

A REVIEW OF ASTRAGALUS SPECIES AS FOODSTUFFS, DIETARY SUPPLEMENTS, A TRADITIONAL CHINESE MEDICINE AND A PART OF MODERN PHARMACEUTICAL SCIENCE

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Abstract. Astragalus is a common Traditional Chinese Medicinal plant and is a widely used herbal product in China and other countries. Saponins, polysaccharides, amino acids, flavonoids, organic acid, glycosides, alkaloid, and trace elements, are the major classes of chemical compounds occurring in the species of Astragalus genus. In Traditional Chinese Medicine, Astragalus is considered to be effective in the treatment of diabetes, mellitus, nephritis, leukemia, uterine cancer, besides its tonic agent and diuretic effects. Some uses of Astragalus are in the treatment of kidney and urinary problems, digestion, liver problems, female reproductive system problems, muscular, skin problems, cardiovascular and blood related issues, immune and lymphatic system, nervous system, respiratory system, and for some specific diseases. It helps protect the body against various types of stress such as physical and emotional stress. Astragalus root has anti-aging properties, and also help in the prevention of bone loss. *Astragali radix*, the root of *Astragalus membranaceus* Bunge, has been reported to exert hepatoprotective effects, anti-oxidative effects, antiviral activity, anti-oxidative effects, anti-hypertensive effects, and immunostimulant properties; it has also been reported to strengthen superficial resistance, drainage action and new tissue growth. More clinical studies are necessary to discover the effects of Astragalus.

Keywords: *health benefits, traditional Asian medicine, Yin-Yang balance, Silk Road, herbal medicine*

Introduction

Chinese herbs have been used as traditional medicine immune booster for human being for thousands of years in China (Yin et al., 2009; Shahrajabian et al., 2018). More than 3 million tons of herb medicines were produced in China, and their medicinal parts were consumed in traditional Chinese medicine (TCM) clinic (Soleymani and Shahrajabian, 2012, 2018; Zhang et al., 2016; Ogbaji et al., 2018). In traditional Chinese medicine, some herbals have been used for anti-aging since ancient times (Liu et al., 2017). *Astragalus membranaceus* as one of the most important Qi tonifying adaptogenic herbs in traditional Chinese medicine has a long history of medicinal use (Yang et al., 2010; Zhong et al., 2012; Liu et al., 2017). In traditional Chinese medicine, which laid a lot of emphasis on Qi (vital energy) and Yin-Yang balance (negative and positive equilibrium). Chinese herbs have used as traditional medicine immune booster for human being for thousands of years in China and many parts of Asia (Shahrajabian

et al., 2019a, b, c, 2020; Sun et al., 2020). The goal of this review is survey on some important ancient and modern pharmaceutical sciences of astragalus.

Materials and methods

All relevant papers in the English language of researchers from different countries were collected. The keywords of astragalus, traditional Chinese medicine, traditional Asian medicine, modern pharmaceutical science, health benefits and western medicine were searched in Google Scholar, Scopus, Research Gate and PubMed.

Results and discussion

Astragalus in traditional Chinese medicine and other parts of the world

Astragalus is considered as benefiting Qi and helping to pass water (Li et al., 2011). It has been used as therapy for Wei Zheng, a term for skeletal muscle fatigue and wasting (Zhou and Mei, 2014). The dried root of *A. membranaceus*, first documented in Shennong Bencao Jing (Shennong's Classic of Materia Medica, 200-300 AD), is one of the most popular health promoting herbal medicines commonly used in China for more than 2000 years. In modern Chinese medicine, it is used in Fu zheng therapy as an immune stimulant (Ionkova et al., 1997). Also known as Huang Qi (Chinese), Milk-Vetch (English), Hwanggi (Korean), and Ogi (Japanese) (Chou et al., 2007; Li et al., 2019). It is sold in dietary supplements in tea or capsule form in the USA, and in the tea, beverages, soup, and trail mix (gorp) in Asia (Song et al., 2008; Zhang et al., 2011). Chinese milk vetch (*Astragalus sinicus* L.) is also a traditional leguminous green manure which plays an important role in maintaining paddy soil fertility and in the popularizing of the double-rice farming system in southern China; it is ploughed into soil at full blooming stage and serves as an alternative to chemical nitrogen fertilizer in the region (Zhu et al., 2012). *Astragalus membranaceus* was originally described in the Shennong's Classic of Meteria medica, the earliest complete Pharmacopoeia of China written from Warring States Period to Han Dynasty (Hei et al., 2005; Auyeung et al., 2016). It is valued for its ability to strengthen the primary energy of the body which we know as the immune system, as well as the metabolic, respiratory and eliminative functions (Liu et al., 2017). This fact is being increasingly substantiated by pharmacological studies showing that it can increase telomerase activity, and has antioxidant, anti-inflammatory, immunoregulatory, anticancer, antitumor, antioxidant, hypolipidemic, antihyperglycemic, hepatoprotective, expectorant, immunomodulatory activity, and diuretic effects (Anon, 2003; Ma et al., 2011; Zhao et al., 2011). *Astragalus membranaceus* (Fisch.) Bunge. has been widely used an anti-osteoporosis herb is traditional Chinese medicine for many years (Du et al., 2004; Wong et al., 2007; Xi et al., 2008; Jiao et al., 2014). In Traditional Chinese Medicine, *Astragalus membranaceus* is a major component in a prescription to treat chronic phlegmatic disorders and general gastrointestinal disturbances including stomach ulcer, chronic diarrhea and intestinal inflammation (Kim et al., 2008; Yang et al., 2014). Other researchers have reported the values of Astraglaus s roots in traditional Chinese medicine with the function of strengthening exterior and promoting health for thousands of years (Ma et al., 2017; Zhao et al., 2011). Traditional Chinese herbs are generally applied in the form of multi-herb formulas in medical treatments and as dietary supplements (Takagi and Ishii, 1967; Li et al., 2011). Lu et al. (2013) reported that *Radix Astragali* is the root

of *Astragalus membranaceus* Bunge, and as a famous traditional Chinese medicine (TCM), it has been used to improve muscle wasting-related disorders for a long history. They have also introduced Astragalus polysaccharide (APS) as an important bioactive and a therapeutic agent in the management of muscle wasting. *Astragalus trojanus* Stev. is an endemic plant mostly found in eastern and central Anatolia (1300-3500 m), central Aegean region and slopes of Toros mountain (1300-2300 m) in Turkey (Nartop et al., 2015). This genus is widely distributed throughout the temperate and arid regions of the world, and is principally located in Asia (1500 species), North American (500 species) and South American (150 species), and Europe (120 species), but also on mountains in Africa. However, the centre of origin and biodiversity of Astragalus plants is Eurasia, especially the mountainous parts of South-Western and South-Central Asia (Lysiuk and Darmohray, 2016). Iran alone, being the richest centre of Astragalus habitation, shelters more than 850 species, 527 of which are endemic in the flora of Iran (Ranjbar and Karamian, 2002; Aslanipour et al., 2017; Ghasemian-Yadegari et al., 2017). Aslanipour et al. (2017) stated that the crude drugs prepared from Astragalus roots are used for treating some illnesses such as leukemia, respiratory infections and diabetes in Iranian folk medicine. In South Eastern Turkey (Anatolia district), the aqueous extract of the roots of different *Astragalus spp.* are traditionally used against leukemia and for its wound-healing properties (Yesilada et al., 2005; Nalbantasy et al., 2012; Napolitano et al., 2013). In the district of Anatolia, located in South Eastern Turkey, an aqueous extract of the roots of Astragalus is traditionally used against leukemia and for its wound healing properties (Bedir et al., 2001). *Astragalus corniculatus* Bieb. (Fabaceae) is distributed in Southeastern Romania, South Ukraine and Moldova (Tutin et al., 1972). *Astragalus Tragacantha* L. (Fabaceae) is a western Mediterranean perennial cushion-like plant species well-adapted to drought that grows even in the trace metal and metalloids polluted soils (Salducci et al., 2019). It has been reported that Astragalus is an adaptogen and is usually used in combination with other herbs, such as, ginseng, Echinacea, and glossy privet. Astragalus is primarily used in American medicine to potentiate the function of the immune system and in cardiovascular disease. In traditional Chinese medicine, it is used for influenza and the common cold (McKenna et al., 2002). Nishiyama et al. (1995) reported that in traditional oriental medicine, it is conventional to combine different herbs in order to achieve a variety of treatment purposes simultaneously, or to enhance a single effect without causing severe side effects. Erect milkvetch (*Astragalus adsurgens* Pall.), also as a palatable forage, are also widely used in returning farmland to grassland, it has an important role in restoring the degraded ecosystems and could be an effective and applicable to improve soil nutrients and prevent further soil degradation and erosion, because it grows rapidly, and was characterized by barren-tolerance, wide adaptability and strong resistance (Wang and Wang, 2013).

Bioactive phytochemicals, medicinal uses and potential health benefits of Astragalus in traditional and modern medicine industry

Constituents of the dried roots of *Astragalus spp.* *Radix Astragali* provide significant protection against heart, brain, kidney, intestine, liver and lung injury in various models of oxidative stress-related disease (Hong et al., 1992; Shahzad et al., 2016). Zhang et al. (2007) stated that Astragalus is an important traditional Chinese medicine (TCM), and now widely used as an immune modulator, especially to support immune health for various chronic degenerative diseases. Recently, *Astragalus radix* was proved efficacious to be an adjunctive therapy medicine for cancers (Wang et al., 2003). In the

Bulgarian traditional medicine, *Astragalus glycyphyllos* is used as an antihypertensive, diuretic and anti-inflammatory remedy (Nikolov, 2006). Major classes of compounds of *Astragalus* species (Table 1) are polysaccharides, saponins and isoflavonoids, alkaloid, choline, betaine, folic acid, organic acid, various amino acids, mucic acid, gum, cellulose and fourteen trace elements, including selenium, zinc, and iron, which are essential micronutrients for man and animals (Bedir et al., 2000; Block and Mead, 2003; Yin et al., 2006; Lu et al., 2016). *Astragalus* genera are the richest source of cycloartanes, the unique triterpenoids with a characteristic 9,19-cyclopropane (Nartop et al., 2015). According to the systematic review by 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). Under high soil moisture and wet conditions, *Astragalus* is susceptible to root rot caused by fungi, which is the main constraint to cultivation. Land must be well drained for *Astragalus*. Loose soil and raised beds can be used to control soil moisture (Shannon et al., 2014). The chemical structures and chain conformations of polysaccharides play a vital role in their biological activities; however, polysaccharides belong to a structurally diverse class of macromolecules (Jin et al., 2014). Cycloastragenol (CA) is the main aglycon of many cycloartane-type glycosides which are only found in the *Astragalus* genus, extends T cell proliferation by increasing telomerase activity which helps to delay the onset of cellular aging (Valenzuela et al., 2009). *Astragalus* root also contains a series of cycloartane triterpene glycosides, including astragalosides I-VIII, acetylastragaloside, isoastragaloside I and III, astramembrannin II, cycloastragenol, cyclosieversigenin, soyasaponin I, soyasapogenol B, and lupeol (Ko and Chik, 2009). Among these, *Astragalus membranaceus* has a high content of astragaloside IV, which is commonly used as a qualitative marker.

Table 1. *Astragalus membranaceus* main compounds

Compound	Effect
Flavonoids	Plant metabolites with antioxidant effects; give plants yellow color
Isoflavones	Polyphenolic compounds that are classified as phytoestrogens; formononetin is one of the prominent ones
Lectin	Carbohydrate-binding proteins
Polysaccharides	Carbohydrates whose molecules contain linked monosaccharides; starch, inulin, cellulose
Saponins	Amorphous glycosides of terpenes and steroids that can form emulsions and can foam (soap-like); Astragaloside IV is one of the most-studied saponins in Huang Qi

On the basis of traditional Chinese medicine view of cancer, causes are endogenous causes and exogenous causes. Endogenous causes are the seven emotional states (anger, grief, fear, worry, over joy, shock and melancholy) can be seen as the way that stress, worry, over work, and emotional grief can suppress the immune system and allow predispositions for cancer growth to take hold. So, while it can seem simplistic to attribute cancer to normal emotions such as sadness, worry, fear, etc., the TCM view is that when these emotions are excessive, prolonged or unresolved, they can cause disease. The concept of Jing in TCM can be likened to the role of genetics in cancer, which is an important factor indeed. Exogenous causes consist of six exogenous causes for all illness, including cancer, are climatic factors of wind, cold, dampness, dryness,

summer heat and fire. And, other miscellaneous causes are environmental causes, dietary causes, and drugs. The TCM concepts of yin/yang balance, the need for calmness of mind, absence of strife, the practice of health promotion through movement, all support modern ideas on the role of psychological, neurological and immunological health in cancer prevention (Shahrajabian et al., 2019d, e, f, g, h). Liu et al. (2011) reported that in many parts of the world, especially in China and Germany, the combined use of herbal treatment and conventional cancer treatment is far more widespread than in America. They have also mentioned that 66.44% of cancer patients in China combined the use of herbal medicine with Western treatment. A prospective, controlled study conducted in Israel (Yaal-Hahoshen et al., 2011) found significant improvement in anemia and neutropenia in breast cancer patients who were given an herbal mixture containing Huang Qi and other Chinese herbs. Rios and Waterman (1997) reported that cycloastragenol (CAG) is a secondary metabolite isolated from *Radix Astragali*, present in all known *Astragalus spp.*, CAG (9,19-cycloanostane-3,6,16,25-tetrol,20,24-epoxy-(3 β , 6 α ,16 β ,20R,24S); is both a triterpene aglycone and the most common genuine aglycone in the bioactive triterpenoid saponins called astragalosides. *Astragalus polysaccharides* (APS) are one of the main efficacious principles of *Radix Astragali* (*Astragalus membranaceus*), which is reported to have anti-oxidant, anti-diabetic, anti-hypertensive, and immunomodulatory activities (Wu and Chen, 2004; Wu et al., 2005). It has been noted that the crude polysaccharide extract of *A. membranaceus* was mainly composed of carbohydrates with small amount of proteins (Cho and Leung, 2007). It has been demonstrated that the main components of the ethylacetate extract of *Astragalus* were isoflavonoids such as calycosin-7-O- β -D-glycoside, formononetin-7-O- β -D-glycoside and (6R, 10R)-9,10-dimethoxypterocarpan-3-O- β -D-glycoside, and these glycosides and other their aglycones were proved to exhibit strong antioxidant activity (Zhang et al., 2007). Li et al. (2010) also mentioned that the dried root of *Astragalus* contains 2',4'-dihydroxy-5,6-dimethoxyisoflavone, kumatakenin, choline, betaine, polysaccharides, saponins, glucuronic acid, sucrose, amino acids, traces of folic acid and astraisoflavanin. So many other scientists also revealed that *Astragalus membranaceus* has a notable functional role in various pharmacopoeias as a herbal immunomodulator and an anti-diabetic drug (Wei et al., 2011; Agyeman et al., 2013). Its roots have been used in many state-approved Chinese Herbal formulas for the treatment of diabetes (Jai et al., 2003; Wei et al., 2011). Some experiments have showed that *Astragalus* exhibits immunomodulating and immunorestorative effects both in vitro and in vivo (Guo et al., 2005), and have shown preliminary promise against the experimental coccidial infection when used in conjunction with vaccine (Cho and Leung, 2007). Song et al. (2017) reported that *Astragalus* extract mixture HT042 is a combination of three standardized herbal extracts from *Astragalus membranaceus* root, *Elutherococcus senticosus* stem, and *Phlomis umbrosa* root, and it has been developed to promote height growth in children with short stature. Sun et al. (2012) revealed that *Astragalus membranaceus* is a popular traditional Chinese medicine, commonly used in Chinese herb prescription to treat liver disease, and the extract prepared from the roots of *Astragalus membranaceus* and *Paeonia lactiflora* demonstrated better hepatoprotective activity than the herbs used individually. Ko and Chik (2009) demonstrated that root extract of *Astragalus membranaceus* administrated orally and locally can protect rats against hapten-induced colitis through attenuation of TNF- α and IL-1 β and up-regulating of IL-10. Shen et al. (2008) indicated that *Astragalus membranaceus* has a potential role in treating allergic

asthma. Zhang et al. (2009) *Astragalus membranaceus* and its effective components are effective in reducing fasting blood glucose and albuminuria levels, in reversing the glomerular hyperfiltration state, and in ameliorating the pathological changes of early diabetic nephropathy in rat models. Ko and Chik (2009) demonstrates that both oral and locally administered *Astragalus membranaceus* possess protective effects against experimental colitis through differential modulation of colonic cytokines. Yang et al. (2013) found that *Astragalus membranaceus* polysaccharide (AMP) has antitumor activity in vivo at least partly via improving immune responses of host organism, and seems to be safe and effective for the use of anti-tumor therapy. Lv et al. (2017) suggest that *Astragalus polysaccharide* (APS) which is a bioactive extract of *Astragalus membranaceus* may represent a natural therapeutic approach for treating inflammatory bowel disease, such as ulcerative colitis. Yan et al. (2010) found that administration of *Astragalus mongholicus* polysaccharides could significantly increase serum and liver antioxidant enzyme activities in mice and decrease peroxidative lipid levels. Jalsrai et al. (2010) found that doses of *Astragalus mongholicus* extract which did not interfere with locomotor activity and situational anxiety appear to be useful in the treatment of convulsive disorders. Kim et al. (2016) highlighted the ability of *Astragalus membranaceus* to facilitate sperm development and semen quality. Tian et al. (2016) reported that *Astragalus* may be beneficial as an adjuvant therapy in the treatment of type 2 diabetes. Zhou et al. (2018) demonstrated that the extract from *Astragalus membranaceus* with water extraction-ethanol supernatant method inhibit cell growth and induce apoptosis in cultured breast cancer cells. This effect astragalus extract to suppress breast cancer cells growth was associated with its ability to inhibit PI3K/Akt/mTOR activity. Maresca et al. (2017) concluded that the 50% hydroalcoholic extract of *Astragalus radix* is a valuable candidate for the adjuvant treatment of articular disease. Liu et al. (2017) concluded that the appropriate dose of *Astragalus* depends on several factors, such as the user's age, health status, and several other conditions. They have also found that natural products are not always necessarily safe, and dosages can be important. Sheng et al. (2005) found that one of the most important biological role of saponins is modulating the cellular oxidant antioxidant balance.

Conclusions

Traditional Chinese medicinal materials have been used for thousands of years and are believed to be abundant, safe, and inexpensive. *Astragalus* has been used in Chinese traditional medicine as an immunity booster for almost 2000 years. The genus *Astragalus* is a member of the Fabaceae of Legume family and it is native to northern China and Mongolia. It is widely distributed in China, Siberia, and northern Korea. Some actions of *Astragalus membranaceus* are anti-viral, anti-bacterial, immune system enhancing, immune stimulant, anti-infective some viruses, adaptogen, cardio-tonic, diuretic, hypotensive, anti-oxidant, immunomodulator, hypoglycaemic, circulatory stimulant, vasodilator, anti-fatigue, anti-cancer and hepatoprotective. Chemical constituents are polysaccharides, triterpenoid saponins (*Astragalosides*), flavonoids, choline, phytosterols, volatile oils, amino acids (Asparagine, Gamma-aminobutyric acid, Canavanine), aglycones, coumarins, astrapterocarpan, betaine, calcium, copper, isoflavonoids, rich in potassium and magnesium. *Astragalus membranaceus* classically prescribed in TCM in combination with other Chinese medicinal herbs as a dried root, powdered or as a decoction, with the combination depending on the desired therapeutic

effect and the specific TCM diagnosis. Polysaccharides in *Astragalus* intensify phagocytosis in reticuloendothelial systems, stimulate pituitary-adrenal cortical activity, and restore depleted red blood cell formations in bone marrow. *Astragalus* uses are in kidneys problems, strengthens the kidneys, incontinence and frequent urination, urinary tract infection, gastric ulcers, decreased appetite, chronic diarrhea, strengthens the spleen, poor digestion, liver problems, viral hepatitis, strengthen the liver, postpartum fever, uterine bleeding, topical adjuvant therapy for chronic viral cervicitis, vaginitis, edema, lupus, rheumatoid arthritis, myasthenia gravis, strengthens and builds bone marrow, excessive sweating, night sweats, slow healing wounds, increasing white blood cell count, leukopenia, ischemic heart disease, angina pectoris, recovery from severe loss of blood, diabetes, anemia, high blood pressure, heart palpitations, congestive heart failure, strengthens the blood, increases interferon production, impaired immunity, chronic viral infections, general debility, increases energy, HIV/AIDS, cancer, myalic encephalomyelitis (chronic fatigue syndrome), improves sleep quality, upper respiratory infection, common cold, chemotherapy, radiation therapy, flu, combats coxsackie B myocarditis, ameliorates side effects of drugs, appropriate herb for weak and elderly. Isoflavonoids, such as calycosin-7-O- β -D-glucoside, ononin, astraisoflavan-7-O- β -D-glucoside, calycosin and formononetin, are principle bioactive compounds found in *Radix astragali*-based drugs or foods. In summary, *Astragalus* is an ancient herb for modern medicine which can promote good health and as drugs to treat diseases. Further clinical researches are necessary to uncover various substances and their effects on *astragalus* which contribute to public health.

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