that these two components could suppress the protein transportion function of ADP/ATP *in vivo*, and cause significant decerease of blood glucose and subsequent metabolic disturbance, and therefore be taken as the main toxic ingredients of *Xanthium sibiricum*.

Xanthium is also rich in oils and fats, sterols, sesquiterpene lactones and water-soluble glycosides. Su et al. (10) reported that *Xanthium sibiricum* also contains some alkaloids, triterpenoids, tannins, amino acids, proteins, and glucose. Cheng et al. (11) isolated and identified 7 compounds from *n*-butanol extract of *Xanthium sibiricum*: ferulic acid, caffeic acid, chlorogenic acid, 4-O-caffeoyl quinic acid methyl ester, 6, 7-Dimethyl-1,4-dihydro-2,3-quinoxalinedione, caffeic acid choline ester, and 4'-O-dihydroerythroate sodium salt-β-D-glucoside. Among them, latter 4 compounds were isolated from this plant for the first time. Kan et al. (12) identified 15 compounds from the root of *Xanthium sibiricum*: stigmast-4-en-6β-ol-3-one, β-sitostenone, β-sitosterol, nonadecanoic acid, 5α,8α-epidioxy-22E-ergosta-6,22-dien-3β-ol, scopoletin, Jatrocin B, (±)syringaresinol, 9,9'-O-di-(E)-feruloyl-(-)-secoisolariciresinol, cleomiscosin A, cleomiscosin C, N-trans-feruloyl tyramine, daucosterol, 5-methyluracil, and uracil. Moreover, reports revealed that caffeoylquinic acids (13), and xanthiazinone (14) were isolated from the fruits of *Xanthium sibiricum*.

Nutrition

Xanthium sibiricum has high nutritive values due to the abundant proteins, fats, sugars, calcium, iron that the plant contains (Figure 2). Traditional medicine have revealed that *Xanthium sibiricum* is effective for the treatment of infection, inflammation, cancer and pain, *etc*. (Table 1). The food therapy by the prescriptions made of the young seedling, peeling fruits, fruit kernel, and fresh leaves of *Xanthium sibiricum* can be effective for mantitis and tinea capitis (15).

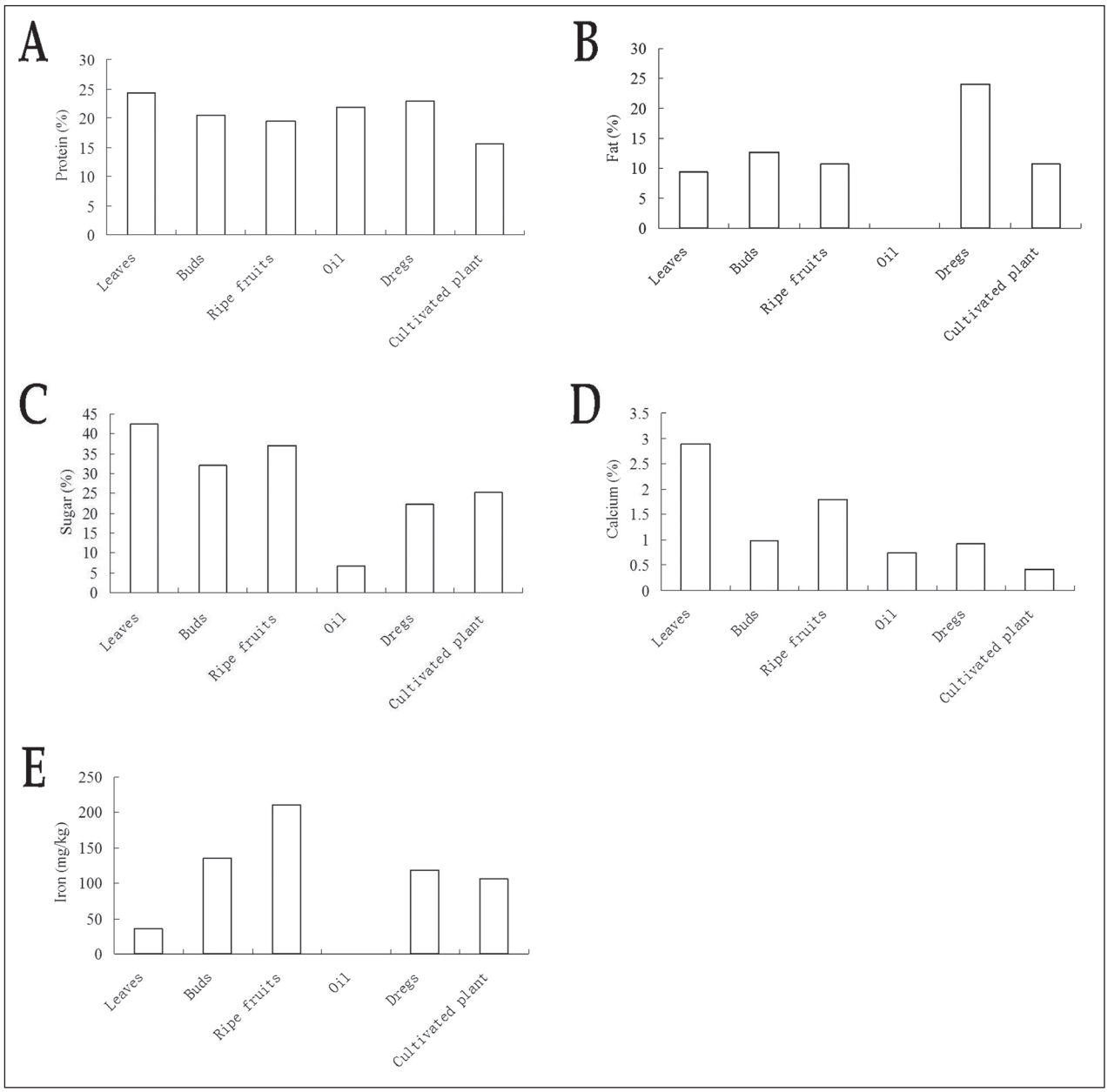

Figure 2. Nutrient ingredients of *Xanthium sibiricum*: (A) proteins; (B) fats; (C) sugars; (D) calcium; (E) iron.

Pharmacology

The chemical constituents of *Xanthium sibiricum* are mainly sesquiterpene lactones, volatile oils, phenolic acids and water-soluble glycosides. Xanthinin, Xanthumin, Xanthatin, and their derivatives are the main guaiacyl and cleavage guaiacyl lactones in *Xanthium sibiricum* (16). The pharmacological activities of *Xanthium sibiricum* are attributable to the chemical constituents contained in the plant, seed, Siberian cocklebur borers (an insect larva, like a silkworm, parasitized in the stem of *Xanthium Sibiricum Patr. et Widd* (*X. strum-atium non L.*)), flower, and root of *Xanthium sibiricum* (16). *Xanthium sibiricum* fruits have the most extensive clinical applications, for the hypoglycemic, anti-allergy, anti-bacterial, anti-inflammatory, analgesic and anti-tumor effects (Table 2) (17).

Table 1. Medicinal value of every part of *Xanthium sibiricam* in traditional medicine

Part of plant	Function	Preparation	Indication
(Whole) plant	Dispel wind and dampness, detoxify, relieve pain, relieve rheumatic pains	Fried juice	Bacillary dysentery, tympanitis, rhinitis, dysfunctional uterine bleeding, intractable eczema, schistosomiasis & falciparum malaria, leprosy
	Anti-cancer	Whole plant (or fruit)	Brain tumor, nasopharyngeal carcinoma, thyroid cancer, osteosarcoma, lymphosarcoma
	Skin disease	Decoct soup to wash the affected site	Rubella, eczema, itching; gangrene, insect dermatitis, contact dermatitis;
	Skin disease	Cointment external application	Bedsore, traumatic hemorrhage
	Inflammation	Compatibility with *Lonicera japonica Thunb* & *Radix isatidis*; Compatibility with *Ilex rotunda Thunb*., *Nelumbo nucifera*, *Boswellia carteri*, myrrh, borneol and so on.	Aching muscles and joints; prostatitis & pelvic inflammatory disea
Fruit	*Orifice*-opening	Compatibility with *Flos Magnoliae*, *Angelica dahurica* and peppermint, or make tea	Rhinitis, headache
	Dispelling wind & dampness	Finely ground powder use separately, or fried with *fructus arctii*	Rheumatic fever
	Skin disease	Orally taken or decoct soup to wash the affected site	Rubella and scabies
Root	Infection		Furculosis, erysipelas, acute laryngeal infection, appendicitis, cervicitis, urinary tract infection, dysentery, chyluria, hypertension, diabetes, ascariasis in children
Siberian cocklebur borers	Infection	Powdered or dipped in oil for external use	Furuncle, carbuncle, parotitis, mastitis, facial furuncle, ear furuncle & nasal vestibular furuncle; acute puralent infection of skin; hemorrhoids; corneal ulcer

Xanthium sibiricum Patrin ex Widder water extract can increase the sugar tolerance in normal mice and decrease the blood sugar level in diabetic mice, and it has stronger effect in inhibiting α-glucosidase activity than acarbose (18).

Xanthatin, the sesquiterpene lactone isolated from leaves of *Xanthium sibiricum*, had potent activity against *S. aureus* species, and other bacteria,including *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Salmonella typhi* (19). Moreover, a naphthoquinone from the the roots of *Xanthium sibiricum* showed moderate antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Micrococcus tetragenus*, and *Staphylococcus aureus* (20). It demonstrated that the methanol extracts of *Xanthium sibiricum* roots inhibited inflammatory responses via the inhibition of nuclear factor-κB and signal transducer and activator of transcription 3 in murine macrophages (21). In addition, xanthiumnolics A-E, the phenylpropanoid derivatives from the fruits of *Xanthium sibiricum* showed anti-inflammatory activities on lipopolysaccharide-induced nitric oxide production (22). Jiang et al. (23) investigated the anti-inflammatory activity of xanmonoter A and xanmonoter B, the two new monoterpene glucosides, isolated from the plant, showed their IC50 values were 17.4 and 22.1 μM, respectively.

Fang et al. (24) observed that 1β-hydroxyl-5α-chloro-8-epi-xanthatin, a sesquiterpene lactone isolated from *Xanthium sibiricum*, had an potent anti-cancer effect. The underlying mechanisms were to inhibit cell growth and induce apoptosis in human hepatocellular carcinoma cells through reactive oxygen species-mediated extracellular signal-regulated kinase/p38 mito-

Table 2. Pharmacology and clinical application of *Xanthium sibiricum*

Part of plant	Preparation or effective ingredient	Pharmacology	Clinical application
Plant (stem and leaf)	Infusion of leaf	Inhibite conduction of excitation of frog heart	Anti-hypertension
	50% ethanol extract	Anti-trypanosomiasis activity	Anti-trypanosomiasis
	Crude extract & xanthatin	*In vitro* cytotoxicity to cell lines of leukemia and human bronchial epidermoid tumors	Anti-tumor
	Sesquiterpene lactones (ziniolide)	Cytotoxicity and anti-tumor activity	Anti-tumor
	Extract	Diuresis & maintenance of electrolyte balance	Diuresis and maintenance of electrolyte balance
	Xanthumin	Inhibite central nervous system	Sedative
Fruit	Water extract, glycosides AA_2	Decrease blood glucose; anti-glycemic effect of adrenaline; significant reduction of liver glycogen level	Anti-glycemic
	Decoction	Anti-microorganism	Bacteriostatic, antifungal & antiviral effects
	Decoction	Inhibition of isolated frog heart and guinea pig heart	Mild anti-hypertensive effect
	Extract	Anti-coagulation effect against thrombin; recover the decrease of cholesterol, triglycerides and phospholipids in rabbits	Anti-coagulation
	Fruit	Significant inhibition of cellular immunity & humoral immunity; reduce β-endorphin in the hypothalamus and plasma; decrease interleukin-2 and its receptor; decrease the release of intracellular histamine	Treatment of allergic diseases
	Fruit	Reduce lipid peroxidation; enhance superoxide dismutase; scavenge oxygen free radicals	Anti-oxidant
	Supplemented *Xanthium* fruit	Reduce the amount of Evans blue exudation from abdominal cavity of mice induced by acetic acid, significantly reduced the swelling degree of ear inflammation induced by xylene, and significantly prolonged the time of writhing reaction induced by acetic acid in mice	Anti-inflammation and analgesia
Siberian cocklebur borers	Siberian cocklebur borers	Stimulating exudation of local neutrophils and phagocytic cells	Acute purulent infection
	Siberian cocklebur borer oil	Expanding corneal capillaries, accelerating blood circulation around cornea, forming protective film on corneal surface, cushioning mechanical friction between cornea and eyelid conjunctiva, and promoting the healing of corneal injury	Corneal ulcer
Root	Glycosides, water extracts and alcohol extracts	Anti-inflammation; prolonging the life span of mice inoculated with Ehrlich ascites carcinoma	Anti-inflammation; anti-cancer
Flower	Flower	Dispelling wind, removing dampness and relieving itching	The white leprosy itching; dysentery

gen-activated protein kinase activation and Janus kinase 2/signal transducer and activator of transcription 3 inhibition by glutathione depletion. Xanthatin, a natural bioactive compound of sesquiterpene lactones, isolated and purified from air-dried aerial part of *Xanthium sibiricum Patrin ex Widder*, indicated that the antiproliferative activity induced by xanthatin might be executed via G2/M cell cycle arrest and proapoptosis

in MKN-45 cells, and hat xanthatin may have therapeutic potential against human gastric carcinoma (25).

Cardiovascular Pharmacology

Xanthium sibiricum decoction can inhibit isolated frog heart and guinea pig heart, slow down cardiac rhythm, weaken myocardial contractility, and expand rabbit ear blood vessels, expand first and then contract frog blood vessels. *Xanthium* injection can reduce blood pressure of rabbits and dogs. Glycoside AA_2 has mild anti-hypertensive effect on rats and can enhance vascular permeability (16). Determined by measurement of the Rb concentrations, *Xanthium sibiricam* root could significantly increase myocardial nutritional blood flow in mice (26).

Ethyl acetate fraction of *Xanthium sibiricum* has strong anti-oxidant activities. *Xanthium sibiricum* could effectively reduce lipid peroxidation, reduce the content of lipid peroxide, and increase the activity of superoxide dismutase, indicating that *Xanthium sibiricum* could enhance the ability of scavenging free radicals and reduce the damage of free radicals to the body. Five chemical constituents isolated from *Xanthium sibiricum*, 5,7,3',4'-tetrahydroisoflavone, 3'-methylmyricetin, facarinol, heptadecanol-1,8-diene-4,6-diacetylene-3,10-diol and 3,4-dihydroxybenzoic acid, showed the highest anti-oxidant activity (27).

Xanthium sibiricum extract 0.2 g/mL could significantly prolong the coagulation time of bovine thrombin to human fibrinogen, and showed obvious antithrombin effect. The methanol extract of *Xanthium sibiricum* could quickly restore the decrease of cholesterol and triglyceride in rabbits caused by fasting, and could also make the phospholipid content rise to a certain extent (16).

Toxicology

A glycosidic substance (temporarily named AA_2) was isolated from the aqueous extract of *Xanthium sibiricum*, which may be the main toxic component of *Xanthium sibiricum* (16). The main toxic components of *Xanthium sibiricum* are atractyloside, carboxyl atractyloside, and 4'-desulfonated atractyloside (28-29). The content of carboxy atractyloside in deburring *Xanthium sibiricum* from 10 batches of different producing areas was higher than that in *Xanthium sibiricum*, which indicated that deburring *Xanthium sibiricum* could not reduce the toxicity of the plant (28). It may cause damages to hepatocytes, nephrocytes and myocytes and coagulopathies and even lead to death (30).

Cang Er Zi Wan (CEZW) is a herbal medication derived from *Xanthium sibiricum* used for allergic and respiratory disorders, but the intake of this drug has incidentally caused spasm, somnolence, hypoglycemia, renal, and liver toxicity (31). *In vitro* renal cytotoxicity and *in vivo* acute and chronic toxicity studies of the fruits of *Xanthium sibiricum* have shown that the water extraction of the fruits of *Xanthium sibiricum* had no cell membrane damage effects even at a high concentration of 100 μg/mL; however, it might affect the function of renal cell mitochondria (32).

In addition to liver and kidney injuries as the major side effects of the fruits of *Xanthium sibiricum*, neurotoxicity and cardio-toxicity of the fruits of *Xanthium sibiricum* were also common clinical adverse events. Oral administration and external application with the fruits of *Xanthium sibiricum* have often caused skin reactions, such as exfoliative dermatitis. It was suggested to standardize the clinical medication, avoid using untreated prescriptions and unprocessed herbs, thereby ensuring the effective and safety use of the fruits of *Xanthium sibiricum* (33).

Conclusions

The nutritive values of *Xanthium sibiricum* are attributable to its abundant contents like proteins, fats, sugars, calcium, and iron. Prepareatinos of the plant, fruit, Siberian cocklebur borers, flower, and root of *Xanthium sibiricum* can be effective for the hypoglycemic, anti-allergy, anti-bacterial, anti-inflammatory, analgesic, and anti-tumor effects. *Xanthium sibiricum* also shows anti-hyertensive, anti-coagulation, and anti-oxidant properties. However, *Xanthium sibiricum* contains toxic components, such as atractyloside, carboxyl atractyloside, and 4'-desulfonated atractyloside. To avoid using untreated prescriptions and unprocessed herbs may ensure the effective and safety use of *Xanthium sibiricum*.

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