CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF ASTRAGALUS HAMOSUS AND ASTRAGALUS TRIBULOIDES GROWN IN IRAQ

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ABSTRACT
Two members of Astragalus genus grown in Iraq, Astragalus hamosus and Astragalus tribuloides. They possessed a wide range of pharmacological effects. This review highlights the chemical constituents and pharmacological effects of Astragalus hamosus and Astragalus tribuloides.

Key words: Astragalus hamosus and Astragalus tribuloides, Biopesticides.

INTRODUCTION
Medicinal plants are the oldest form of healthcare known to mankind. Medicinal plants had been used by all cultures throughout history. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colors, biopesticides and food additives. In the early nineteenth century, many sensitive ingredients were isolated and introduced in the medical practice [1-54]. Astragalus L., is one of the largest genuses of flowering plants in the Leguminosae family. As annual or perennial herbs, subshrubs, or shrubs, the plants of Astragalus L. are widely distributed throughout the temperate and arid regions. So far, the genus has been estimated to contain 2000–3000 species and more than 250 taxonomic sections in the world [55-56]. Two members of Astragalus genus grown in Iraq, Astragalus hamosus and Astragalus tribuloides. This review was designed to highlight the chemical constituents and pharmacological effects of Astragalus hamosus and Astragalus tribuloides.

Astragalus hamosus
Synonyms

Taxonomic classification

Common names
Arabic: Ikil el malik, Adhafer el Shitan, Kethera, Krena; English: Tonkin bean, Melilot, King’s rown, King’s clove, Hook-pod milk-vetch, Yellow milk-vetch, European
milkvetch; Hawaiian: Puruk; Italian: Meliloto Falso; Russian: Astragal Kryuchkonosnyi [61-62].

Distribution
It was distributed from North Western Africa to Asia [57]. The plant nowadays is found in Africa: Algeria, Egypt, Libya, Morocco, Tunisia; Asia: Armenia, Azerbaijan, Gruzia, Iran, Iraq, Pakistan, Russia in Asia, Turkmenistan, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey in Asia, United Arab Emirates; Australasia: Australia; Europe: Albania, Bulgaria, Corsica, Crete, former Yugoslavia, France, Great Britain, Greece, Hungary, Italy, Malta, Portugal, Romania, Russia in Europe, Sardinia, Spain, Turkey in Europe, Ukraine; North America: United States [57,61].

Traditional uses
The plant was used as demulcent, emollient, galactagogue and laxative. It was also used in treating irritation of the mucous membranes, nervous affections and catarrh. Young seedpods were used in salads [63-67]. It is described to possess anti-inflammatory effect and is used as an anti-inflammatory agent by Unani physicians in various inflammatory disorders [68].

Description
Herbs, undershrubs or shrubs. Leaf paripinnate or imparipinnate, rarely unifoliate or digitately trifoliate; leaflets entire, stipels absent; stipulate. Inflorescence racemose, spicate umbellate or solitary; peduncules generally axillary. Flowers bracteate; bracteoles present or absent; pedicellate or sessile, violet or purple to white or pale yellow. Calyx tubular, teeth subequal. Vexillum ovate, obovate, oblong, panduriform or sometimes appendiculate. Wing and keel generally with long claws. Stamens diadelphous, vexillary stamen free, anthers uniform. Ovary sessile or stipitate, glabrous or pubescent; style straight or incurved, stigma mostly terminal, some times penicillate. Fruit sessile or stipitate, 2-valved, unilocular, partly or completely bilocular by an intrusive membrane. Seed often reniform [62].

Part used: The primary medicinal parts of the herb were the roots. Seed pod are edible [26].

Chemical constituents
The callus of the plant contained amino acids, the roots contained saponins and sterols. The leaves yield 3-nitropropionic acid [69]. The plant contained flavonols including hyperoside, isoorcitrin, astragalin and rhamnocitrin 4’-beta-D-galactopyranoside [70].

The composition of the volatile substances (% of the total volatiles) at the stage of leaf development in Astragalus hamosus were: alcohols (total) 0% (1-butanol, 2,3-butanediol 1.3, butanediol, 3-hexen-1-ol, 2-hexen-1-ol, 1-hexanol, 1-octen-3-ol, 3-ethyl-4-methylpentan-1-ol, benzyl alcohol, eugenol, 2-methoxy-4-vinyl phenol). Aldehydes 0% (nonanal, decanal, ketones, 3-methyl-2-pentenyl)-2 -cyclopenten-1-one). Acids 0.3% (nonanoic acid 0.1%, tetradecanoic acid 0.1%, pentadecanoic acid 0%, hexadecanoic acid 0.1%). Esters 2.1% (3-hexen-1-ol acetate 0%, 2,3-butanediol diacetate 0%, hexadecanoic acid methyl ester 0%, (18:1)-methyl ester 0%, glycerol tricaprylate 2.1%). Ethers 0% (2-ethoxybutane, 1-ethoxybutane, 1,1-dioctethoxylate). Hydrocarbons 14.9% (heptane 0.1%, heptadecane 0%, eicosenoic 0%, nonadecane 0.1%, eicosane 0%, docosane 0%, docosanoic acid 0.1%, heptacosane 2.1%, heptacosanoic acid 0%, octacosane 0%, onacosane 0.1%, triacontane 0%, octacosanoic acid 0%, hentriacontane 0%, docosene 0.1%, eicosanoic acid 0%, hexacosane 0.3%, squalene 0%). Aromatic hydrocarbons 0%, phenanthrene 0%, terpenes 10.1% (linalool 0%, 2-terpineol 0%, geraniol (nerol) 0%, hexahydrofarnesyl acetone 0.1%, phytol 10.0%). Others 0% (Isobutyl-isothiocyanate, 2,3-Dihydro benzofuran). However, the composition of the volatile substances (% of the total volatiles) at the stage of flowering in Astragalus hamosus were: Alcohols (total) 1.5% (1,3-butanediol 1.0%, 2,3-butanediol 0.2%, 2-hydroxy-6,10-dimethyl-5,9-undecadien 0%, 2-Methoxy-3-(2-propenyl) phenol 0%, 2-phenyl phenol 0.3%). Aldehydes 0.7% (hexanal 0.2%, heptanal 0%, nonanal 3.6%, decanal 0.2%). Acids 18.1% (octanoic acid 0.3%, butanoic acid 0.2%, nonanoic acid 0.3%, decanoic acid 0.2%, dodecanoic acid 0.8%, tetradecanoic acid 0%, hexadecanoic acid 16.3%). Esters 0.1% (2-ethoxybutane 0.1%). Esters 0.2% (hexanedioic acid ethylhexyl diester 0.1%, hexadecanoic acid hexadecyl ester 0.1%, isopropyl myristate 0.2%, hexadecanoic acid methyl ester 0.2%). Amines 0% (N-butyl-1-butanamine). Amides 0.4% (N,N-diethyl-formamide 0.4%), halogenated compounds (1,3-dichloro-2-propanone, 1,3-dichloro-2-propanol, hydrocarbons 26.1%, heptane 0.3%, cyclohexane 0%, pentane 3.9%, hexane 0%, heptane 0%, 4,11-dimethyl pentane 0%, octane 0%, nonane 0.1%, eicosane 1.7%, hecicosane 0%, 2-methyl eicosane 0%, docosane 0%, tricosane 0%, tetraicosane 0%, pentacosane 4.2%, hexacosane 2.0%, heptacosane 5.3%, octacosane 2.2%, nonacosane 8.0%, triacontane 0.1%, hentriacontane 0%, dotriacontane 0%, squalene 0%). Terpenes 6.3% (linalool 0%, hexahydrofarnesyl acetone 3.2%, phytol 0% and phytol 3.1%) [71]. Flavonol glycoside 7-O-methyl-kaempferol 4’-beta-D-galactopyranoside (rhamnocitrin 4’-beta-D-galactopyranoside), isoorcitrin and astragalin were isolated from Astragalus hamosus [72].

Pharmacological effects
Astragalus has a wide range of potential therapeutic applications in immunodeficiency syndrome, as an adjunct cancer treatment, and for its adaptogenic effect on the heart and kidneys. When ligusticum combined with astragalus, they have exerted a notable immunopotentiating
effect. They were included in many classic Chinese formulations, astragalus was also part of the Japanese and Korean herbal formularies [72].

**Antiinflammatory analgesic effects**

Astragalus hamosus pod extract showed anti-inflammatory activity, it induced significant reduction in the size of rats’ hind paws 3 hours after injection. The aqueous and alcoholic fractions of the pod exhibit a similar significant effect [68].

The anti-inflammatory effect of the hydroalcoholic extract of the pods of Astragalus hamosus (HAAH) was evaluated by the rat paw edema induced by formalin. Also the analgesic effect was examined by the acetic-acid-induced writhing response and hot plate test. The analgesic effects of chloroform, hexane, ethyl acetate and aqueous fractions were evaluated by the hot-plate method. The hydroalcoholic extract of Astragalus hamosus could reduce the edema in a dose-dependent manner (P<0.05). In the acute phase, the result of 1000 mg/Kg and in the chronic phase, the result of 100 and 300 mg/Kg of the extract were more significant and comparable with the effect of sodium salicylate. Also application of different doses of HAAH had significant anti-nociceptive effects on both animal models. The findings showed that HAAH at doses of 700 and 1000 mg/Kg produced analgesic effects comparable to sodium salicylate. The hexane and ethyl acetate (but not the other fractions) showed significant analgesic activity in hot plate test, when compared to morphine [74]. An aqueous and alcoholic extract of Astragalus hamosus (0.58 gm/kg) once a day for 13 days, orally produced highly significant anti-inflammatory effect in comparison to the control [68].

In the evaluation of the anti-viral effect of emodin plus astragalus polysaccharide (APS) in hepatitis B virus (HBV) transgenic mice, emodin and astragalus had a weak but persistent inhibitory effect on HBV replication in mice which may function as a supplementary modality in the treatment of hepatitis B infection. After 21 day of treatment with physiological saline containing (emodin and astragalus, 57.59 and 287.95 mg/kg per day, respectively), HBV DNA levels was significantly declined when compared with normal control group. A reduction in the contents of HBsAg, HBeAg and HBcAg in the mice was observed when compared with normal control group [75].

**Antioxidant and cytotoxic effects**

Pharmacological evaluations have shown antioxidant activity of methanolic extract of Astragalus hamosus [76].

The hepatoprotective activity of flavonoid rhamnocitrin 4-β-D-galactopyranoside (RGP) obtained from leaves of Astragalus hamosus L., was studied against N-diethylamino (DENA)-induced hepatic cancer in Wistar albino rats. Hepatic cancer in rats was induced by single-dose intraperitoneal administration of DENA (200 mg/kg). Induction of hepatic cancer was confirmed after 7 days of DENA administration by measurement of elevated level of serum α-feto protein (AFP). Administration of DENA in a single dose lofted the levels of serum biochemical parameters like alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total protein and AFP. Antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST) and lipid per oxidation (LPO) were annealed significantly by administration of RGP in a dose-dependent manner. The histopathological examination of rat liver section was found to reinforce the biochemical observations significantly. It was observed that a substantial and dose-dependent reversal of DENA-diminished activity of antioxidant enzymes like SOD, CAT, GPx, GST and the reduced DENA-elevated level of LPO with a marked change. Any elevation in the levels of serum markers along with suppression of free radical formation by scavenging the hydroxyl radicals is significantly prevented by RGP. It also modulates the levels of LPO and perceptibly increases the endogenous antioxidant enzymes level in DENA-induced hepatocellular carcinogenesis [77].

The purified saponin mixture from A. hamosus cytotoxicity was evaluated against a panel of human tumor cell lines. The saponin mixture demonstrated significant antiproliferative effects against a multi-drug resistant cell line HL-60/Dox, with a collateral sensitivity phenomenon, i.e. the IC_{50} value was lower in the resistant sub-line in comparison with the chemosensitive parent cell line HL-60 [70].

Evaluation of antiproliferative effect of a flavonol glycoside and saponins of Astragalus hamosus by MTT-dye reduction assay showed concentration-dependent inhibition of malignant cell proliferation by saponins, while the flavonoid exerted only marginal effects [78].

The anticancer activity of dinaline (histone deacetylase inhibitor), decitabine (DNA methylation inhibitor), erufosine (alkylphosphocholine derivate), tamoxifen (estrogen modulator) were compared with the isolated mixture of two saponins, derived from Astragalus hamosus, L. (Fabaceae) in two breast carcinoma cell lines MCF-7 estrogen receptor (ER) positive and MDA-MB 231 - ER negative. The study confirmed the antineoplastic activity of the saponin mixture, derived from Astragalus hamosus, which were previously found to be active against human leukemia cells. Moreover, the saponin mixtures showed dramatic decrease in the expression level of the mitochondrial protein BclXL, which outlines its special influence on the cell death signal transduction and suggests a probable mechanism of action [79].

Volatile compounds of this plant showed significant cytotoxic activity against human acute lymphoid leukemia in concentration dependent manner [80].

**Neural and hepatic protective effects**
The hepatoprotective activity of flavonoid rhamnocitrin 4′-β-D-galactopyranoside (RGP) obtained from leaves of Astragalus hamosus L. was documented against N-diethylthiourosamine (DENA)-induced hepatic cancer in Wistar albino rats [77].

The effects of rhamnocitrin 4-β-D-galactopyranoside (RGP), isolated from A. hamosus were evaluated on isolated rat brain synaptosomes, prepared by Percoll reagent and on rat hepatocytes, isolated by two-stepped collagenase perfusion. In synaptosomes, RGP had statistically significant protective effect, similar to those of silymarin, on 6-hydroxy (OH)-dopamine-induced oxidative stress. These results correlate with the protective effects of kemperol and rhamnocitrin on oxidative damage in rat pheochromocytoma PC12 cells. In rat hepatocytes, the effect of RGP on two models of liver toxicity: Bendamustine and cyclophosphamide showed that the compound had statistically significant cytoprotective and antioxidant activity, similar to those of silymarin [81].

Contraindications and adverse effects

The LD₉₀ of Astragalus is approximately 40g/kg when administered by intraperitoneal injection to rats. Overall it is very safe and doses as high as 100g/kg of the raw herb have been given to rats by lavage with no adverse effects [82]. However, water extracts of A. hamosus leaves were toxic to chicks at the equivalent of 3 g of dried plant per chick, and lethal at 6 to 8 g [83].

Astragalus tribuloides

Synonym

Astragalus kirghisicus Stschegl., Astragalus tribuloides Delile variety leiocarpus Boiss., Astragalus tribuloides var. leiocarpus Boiss [84-85].

Taxonomic classification

Kingdom: Plantae; Phylum: Tracheophyta; Class: Magnoliopsida; Order: Fabales; Family: Fabaceae; Genus: Astragalus L; Species: Astragalus tribuloides Delile [69, 86].

Common names

Arabic: Khazna, Jerna,Kufaia, Rukhami, English: Locoweed [26].

Distribution

It was widely distributed in the South Eastern Mediterranean area and temperate and tropical Asia. It was native in Afghanistan, Algeria, Armenia, Azerbaijan, Bahrain, China, Egypt, India, Iran, Iraq, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Libya, Morocco, Oman, Pakistan, Qatar, Syrian, Tajikistan, Tunisia, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, and Yemen [85, 87-91].

Traditional use

The herb was used as emollient and demulcent [91]. In the Chinese medical system, astragalus affects both the spleen and the lung meridians. It was indicated for spleen deficiency symptoms such as diarrhea, fatigue, spontaneous sweating, and lack of appetite. Astragalus tonifies the lungs and was used in cases of frequent colds and shortness of breath [92]. Other traditional indications include wasting disorders and night sweats [93].

Description

Plant with appressed to ascending white hairs 0.2-1.5 mm. Stems from nearly absent to 40 cm, prostrate to ascending, hairy. Leaves 1.5-7 cm; stipules membranous, 2-3 mm, hairy; petiole 0.5-2 cm, like rachis hairy; leaflets in 4-10 pairs, nar-rowly elliptic, 2.5-15 × 0.8-4 mm, both surfaces sericeous with appressed hairs, apex acute. Racemes sessile, rarely with a pe-duncle up to 2.5 cm, (1 or)2-8-flowered; bracts membranous, 1-3 mm. Calyx tubular, 3-5 mm, densely hairy; teeth 1-2 mm. Petals whitish or white suffused with mauve or pink; standard narrowly oblong, 4-10 × 1.2-2.5 mm, apex retuse; wings 4-6 mm; keel 3-5 mm. Legumes mostly starlike spreading, straight or slightly curved, oblong-triangular, 4-12 mm, 2.5-4 mm high and wide, distinctly bigibbous at base, acute at apex, with a deep dorsal groove widened at base; valves with short appressed hairs 0.05-0.15 mm and with much longer appressed to subapressed hairs up to 1.5 mm [94].

Part used: The primary medicinal parts of the herb were the roots [26].

Chemical constituents

Astragalus genus contained many compounds, these included : polysaccharides and triterpenoid saponins from the root: astragalans, astraglucans, astragalosides I – IV and trigonosides I-III. Flavonoids were isolated from the root including afromormosin, calycosin and odoratin. Indolizidine alkaloids, aliphatic nitro compounds, selenium, and biogenic amines such as g-aminoxybutyric acid (GABA, 0.024%) , and tragacanthin or tragacanth gum were also isolated from the plant [95].

Pharmacological effects

Astragalus has a wide range of potential therapeutic applications in immunodeficiency syndrome, as an adjunct cancer treatment, and for its adaptogenic effect on the heart and kidneys [96-99].

Astragalus injection was effective in lowering β(2)-microglobulin , microalbuminuria compared with placebo, and it was also superior to prostaglandin in lowering blood urea nitrogen, creatinine clearance rate. There were no adverse effects reported in the trials from astragalus injection [100].

It can grow adequately in both seliniferous and non-seliniferous soils, and can contain up to 1000 ug Se g⁻¹ dry matter [101-102]. Selenium is an essential element for all animals and humans. The US recommended dietary
allowance is 55–70 ug d^{-1} and the UK reference nutrient intake is 60–70 ug/d. However, human diets in several countries lack sufficient Se. To address this dietary Se deficiency, agronomists and plant breeders are pursuing two complementary strategies to develop crops with enhanced Se content. The first strategy is through improvements in crop husbandry. For this strategy, it was important to determine the potential for different crops to accumulate Se. The second strategy was to develop crop genotypes with improved Se accumulation and tolerance traits [103-106].

Selenium has an important role in cellular antioxidant defenses as a necessary component of selenoproteins. Selenium is incorporated into selenoproteins as selenocysteine. The glutathione (GSH) peroxidases are selenoproteins. The probable therapeutic effects of Date palm pollens in treatment of male infertility. The miraculous nature of the prophet medicine: Analytical study. Al Diaa Publication house, Iraq. 2009.

In laboratory animals, parenteral administration of organic and inorganic selenium (210 to 12,000 ug/kg) has been shown to protect against anticancer toxicity [107].

Contraindications and Side effects
Allergic reactions in rare cases [108].

Dosage
Liquid; astragalus extract 1:3 (equiv. of 330mg of astragalus herb in 1ml) [109].

CONCLUSION
This review discussed the chemical constituents and pharmacological effects of Astragalus hamosus and Astragalus tribuloides, the members of Astragalus genus grown in Iraq.

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