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Review Article

Clinical Treatments of Various Diseases with The Root of Astragalus Membranaceus

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Abstract

Astragalus L., is one of the largest genuses of flowering plants in the Leguminosae family. As annual or perennial herbs, sub shrubs, 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. Astragalus can significantly improve motor and memory impairment following D-galactose induced senescence in mice, which suggests anti-aging effects and possibly a delay in senility of middle-aged mice. The root of A. membranceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao (Radix Astragali) is a precious medicine in TCM, which has the properties of intensifying phagocytosis of reticuloendothelial systems, stimulating pituitary-adrenal cortical activity, and restoring depleted red blood cell formation in bone marrow. Clinically, it is used to treat chronic phlegmatic disorders and general gastrointestinal disturbances including stomach ulcers and diarrhea. It has been used in traditional Chinese medicine (TCM) in the treatment of various renal diseases for over 2000 years and was recorded in Shen Nong's Materia Medica, which was written in the Han dynasty. Also, it is famed for its antimicrobial, antiperspirant, anti-inflammatory, diuretic and tonic effects. Some plants in the Astragalus genus are well known for their pharmacological properties, particularly hepatoprotective, immunostimulant, and antiviral activities. While, the most common use of this genus is as forage for livestock and wild animals, some plants in this genus have been recognized as being used in foods, medicines, cosmetics, as substitutes for tea or coffee, or as sources of vegetable gums. Saponins, flavonoids, and polysaccharides are believed to be the principle active constituents of Astragalus. This herb possesses tonic, hepatoprotective, diuretic, and expectorant properties and has been shown to exhibit immunomodulating, antihyperglycemic, and antiviral activities, among others. Traditionally, it was used to treat weakness, wounds, anemia, fever, multiple allergies, chronic fatigue, and loss of appetite, uterine bleeding, and uterine prolapse. The plants have also been used for treatment of diabetes, nephritis, leukemia, stomach ulcers, hypertension and chronic bronchitis.

Keywords: diuretic; hepatoprotective; immunostimulant; antihyperglycemic; expectorant

Multiple Clinical Utilizations of Astragalus Membranaceus Root

A clinical trial where 90 patients with cardiovascular disease were randomized to one of three Astragalus granule treatments twice a day for thirty days, at a low (2.25 g/time), moderate (4.5 g/time), or high (7.5g/time) dosage, suggests that Astragalus granule treatment results in dose-dependent improvement of heart function grades. Improvements in the high-dose and moderate-dose groups were better than those in the low-dose group. Measures included an increase in left ventricular ejection fraction (LVEF), an increase in walking distance in six minutes, and improvements in Minnesota Living with Heart Failure Questionnaire scores, which assesses the ways heart failure and treatments can affect measures related to quality of life (Yang *et al*., 2011). These findings are supported by preclinical animal studies that suggest Astragalus blocks extracellular calcium influx and helps to relax endothelium vessels in normal and hypertensive rats (Zhang *et al*., 2006), reduces blood pressure and triglyceride levels in rats (Li *et al*., 2005), and also improves glucose tolerance in fructose-fed rats (Zhang *et al*., 2011).

Additional preclinical studies show that Astragalus can significantly improve motor and memory impairment following D-galactose induced senescence in mice, which suggests anti-aging effects and possibly a delay in senility of middle-aged mice (Lei *et al*., 2003).

Based on the clinical trials reviewed, doses ranging from 30 mg, and 2.5 g to 7.5 g daily have proved to be generally safe when taken for 1-3 months (Chao *et al*., 2009; Yang *et al*., 2011). A double-blind, randomized controlled clinical trial examining the effect of Astragalus on allergies reported few adverse effects using an 80 mg dose for six weeks (Matkovic et al, 2010). Additionally, a review of 22 studies, conducted in China, evaluated the effects of Astragalus, as a crude herb, extract, and as part of a combination of other extracts, on patients with chronic kidney disease. The results demonstrate that injections of Astragalus were generally safe with few reported adverse effects (Zhang *et al*., 2014).

Astragalus has the potential to interfere with drug metabolism through inhibition of CYP3A4, a liver enzyme key to the metabolism of many common drugs (Or *et al*., 2012; Pao *et al*., 2012) but it has not been evaluated beyond that for drug interactions in humans.

Multiple preclinical animal studies suggest Astragalus may improve learning and memory through multiple mechanisms. Astragalus treatment reversed Aβ-induced memory loss and prevented the loss of axons and synapses in the cerebral cortex and hippocampus in mice (Tohda *et al*., 2006), and showed a statistically significant reduction in stress-induced deficits on learning and memory for spatial memory tasks in rats (Park *et al*., 2009).

Additionally, it protected mice against damage induced by the drug dexamethasone by inhibiting caspase-3 and caspase-9 activity, resulting in statistically significant improvements in learning and memory (Li *et al*., 2011). Astragalus also protected mitochondria by scavenging reactive oxygen species in mice (Li *et al*., 2012), and increased neurocyte survival and decreased the neuron apoptosis rate in mice (Huang *et al*., 2012). While these results demonstrate potential for Astragalus' neuroprotective properties, these effects have not been tested in human or human cell populations and further research is required.

One double-blind randomized-controlled trial in China randomized 43 participants with recently diagnosed Type II diabetes to a treatment of a traditional Chinese herb compound made up of three kinds of plants, including 30 mg of Astragalus membranaceus, for three months. The treated group had significantly improved glucose disposal rate compared to a placebo group (Chao *et al*., 2009). There is also preclinical evidence from mice studies showing that Astragalus can attenuate insulin resistance and endoplasmic reticulum (ER) stress prompted by high glucose in vivo and in vitro, respectively (Mao *et al*., 2009).

Astragalus L., is one of the largest genuses of flowering plants in the Leguminosae family. As annual or perennial herbs, sub shrubs, 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 (Podlech, 2008; Benchadi *et al*., 2013; Xu and Podlech, 2014).

Some species of Astragalus in Asia are a source of the economically important natural product, gum tragacanth. In addition, the dried roots of some species grown in East Asia are well used in Traditional Chinese Medicines (TCM) as antiperspirants, diuretics, and tonics for a wide array of diseases such as empyrosis, nephritis, diabetes mellitus, hypertension, cirrhosis, leukaemia, and uterine cancer (Avunduk *et al*., 2008; Choudhary *et al*., 2008).

For example, the root of A. membranceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao (Radix Astragali) is a precious medicine in TCM, which has the properties of intensifying phagocytosis of reticuloendothelial systems, stimulating pituitary-adrenal cortical activity, and restoring depleted red blood cell formation in bone marrow. Also, it is famed for its antimicrobial, antiperspirant, anti-inflammatory, diuretic and tonic effects (Fathiazad *et al*., 2010). Some plants in the Astragalus genus are well known for their pharmacological properties, particularly hepatoprotective, immunostimulant, and antiviral activities (Linnek *et al*., 2011). While, the most common use of this genus is as forage for livestock and wild animals, some plants in this genus have been recognized as being used in foods, medicines, cosmetics, as substitutes for tea or coffee, or as sources of vegetable gums. Saponins, flavonoids, and polysaccharides are believed to be the principle active constituents of Astragalus (Ibrahim *et al*., 2013).

Astragali Radix (AR), known as Huangqi in China, isone of the most popular herbal medicines worldwide. It is the dried root of Astragalus membranaceus (Fisch.) Bge. Or Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao. This herb possesses tonic, hepatoprotective, diuretic, and expectorant properties(Chinese Pharmacopoeia Commission, 2010) and hasbeen shown to exhibit immunomodulating (Bedir *et al*., 2000; Wang *et al*., 2009), antihyperglycemic (Chan *et al*., 2009), antiinflammatory (Choi *et al*., 2007), antioxidant (Yu *et al*., 2005; Li *et al*., 2010), and antiviral activities (Zhu *et al*., 2009), among others. Traditionally, itwas used to treat weakness, wounds, anemia, fever, multiple allergies, chronic fatigue, loss of appetite, uterinebleeding, and uterine prolapse (Kim *et al*., 2003). Clinically, it is used to treat chronic phlegmatic disorders and general gastrointestinal disturbances including stomach ulcers and diarrhea. It has been used in traditional Chinese medicine (TCM) in the treatment of various renal diseases for over 2000years and was recorded in Shen Nong's Materia Medica, which was written in the Han dynasty (Hei *et al*., 2005).

The roots have been shown to contain triterpene saponins, isoflavonoids, polysaccharides, and some trace elements (Lin et al., 2000; Wu and Chen, 2004; Aldarmaa et al., 2010). More than 100 compounds, such as flavonoids, saponins, polysaccharides, and amino acids, have so far been identified in AR, and various biological activities of the compounds have been reported (Xu *et al*., 2006; Chu *et al*., 2010). The amount of active compounds varies widely, depending on the region on which the plants were grown and the period at which they were harvested (Ma *et al*., 2002). Thus far, only a few studies have been conducted to evaluate the quality of AR collected in China and Japan, and isoflavonoids, such as calycosin, calycosin 7-O-gluco-side, formononetin 7-O-glucoside, methylnissolin 7-O-glucoside, and isomucronulatol 7-O-glucoside, as well as astragalosides I to IV, have been used as indices of the quality of the Radix (Gonzales *et al*., 2001).

Several approaches using multi variate statistical analysis have been proven effective for the differentiation of a large number of similar samples (Gonzales *et al*., 2001).

Astragalus maximus belongs to the family Fabaceae (also called Leguminosae). Astragalus L. is the most abundant genus of the family comprising about 2000–3000 species of herbaceous and shrub species, mostly perennial, with more than 250 taxonomic sections in the world (Niknam and Brahimzadeh, 2002; Turgut-Kara N and Arı, 2006). This genus is widely distributed throughout the temperate region of the world. Till date, about 800 species of Astragalus L. have been identified in rangelands and mountainous regions of Iran (Mozaffarian , 2003). Numerous Astragalus species have been long used in traditional medicine particularly in Asia in variety of disorders. Astragalus radix, the dried roots of Astragalus species is a well-known tonic or adaptogenic herbal remedy that is widely applied to promote general health (Siwicka *et al*., 2011). The plants have also been used for treatment of diabetes, nephritis,

leukemia, stomach ulcers, hypertension and chronic bronchitis (El-Hawiet *et al*., 2010).

The biological functions of various phytochemicals from Astragalus L. have been extensively studied by many researchers (Sun *et al*., 2006; Li *et al*., 2013).

The principal active ingredients were proved to be saponin glycosides, flavonoids and polysaccharides (Matkowski *et al*., 2003; Ma *et al*., 2003; 2004; Qi *et al*., 2006; Pistelli *et al*., 2008). According to the systematic review by a Chinese scientists on the chemical constituents of the plants (genus Astragalus L.) more than 140 cycloartane-type triterpene glycosides, 60 flavonoids and 18 different polysaccharides have been identified so far (Li *et al*., 2014).

In pharmacological studies, such ingredients as well as crude extracts of Astragalus species have demonstrated anti-cancer (Yesilada *et al*., 2005), immunostimulant (Bedir *et al*., 2000), antihypertensive, neuroprotective, hepatoprotective (Luo *et al*., 2008), antimicrobial (Pistelli *et al*., 2002), antiviral (Huang *et al*., 2008), cardioprotective (Zhang *et al*., 2006; Ma *et al*., 2013) and antiaging activities (Fathiazad *et al*., 2012).

Despite the vast distribution of Astragalus species in Iran, there have been few investigations on the chemical constituents of the plants. In the course of our study on Astragalus genus we previously reported four saponins from A. caspicus and two flavonoids from A. microcephalus (Fathiazad *et al*., 2010; 2012).

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