



Astragalus (*Astragalus membranaceus* Bunge): botanical, geographical, and historical aspects to pharmaceutical components and beneficial role

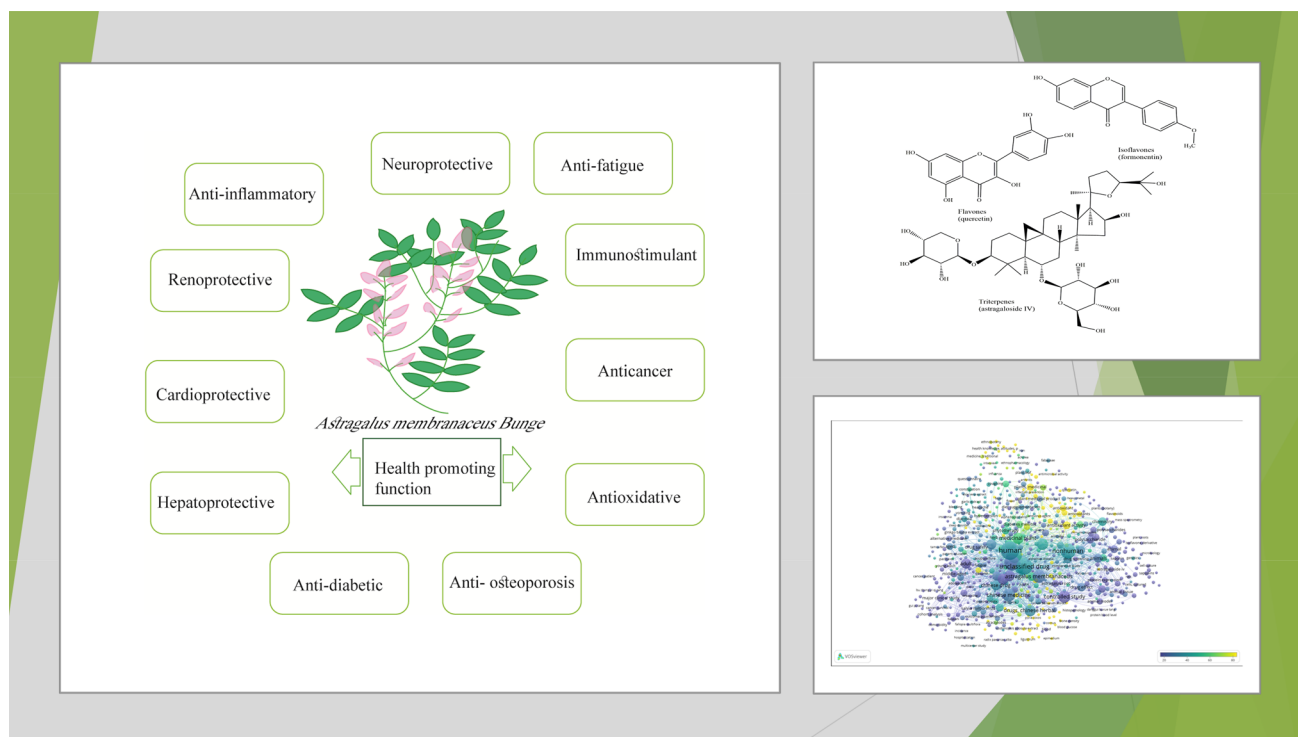
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Abstract

Medicinal plants always are part of folk medicine and are nowadays receiving worldwide attention for prophylaxis, management, and treatment of several diseases, as an alternative to chemical drugs. The current work provided a comprehensive overview and analysis of the *Astragalus* and health relationship in literature. The analysis of their therapeutic potential is thus instrumental to understand their bioactivity. Among these, the flowering medicinal plant *Astragalus membranaceus* has raised interest due to several beneficial health effects. This perspective review discussed the botanical, geographical, historical, and the therapeutic properties of *A. membranaceus*, with a special focus on its health improving effects and medicinal applications both in vitro and in vivo.

Graphic abstract



Keywords *Astragalus membranaceus bunge* · Botany · Biodiversity · Territory · Herbal medicine · Bioactive compounds · Biological properties · Medicinal applications · In vitro studies · In vivo studies

1 Introduction

Medicinal plants have long been used as a global strategy for the treatment of various diseases (Izzo et al. 2016). The International Union for the Conservation of Nature (IUCN) declared the use of 50,000–80,000 medicinal plants for medicinal purposes (Chen et al. 2016) in line with biodiversity and sustainability concept (Guarino and Pignatti 2010; Pignatti and Cipriani 2010; Pignatti 2013; Attore et al. 2018). *Astragalus membranaceus* (Fisch.) Bunge (syn. *Astragalus propinquus Schischkin*) is a plant from the *Fabaceae* (or *Leguminosae*) family, and a flowering medicinal plant for which several beneficial effects have been identified, e.g., cardio; neuro; reno; and hepato-protection, hypoglycemic, anti-osteoporosis, anti-fatigue, anti-inflammatory, anti-cancer, antioxidant, and immune system boosting. The geographical distribution of this plant has been reported at the edge of mountains and scattered forests and grasslands, which grow predominantly in the inner Mongolia autonomous region and the northeastern regions of Heilongjiang Province, China, as well as traditional medicine widely used the *Radix Astragali*, the dried root of *A. membranaceus* var. Commercial sales volume of *Astragalus mongolicus* is estimated at more than 10 million tons per year (Zhang et al. 2019). The purpose of this review article is to investigate the botanical, geographical and historical characteristics of *A. membranaceus*, in addition to gathering information about the main components and therapeutic purposes of the plant.

2 *Astragalus* and health: quantitative literature analysis

The current work provides a comprehensive overview and analysis of the *Astragalus* and health relationship in the literature. In January 2021, this search was conducted through the Scopus database to *Astragalus* and health publications. Bibliometric data were extracted from the Scopus online database using the search string: "*Astragalus*" and "Health". Bibliographic data were recorded, such as the publication year, publication count, citation count, subject area, countries/territories, institutions, document type the "Analyze" and "Create Citation Report" functions of the Scopus web online platform have been used for the basic analyses. The "full records and cited references" were exported to VOSviewer software (version 1.6.16, VOSviewer software website) for further bibliometric analyses and additional processing.

The VOSviewer software (v.1.6.16, 2020) analyzes the terms/words used in the titles and abstracts of publications, by breaking down the paragraphs into words and phrases, linking them with the citation data of the publications, and visualizes the results in the form of a bubble map using a term map with default settings (Van Eck and Waltman 2009, 2010, 2011; van Eck 2011; Waltman et al. 2010), Default parameters were used for the analyses and visualizations; particularly, the type of analysis was based on co-occurrence; as unit of analysis, all keywords were considered (author and index keywords), and the counting method was full counting. Create a map based on bibliographic data to create a co-authorship, keyword co-occurrence, citation, bibliographic coupling was selected. In a term map, the size of a bubble represents how frequently a term is mentioned in the articles—the frequency of appearance of a term (multiple mentions in one article were counted once). Two bubbles are positioned more closely to each other if the terms co-appeared more often in the analyzed publications. The color of a bubble reflects the average citations per publication (citations per publication, CPP).

To simplify the bubble map, words/terms that appeared in at least five publications have been analyzed and visualized. As per the threshold chosen, the minimum number of occurrences of keyword was set up to 5. Of the 8502 keywords, 678 meet the selected threshold and three of them were manually excluded. This search strategy identified publications that mentioned the relevant words or their derivatives in the title, abstract, or keywords. As a result, the following parameters were assessed: publication year, publication count, citation count, institution, country/territories, and document type.

The search returned 392 publications covering the time period from 1973 to 2021 that were collectively cited 10,270 times, with an H-index of 55 and 26.19 CPP as an average.

A total of 675 terms have been derived from the quantitative literature research on 392 publications and they are visualized as a term map (Fig. 1). The top 10 recurring keywords are listed in Table 1. It is interesting to notice that among the top 10 recurring keywords appears as *Astragalus membranaceus*, which shows as the research is mainly focused on the biological activities of this species.

Publications and citation trends of relationship between *Astragalus* and health research are reported in Fig. 2.

The type of documents related to the 392 publications with regard to *Astragalus membranaceus* retrieved was distributed as reported in Fig. 3. "Article" and "Review" account for the 65.8% and 25.8%, respectively, followed by "Conference paper" (3.6%) and "Book chapter" (2.3%).

Figures 4 and 5 show, respectively, the most productive countries/territories and institutions with regard to *Astragalus membranaceus*. Regarding countries/territories, the most productive was China ($n=175$, $CPP=20.41$), followed by United States ($n=52$, $CPP=27.23$) and Taiwan ($n=30$, $CPP=14.87$).

The most productive institution with regard to *Astragalus membranaceus* was China Medical University Taichung ($n=17$, $CPP=9.18$). All Top 10 Institutions are in China and have at least or more 6 publications.

3 The botanical, geographical, and historical aspects of *Astragalus* (*Astragalus membranaceus* Bunge)

Astragalus membranaceus has been used as a valuable medicinal plant, especially in traditional Chinese medicine (TCM), also known as Huang Qi, in Chinese, Ogi, in Japanese, Milk-Vetch, in English, and Gavan, in Persian (Shahrabadian et al. 2019). The geographical distribution of this

genus, which is estimated to have 2000–000 different species, has been reported throughout the arid and temperate regions of the world (Li et al. 2014a), including about 120 species in Europe, 150 species in South American, 500 species in North American, and 1500 species in Asia. The main habitats of *A. membranaceus* are along sandy rivers, shrub edges, and sunny slopes. The main botanical characteristics defined for this perennial plant with 50–150 cm high, include a straight and long (up to 50 cm) cylindrical root, erect stems branched in the upper parts with small ovate-lanceolate or elliptical leaves with 7–30 mm long and 4–10 mm wide (13–31 lobular pieces), light yellow corolla, puberulous ovary, and black undercoated apex beaked and 2–2.5 cm ovate-oblong pods (Fu et al. 2014). This plant blooms from June to July and fruiting occurs from August to September. *A. membranaceus* dried root (*Astragali Radix*) has been consumed over 2000 years due to health-promoting effects. Traditional Chinese medicine recommended *A. membranaceus* to treat various gastrointestinal disorders, including intestinal inflammation, chronic phlegmatic disorders, chronic diarrhea, and stomach ulcer (Bratkov et al. 2016).

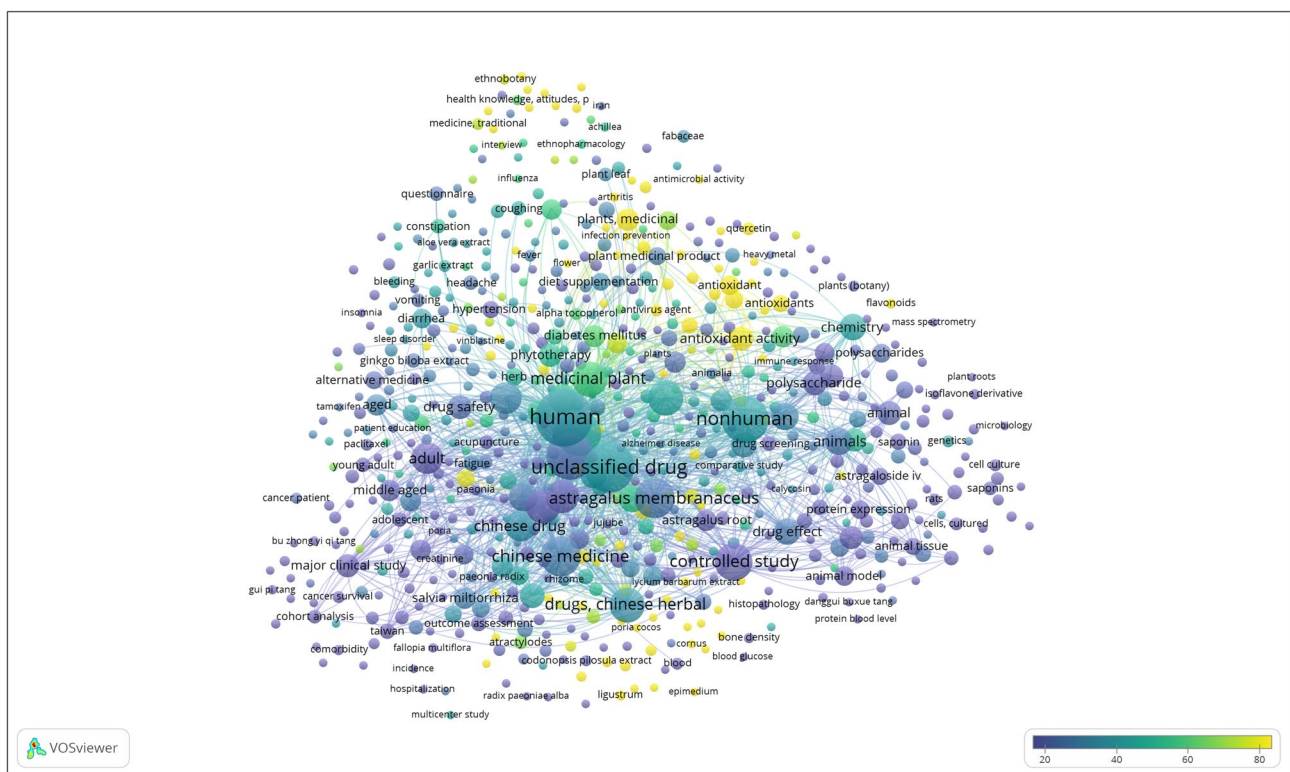


Fig. 1 Term map for relationship of *Astragalus* and health research. Bubble size represents the number of publications. Bubble color represents the citations per publication (CPP). Two bubbles are closer to

each other if the terms co-appeared more frequently. (Bibliometric data were extracted from the Scopus online database and elaborated by VOSviewer software)

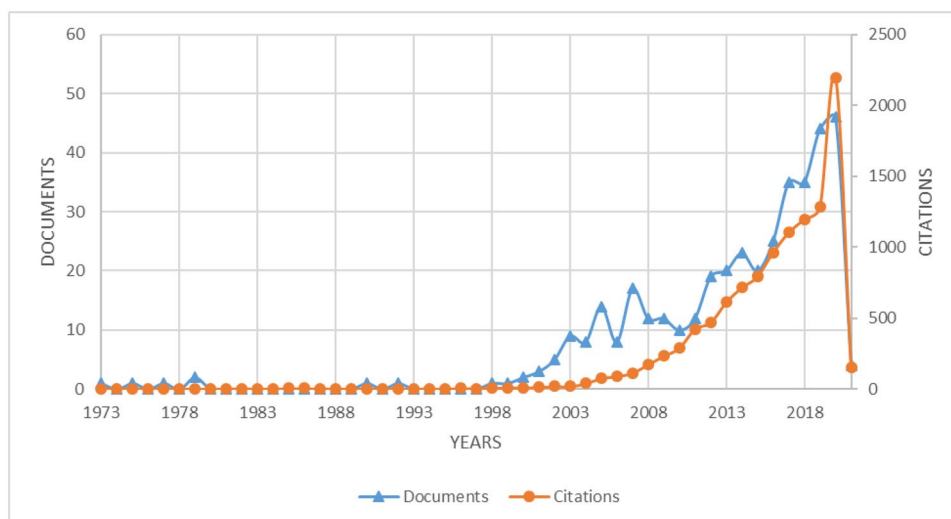
Table 1 The top 10 recurring terms on the relationship *Astragalus* and health research. (Bibliometric data were extracted from the Scopus online database and elaborated by VOSviewer software)

Term	Occurrence	Total link strength
Human	229	6699
Unclassified drug	174	5255
Non-human	154	4329
Herbaceous agent	152	4661
humans	140	4384
Chinese medicine	112	3355
<i>Astragalus membranaceus</i>	112	3001
Controlled study	97	2883
Medicinal plant	87	2642
Drugs, Chinese herbal	87	2783

4 Main components of pharmaceutical character of *Astragalus membranaceus*

The main reported chemical constituents of *A. membranaceus* (Fig. 6) were triterpenes, polysaccharides, flavonoids, and saponins (Li et al. 2014a, b). The presence of compounds such as terpenoids and flavonoids that usually occur in free or glycosidic form is of relevant pharmacological interest due to the bioactivities attributed to these classes of compounds. The flavonoids include flavonols, flavones, flavanones, and isoflavonoids which have been described as having many types of bioactivities. Compounds extracted with 75% methanol from different parts of *Astragalus* (roots, stems, leaves, petioles, and flowers) were analyzed by UPLC-MS/MS technique, to evaluate flavonoids and triterpenoids distribution, together with 13 of their metabolites, showing that isoliquiritigenin, liquiritigenin, daidzein, and bioactive isoflavones

Fig. 2 Publication and citation trends of relationship between *Astragalus* and health research. (Bibliometric data were extracted from the Scopus online database)



accumulate in both roots and flowers (Liu et al. 2018). The content in the isoflavones, calycosin, and calycosin-7-*O*- β -D-glucoside, was found to be the highest in the leaves and roots of *A. membranaceus*, as revealed by HPLC analysis (Kim et al. 2014). With calycosin content in leaf (145.56 μ g/g DW) higher than in root (1.64 μ g/g DW), while calycosin-7-*O*- β -D-glucoside content in root (4.88 μ g/g DW) higher than leaf in (2.0 μ g/g DW) (Kim et al. 2014). Kwon et al. (2013) analyzed the content in Astragalosides, known as the highly bioactive compound in *A. membranaceus* root, and reported that Astragalosides are more concentrated in periderm and cortex than in xylem; and that unpeeled roots were richer in these compounds. Zhang et al. (2011) isolated 24 secondary metabolites (isoflavonoids, astragalosides, and benzoquinone) from *A. membranaceus* roots, and the (-)-methyl-inissolin 3-*O*- β -D-glucosidewas detected for the first time in this study, and shown to possess potent anti-inflammatory activity, evaluated by the inhibition of nitric oxide

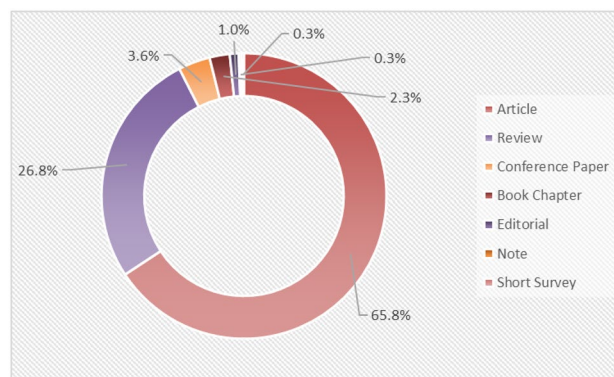


Fig. 3 Distribution of documents with regard to *Astragalus membranaceus* by type. (Bibliometric data were extracted from the Scopus online database)

Fig. 4 Most productive countries/territories with regard to *Astragalus membranaceus*. (Bibliometric data were extracted from the Scopus online database)

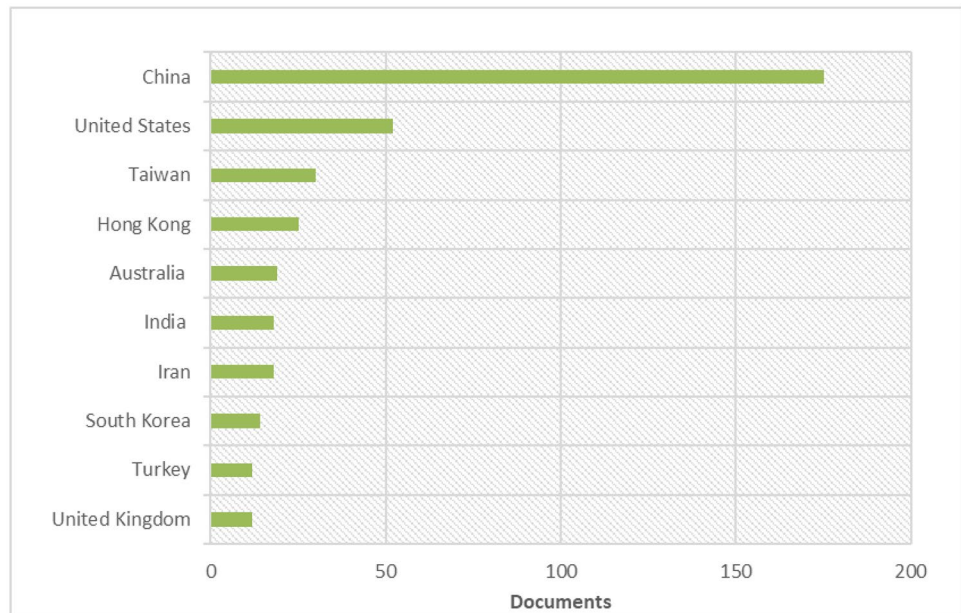
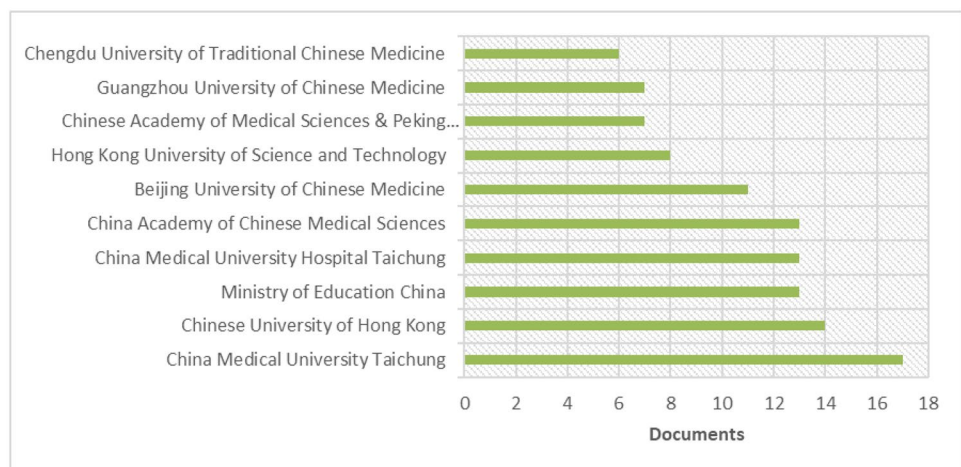


Fig. 5 Most productive institutions with regard to *Astragalus membranaceus*. (Bibliometric data were extracted from the Scopus online database)



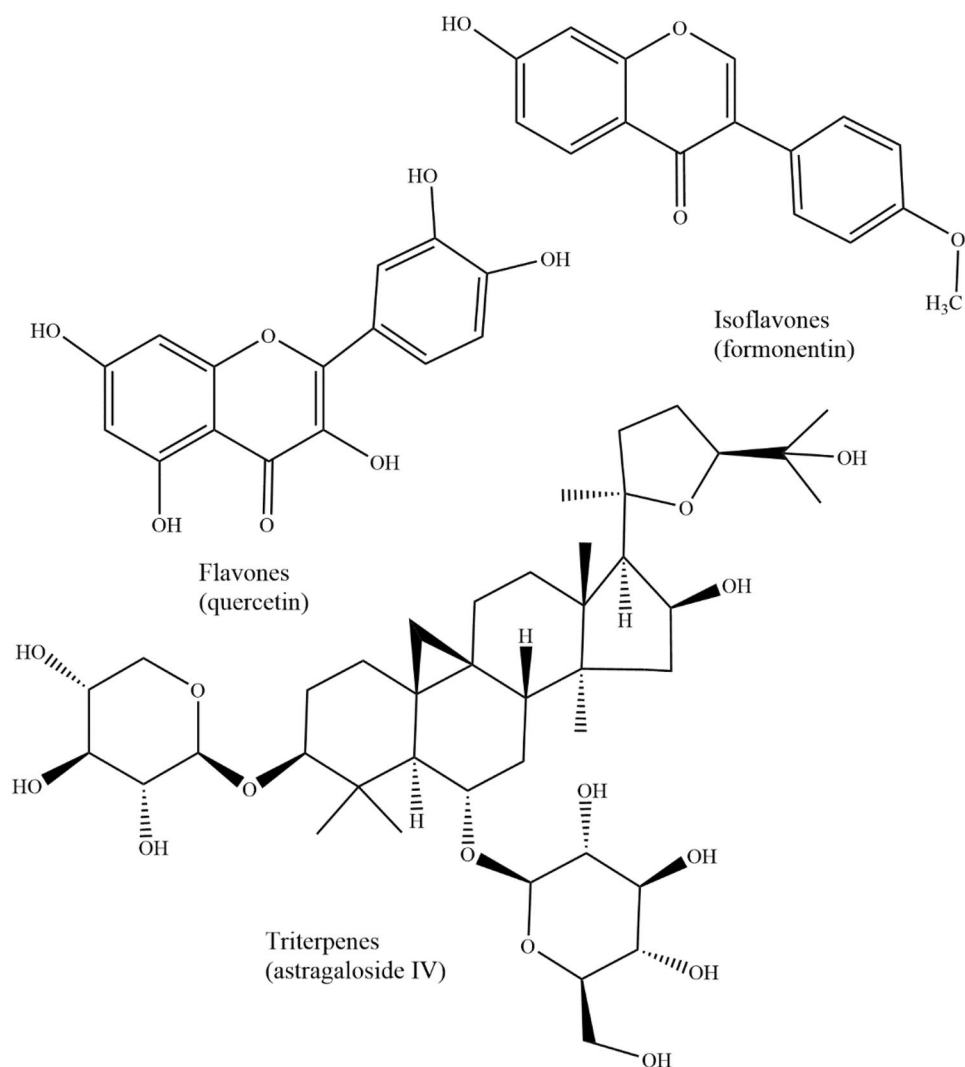
(NO) released by lipopolysaccharide (LPS)-stimulated macrophages (RAW 264.7 cells). Ethanol extract of *Astragali Radix*, analyzed by RP-HPLC, main content included triterpene saponins, namely astragaloside I–IV, isoflavonoids (formononetin and calycosin) which are the main bioactive compounds (Lee et al. 2017).

5 In vitro and in vivo therapeutic potentials of *Astragalus (Astragalus membranaceus)*: an update shot

The evaluation of phytochemical composition can be considered as the first step for the determination of the beneficial health properties of a plant, as it permits a preliminary

approach on the assessment of chemical compound structure-related activities (Souto et al. 2019). Figure 7 shows the potential beneficial effects of this plant, e.g., neuroprotection (Chan et al. 2009), renoprotection (Yin et al. 2004; Wen et al. 2020), hepatoprotection (Ali et al. 2018), hypoglycemic (Kai et al. 2015), anti-osteoporosis (Koo et al. 2013), anti-fatigue (Berezutsky et al. 2019), anti-inflammatory (He et al. 2012), immune system boosting (Lee et al. 2003), anti-cancer (Chen et al. 2019), antioxidant (Lee et al. 2011), and cardioprotection (Zhang et al. 2006).

Fig. 6 Some main compounds present in *A. membranaceus*

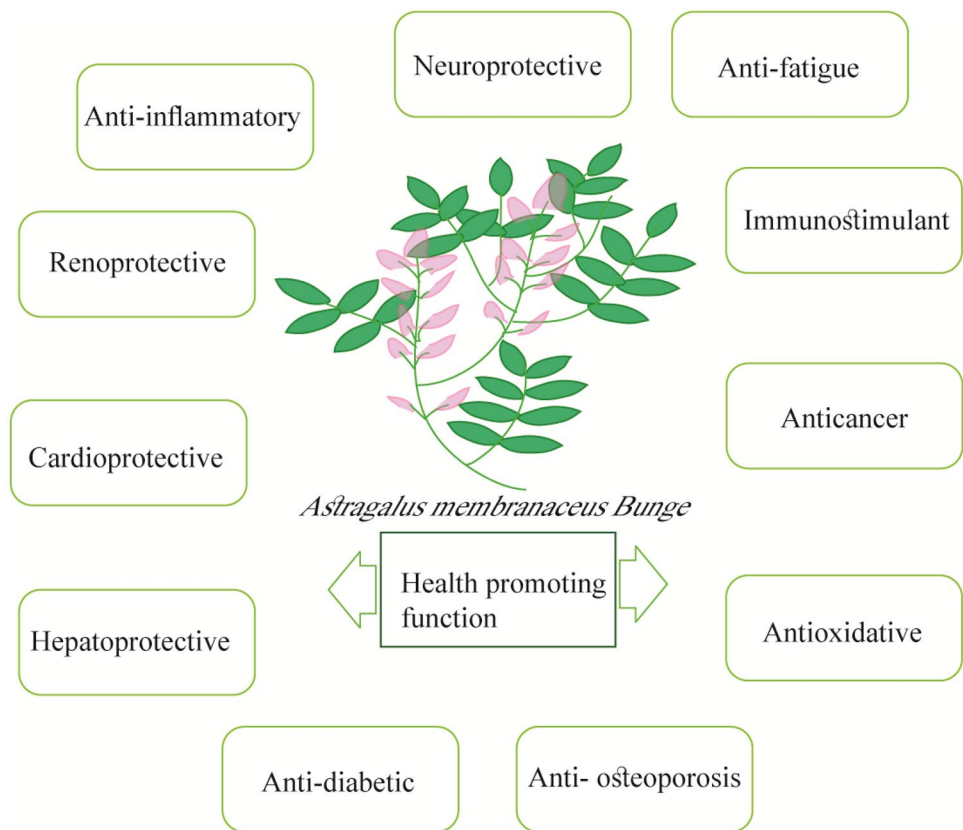


5.1 Health-promoting activities of *Astragalus* (*Astragalus membranaceus*) based on in vitro studies

Many health-promoting effects have been reported for *A. membranaceus* extracts. Table 2 shows the results of the main in vitro studies found in the literature. Zhang et al. (2020a, b) reported the main pharmacological effects of Astragaloside-IV, a major compound obtained with aqueous extraction, including neuroprotection, hepatoprotection, anti-diabetic anti-cancer activity, which were correlated with the antioxidant and anti-inflammatory activities exhibited by the modulation of various signaling pathways. These authors suggested the need for bioinformatics analysis to determine the effective Astragaloside-IV targets, for prediction of drug–target interaction (Zhang et al. 2020a). The

A. membranaceus dried root extract (70% ethanol extract) showed anti-diabetic effect by increasing glucose-stimulated insulin production and secretion from INS-1 cells, action attributed to the extract compounds nucleoside adenosine, formononetin, and calycosin-7-O- β -D-glucoside by pathways that result in the activation of peroxisome proliferator-activated receptor- γ (PPAR- γ) and pancreatic and duodenal homeobox-1 (PDX-1) transcription factors, activation of phosphorylation of Akt, phosphatidylinositol 3-kinase (PI3K) pathway, through insulin receptor substrate-2 (IRS-2) (Lee et al. 2019). Formononetin (7-hydroxy-4'-methoxyisoflavone) was shown potential to treat diabetic retinopathy as it inhibited the vascular endothelial growth factor (VEGF) secretion, from a retinal cell model, through the HIF-1 α /VEGF signaling pathway, compromising retinal neovascularization and reducing the expressions of PHD-2

Fig. 7 Scheme of the *Astragalus membranaceus* Bunge therapeutic properties



(prolyl hydroxylase-2), HIF-1 α (hypoxia-inducible factor 1-alpha), and VEGF proteins (Wu et al. 2016). Anti-diabetic effect of *Astragalus* polysaccharide and Berberine, through improvement of insulin resistance by activation of several genes and signaling pathways in HepG2 cells that decrease reactive oxygen species (ROS) concentration and increasing the cell survival rate was also reported (Lin and Mao 2020). *Astragalus* polysaccharides resulted in a reduction in cellular apoptosis through the modulation of Bcl-2/Bax ratio and the prevention of pro-apoptotic protein expression in both intrinsic and extrinsic pathways (Sun et al. 2017).

In a study, the administration of *Astragalus* extract decreased the viability and induced the apoptosis of gastric cancer cell line via the AMPK pathway (Song et al. 2020). Zhang et al. (2018a) investigated that the ovarian cancer cell invasion and migration were inhibited through a decrease in the phosphorylation of ERK and the expression of MMP-2/9 (Zhang et al. 2018a). *Astragalus* extracts induced apoptosis in non-small cell lung cancer cell line, by increasing cleaved caspase-8, -9 expression (Zhou et al. 2018). Others show that *Astragalus* polysaccharides induced cell-cycle arrest in 4T1 cells (Park and Park 2018). Jiang et al. (2019) reported the anti-cancer activity of formononetin as resulting from mechanisms involving halting metastasis, arresting cell cycle and inducing apoptosis, the IC₅₀ value of 1 μ M for Formononetin against CNE2 (nasopharyngeal cell line)

was reported. Wang and Ba (2015), analyzed the chemical composition of *Astragali Radix* ethanol extract using HPLC and NMR spectroscopy, and identified several compounds including (3R)-8,2'-dihydroxy-7,4'-dimethoxyisoflavan, 7,2'-dihydroxy-3',4'-dimethoxy-isoflavan-7,2'-dioxo- β -D-glucoside, uridine, and astragaloside, which induced increase in the apoptosis rate of HepG2 cells, as evaluated by flow cytometry and MTT assay. Anticancer properties were also reported for the combination of apatinib [selective tyrosine kinase inhibitor of endothelial growth factor receptor-2 (VEGFR-2)] and *Astragalus* polysaccharide by enhancing cellular autophagy and blocking AKT pathway (Wu et al. 2018). The aerobic glycolysis metabolism of colorectal cancer cells (SW620 and HT-29 cell lines) was prevented by the administration of *Astragalus* saponins at the doses 50 μ g/ml; the IC₅₀ values of 35 and 46 μ g/ml, at 24 h, for HT-29 and SW620 cells, respectively, revealed anti-cancer activity, confirmed by a significant reduction in the number of colony formation, after a treatment with 25 μ g/ml for 2 weeks (Guo et al. 2019). In an in vitro study, the pancreatic cancer cell growth was inhibited by the calycosin, extracted from *A. membranaceus*, via the induction of apoptosis and arrest of cell cycle (Zhang et al. 2020b). Calycosin exhibited anti-proliferative activity and inhibit cell migration in a human colorectal cancer cell model (HCT-116 cells), by mechanisms that involve up-regulation of ER β and PTEN

Table 2 Summary of reported activities for *A. membranaceus*

Activity	Compound	Analytical methods	Effect	References
Anticancer activity	Isoflavones, campanulin, ononin, calycosin and formononetin (25 and 50 µg/ml)	HPLC and flow cytometric analysis	<i>A. membranaceus</i> extract inhibit the breast cancer cells' proliferation through PI3K/Akt/mTOR pathway	Li et al. (2020)
Neuroprotective effect	Astragaloside-IV, 6- <i>O</i> -β-D-glucopyranosyl cycloastragenol, 3- <i>O</i> -β-D-xylopyranosyl cycloastragenol, cycloastragenol	¹ HNMR, ¹³ C NMR, ESI-MS data, HPLC analysis, 2D-nano-LC-MS/MS analysis, Western blotting	Astragaloside-IV inhibited the glutamate neurotoxicity in PC12 cells via the Raf-MEK-ERK pathway	Yue et al. (2015)
Anti-inflammatory effect	Astragalus extract (125, 500 and 250 µg/ml)	Microcalorimetry in vitro and by in silico network analysis	It could activate the mouse splenic lymphocytes	Wang et al. (2018a, b)
Protective effect on diabetic cardiomyopathy	Astragalus polysaccharide (0.1, 1.0, 10, 100 µg/ml)	ELISA, ROS, apoptosis assay, western blotting	Activation of NGR1/ErbB pathway by <i>Astragalus</i> polysaccharide	Chang et al. (2018)
Immunomodulatory activity	<i>Astragalus</i> polysaccharide (30, 100, and 300 µg/ml)	ELISA assays, MTT method, western blotting and Real-time quantitative PCR	<i>Astragalus</i> polysaccharide caused induction of inflammatory cytokines, including L-6 and TNF-α, in RAW264.7 cells, and of NO release	Wei et al. (2016)
Anti-diabetic activity	Formononetin, formononetin-7- <i>O</i> -β-D-glucoside, acetylastragaloside I, acetylastragaloside I, Calycosin, calycosin-7- <i>O</i> -β-D-glucoside, adenosine, astragaloside I and II	¹ D and ² D NMR spectroscopic and western blotting	<i>A. membranaceus</i> root extracts caused improvement of Insulin Secretion	Lee et al. (2019)
Cardioprotective effect	Calycosin 7- <i>O</i> -beta-D-glucopyranoside, Ononin, Calycosin, Astragaloside I, II, III, IV, and mononetin (20 and 50 mg/kg)	HPLC analysis	The expression of endogenous Cx43 induced by CVB3 was rescued in the presence of <i>Astragalus</i> root dry extract through the regulation of miR-1 level	Wang et al. (2018a, b)

AIF apoptosis inducing factor, *H/R* hypoxia reoxygenation, *NO* nitric oxide, *ROS* reactive oxygen species

(phosphatase and tensin homolog deleted on chromosome ten) and downregulation of the micro-RNA miR-17, probably through regulation of miR-17/PTEN/Akt pathway (Chen et al. 2015).

Anti-myocardial H/R damage effect and regulation of the PI3K/Akt/HO-1 signaling pathway reported in a study by Yang et al. (2019).

In a study by Adesso et al. (2018), performed with rat intestinal crypt cell line (IEC-6 cells) co-exposed to the interferon- γ , lipopolysaccharide derived from *E. coli* (LPS) and *A. membranaceus* extract (5–100 $\mu\text{g/ml}$) showed that the extract of *A. membranaceus* root produced anti-inflammatory effect that was reported by reducing the activation of nuclear factor- κB (NF- κB), the formation of nitrotyrosine, the expression of inducible nitric oxide synthase (iNOS) and of cyclooxygenase-2 (COX-2), as well as the release of tumor necrosis factor- α (TNF- α). Adesso et al. (2018) also showed the antioxidant properties of *A. membranaceus* extract against hydrogen peroxide-induced oxidative stress by reducing ROS levels and by increasing expression of antioxidant cytoprotective factors, the activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Flavonoids of *Astragalus* extract exhibited anti-inflammatory and immunomodulatory properties in LPS-induced RAW 264.7 cells by blocking the expression of nuclear NF- κB p65 and the phosphorylation of JNK and p38 in the NF- κB and MAPKs pathway, respectively, and by reducing the levels of COX-2 and iNOS (Li et al. 2018). Total flavonoids extracted from *Astragalus* regulated the formation of NO, IFN- γ , IL-6, IL-1 β , and TNF- α in RAW 264.7 macrophages, resulting in *in vitro* anti-inflammatory and immunomodulatory properties (Guo et al. 2016). The *Astragalus* saponins induced an anti-inflammatory effect by inhibiting LPS-induced NF- κB pathway resulting in decreased expression of iNOS (Wang et al., 2016). In a study using a standardized extract containing *A. membranaceus* and two other Korean herbs, KBH-JP-040 extract, caused anti-osteoarthritis potential by inhibiting JNK/p38 MAP-kinase pathway and preventing the production of NF- κB , I $\kappa\text{B}\alpha$, matrix metalloproteinase, and inflammatory cytokines (Rahman et al. 2018). Astragaloside-IV (100 μM) prevented myocardial remodeling and fibrosis in rat cardiomyocytes [H9C2(2–1)] cell line through reduction in the activity levels of Sirt1, Bcl-2, miR-34a, as well as increasing superoxide dismutase activity and reduction of lipid peroxidation (Zhu et al. 2019). *Astragalus* polysaccharide could protect the cardiomyocyte cell line (H9c2) by reducing apoptosis induction that elevated cell viability, and by inhibiting the NF- κB and JNK pathways that suppressed the production of the inflammatory cytokines, possible as a result of down-regulation of miR-127 expression (Ren et al. 2018).

Elevation in the immunosuppressive and the proliferative activities of umbilical cord-derived mesenchymal stem cells

has been attributed to the reduction in the serum levels of IL-1 β , IFN- γ , MCP-1, IL-6, and TNF- α (Chao et al. 2017).

The Bcl-2/Bax mRNA ratio, and GPx and SOD activities were increased, and the expression level of Bax mRNA was reduced in the interstitial cells of Leydig in rats (Jiang et al. 2015).

However, Kumar et al. (2018) reported that *A. membranaceus* root extract altered the cytochrome P450 2B6 (CYP) activity, a reduction in CYP2B6 activity caused by ethyl acetate and ethanol extract was observed, IC₅₀ values of 29.7 and 53.37 $\mu\text{g/ml}$, respectively. These results may indicate potential adverse drug interactions with CYPs, when *A. membranaceus* is co-administered with drugs metabolized by CYP2B6.

The antiviral activity of *A. membranaceus* against influenza virus was shown in infected mouse Raw 264.7 cells by influencing the cell proliferating cycle, and by affecting the TLR3 signaling pathway, by reducing the malondialdehyde level, and increasing the superoxide dismutase level (Liang et al. 2019). Antibacterial activity of the aqueous *Astragalus* extract was demonstrated, as this could mildly inhibit bacterial responsible by dysentery and diarrhea while not affecting normal gut bacteria (Lai et al. 2018).

5.2 Health-promoting activities of *Astragalus* (*Astragalus membranaceus*) in animal models

Several health-promoting effects have been documented for *A. membranaceus* extracts in animal models. Table 3 shows the results of the main studies in animal models using *A. membranaceus* extracts. Wei et al. (2020) reported that the administration of 5 mg/kg/day of Astragaloside-IV in male Sprague–Dawley rats for 2 weeks treated cardiac fibrosis by declining the expression of collagen I, alpha-smooth muscle actin (α -SMA), and transient receptor potential melastatin-7 (TRPM7) as well as by inhibiting the activity of TGF- β /Smads pathway. Administration of *Astragalus* polysaccharides in diabetic cardiomyopathy rat model (induced with streptozotocin, STZ) prevented the cardiomyocyte apoptosis due to down-regulation of PERK–ATF6–CHOP pathways of endoplasmic reticulum stress, which was also observed *in vitro* in high glucose-induced H9C2 cells (Sun et al. 2019). In a study by Cao et al. (2017), administration of 1.5 g/kg/day of *Astragalus* polysaccharide for 3 days improved the cardiomyocyte function in mice with doxorubicin-induced heart failure, so that the induced heart failure by disturbing cardiomyocyte autophagic flux resulted in cell apoptosis that was reduced after *Astragalus* polysaccharide treatment through regulation of AMPK/mTOR pathway, decreasing doxorubicin-induced cardiotoxicity and restoring normal autophagic flux. In another study, administration of astragaloside IV shows protective effect through elevation in the level of oxygen consumption ratio and reduction in the

anaerobic glycolysis in mice with heart failure (Dong et al. 2017). Improvement of endothelial dysfunction, oxidation, matrix metalloproteinase (MMP)-2/9 function because of daily administration of *Astragalus* polysaccharides (128 mg/kg), *Astragalus* total flavonoids (72 mg/kg), and *Astragalus* saponins (22 mg/kg), total extract of *A. membranaceus* (196 mg/kg) for 6 weeks in rats with hyperhomocysteinemia (HHcy) (Qiu et al. 2017). The cardioprotective activity of Astragaloside-IV was found following the down-regulation of miR-92a/-23a through the MAPK/ERK and PI3K/AKT signaling pathways (Gong et al. 2018). The administration of *Astragalus* polysaccharides (200 mg/kg b.w) elevated the antioxidant activity by declining apoptosis and preventing ROS-elicited oxidative damage (Awad et al. 2020). Chen et al. (2018) show that *Astragalus* extract inhibited oxidative damage and ROS production, dropped progenitor cell apoptosis, and enhanced enzyme activities, SOD2 protein levels, the CSCs' cell proliferation, and CSC abundance. Treatment with astragaloside IV inhibited type I collagen synthesis and isoprenaline-induced cardiac fibrosis proliferation through dropping the activation of ROS-mediated MAPK signaling pathway (Dai et al. 2017). Yu et al. (2017) reported taking 2.5 mg/kg of astragaloside in rats for 4 weeks prevented myocardial infarction-induced damage by upregulating Jagged1, Notch1, and HIF-1 α expression. Others show that taking 80 mg/kg/day of Astragaloside-IV in rats reduced energy metabolic disturbance and pressure overload-induced hypertrophy via PGC-1 α /PDK4/CPT-1 pathway (Lu et al. 2016).

Administration of *Astragalus* in arthritis-induced rats for 4 weeks showed anti-arthritic properties attributed to the prevention of inflammatory mediators (Liu et al. 2017). The reduction in immune organ index, inflammatory cell infiltration, synovial hyperplasia and paw swelling, and the elevation of body weight have also been described (Maresca et al. 2017). The administration of 300 mg/kg per os of the hydroalcoholic extract of *Astragali radix* in a rat model showed anti-arthritic activity and relieved the pain by 96% and 78% of complete Freund's adjuvant and monoiodoacetate injection, respectively (Maresca et al. 2017). The daily co-administration of *Salvia miltiorrhiza* with *A. membranaceus* (10 ml/kg SM and 0.59 g/ml AM) in rats with LPS-induced acute lung injury for 3 consecutive days down-regulated the TLR4/IRAK/NF- κ B signaling pathway and thus declined inflammatory cytokine release, vascular leakage and lung wet/dry weight ratio, and improved lung histopathological changes (Qin et al. 2018). In a study by Wang et al. (2019), treatment of mice with astragaloside IV (0.01 mg/g) by gavage for 6 days showed anti-inflammatory activity by inhibiting JNK, p38, and NF- κ B signaling pathways, resulting in reduced the consequences of LPS-induced endometritis like the levels of myeloperoxidase (MPO), NO, TNF- α , and IL-1 β . The administration

of astragaloside at 40–80 mg/kg in rats for 10 weeks could significantly manage diabetic nephropathy by blocking the Wnt/ β catenin signaling pathway, anti-epithelial–mesenchymal transition, anti-inflammatory, and anti-oxidative stress activities (Wang et al. 2020). The administration of *Astragalus* polysaccharide in male Sprague–Dawley rats enhanced bone marrow mesenchymal stem cell (BMSC) differentiation and proliferation by triggering Wnt/ β -catenin and PI3K/AKT pathways through bone morphogenetic protein type 9 (BMP9) overexpression and miR-152 down-regulation (Li et al. 2019a, b). Daily administration of *Astragalus* polysaccharide, in ovariectomized rats, for 3 months, alleviated the osteoporosis caused by oxidative stress via the regulation of FoxO3a/Wnt2/ β -catenin pathway (Ou et al. 2019). Astragaloside-IV extract administration to rats with ischemia–reperfusion injury showed neuroprotective activity, regulated the expression of apoptosis-related genes, improved the pathological brain damage and declined the cerebral infarction volume (Yin et al. 2020). Administration of *Astragali Radix* in mouse model of ischemia-induced brain damage for 3 days suppressed the expression levels of Aquaporin-4 (AQP-4) mRNA and protein, and that caused a reduction in water content, edema, and brain infarct size (Lim et al. 2019). Taking 10 g/day of *Astragalus* in mice inhibited the progression of renal fibrosis through the down-regulation of E-cadherin expression, the inhibition of TGF β -R1, TGF- β 1 and α -SMA expression, and the reduction in blood glucose levels (Yi et al. 2016). In a study by Li et al., anti-edema activity of Astragaloside-IV reported through the regulation of Matrix metalloproteinase-9 and aquaporin 4 (Li et al. 2013).

Rats treated with *Astragalus* polysaccharides exhibited an increase in the immunity function and a prevention of spleen deficiency by interfering with Toll-like receptor 4 (TLR4) and regulating inflammatory cytokines, respectively (Zhao et al. 2019). The Sheng-Nao-Kang decoction containing *A. membranaceus* extract exerted antithrombotic effect in rats by balancing the prostacyclin (PGI2) and thromboxane A2 (TXA2) ratio (PGI2/TXA2), the anticoagulation activity and regulating the active substances produced by vascular endothelium (Dang et al. 2015). Li et al. (2019a, b) used an aqueous *Astragalus* extract, mainly composed of flavonoids, saponins, and polysaccharides, and then evaluated its immunomodulatory potential in mice at a dose of 1 g/kg twice a day for 18 days, and showed an improvement in the immune responses such as serum IgG and IgM levels, spleen lymphocyte subset, NK-cell activity, splenocyte proliferation, thymus and spleen parameters, peripheral white blood cell count, and body weight gain. Yu et al (2018) reported antitumor activity, following the administration of alcohol-soluble *A. membranaceus* polysaccharide extract (100, 200, and 300 mg/kg), for 15 days in murine H22 hepatoma cells, tumor cell apoptosis was induced due to an enhancement

Table 3 Summary of reported activities in animal models for *A. membranaceus*

Activity	Compound	Type of organisms	Effect	References
Anti-osteoporosis	<i>A. membranaceus</i> Bunge extract (60, 120 and 240 mg/kg/day)	Rat	Treated rats with ovariectomy-induced osteoporosis	Li et al. (2016a)
Anticancer	<i>A. membranaceus</i> extract (500 mg/kg/day)	Rat	Reduction in the tumor growth	Tseng et al. (2016)
Anti-fatigue	Astragaloside, calycosin, thorn formononetin (1, 3, and 30 g/kg/day)	Mice	Administration of <i>Astragalus</i> extract in hypoxic mice reduced their physical fatigue	Zhang et al. (2015)
Anti-oxidant	Aqueous extract of <i>A. membranaceus</i> (160 mg/kg)	Rat	Prevented streptozotocin-induced diabetes through enhancing CAT, SOD, GPx, GSH, and insulin level and reduction in fasting blood sugar	Huo et al. (2016)
Anti-inflammatory	Astragaloside-IV (20 and 40 mg/kg/day)	Mice	Astragaloside-IV controlled the inflammation via TLR4/NF- κ B signaling pathway, resulting in protective effect against the progression of renal fibrosis	Zhou et al. (2017)
Anti-diabetic	Astragaloside-IV (40 mg/kg)	Rat	Delayed the development of diabetic nephropathy in rats by improving the podocyte adhesion, and decreasing urine albumin excretion and blood glucose levels	Lu et al. (2015)
Cardioprotective effect	Astragaloside-IV	Mice	PTEN/P13K/Akt activation	Cheng et al. (2019)
Renoprotective effect	Astragaloside-IV (5 mg/kg/day)	Rat	Modulation of podocyte apoptotic through the AS-IV/lncRNA-TUG1/TRAF5 signaling pathway in rats with diabetic nephropathy	Lei et al. (2018)
Neuroprotective function	<i>Astragalus</i> polysaccharide (200, 400, and 800 mg/kg/day)	Rat	<i>Astragalus</i> polysaccharides (APS) caused memory improvement in rats with streptozotocin-induced diabetes by affecting lipid and glucose metabolism as well as anti-oxidative and insulin resistance	Dun et al. (2016)

of immune cell (NK cells, lymphocytes and macrophages) activities and serum levels of cytokines (IFN- γ , IL-2, and TNF- α). The administration of *A. membranaceus* decoction for a week prevented the intestinal mucosal damage due to the inhibition of inflammatory cytokine activity (Cui et al. 2018). Astragaloside-IV modulated the host immune system through the excessive production of inflammatory mediators and the suppression of inflammation (Li et al. 2016b). Diabetic podocyte damage was decreased due to Panax notoginseng co-administrated with *A. membranaceus* via Nox4 and Bax down-regulation as well as Bcl-xl, α -dystroglycan, and nephrin up-regulation (Zhai et al. 2019).

In a mice model of infertility, treated with *Astragalus* root extract showed improvement within 56 days due to PPAR α agonistic activity, so that the expression of ovarian PPAR α mRNA and uterine was up-regulated for 1.5- and 2.5-fold, respectively (Orkhon et al. 2018). Co-administration of *Laminaria japonica* extract with *A. membranaceus* extract (200–400 mg/kg) in rats, for 6 weeks, attenuated the dyslipidemia and hypothyroidism caused by propylthiouracil (Mohibullah et al. 2019). Kim et al. (2016) evaluated the effects of *A. membranaceus* (100, 500, 1000 mg/kg) for 5 days a week for 5 weeks in mice, and reported an increase in the expression of cAMP response element modulator and activator of CREM in testis, as well as increased sperm value, motility, and count.

5.3 Health-promoting activities of *Astragalus* (*Astragalus membranaceus*) in humans, with particular regards to clinical trials

There are several clinical trials evaluating the therapeutic effects of *A. membranaceus* extract. Table 4 summarizes the results of the main clinical trial studies. In the literature, there are some reports of anti-cancer activity attributed to the main compounds extracted from *A. membranaceus*, tested under clinical conditions, although only few studies report the improvement of the bioavailability of these compounds. Mao et al. (2020) reported a study in patients with myocardial infarction who received Tongguan Capsules (TGC), containing a mixture of various herbs (*A. membranaceus*, *Borneolum syntheticum*, *Salvia miltiorrhiza*, and *Grasshopper*), at a dose of 4.5 g/day, for 6 months, in addition to the standard medication; in comparison to control group (only standard medication), the TGC-receiving patients shown significant reduction of left ventricular end-systolic volume index as well as lower incidence of the major adverse cardiovascular events, a decrease in myocardial markers of fibrosis and apoptosis, reduction in the circulating levels of inflammatory cytokines, indicating that the TGC treatment contributed to a more positive outcome.

Positive effect in children with growth retardation syndrome was reported, following the administration of HT042

(NeuMed Inc. (Seoul, Korea) extract mixture (composed of: *A. membranaceus* roots, *Eleutherococcus senticosus* stems, and *Phlomis umbrosa* roots), twice a day for 24 weeks, who demonstrated to have increased serum levels of insulin-like growth factor binding protein-3 (IGFBP-3) and IGF-1, as well as height and weight gain was observed in all children (Lee et al. 2018). In a randomized study, the co-administration of *Astragalus* polysaccharide with vinorelbine and cisplatin, in the patients with advanced non-small-cell lung cancer, improved quality of life and the side-effects of chemotherapy, such as appetite loss, pain, vomiting, nausea, and fatigue (Guo et al. 2012).

Immunostimulatory effect was reported as a result of double-blind study, in individuals subjected to treatment with 7.5 ml of an herbal tinctures consisting of *Glycyrrhiza glabra*, *A. membranaceus*, and *Echinacea purpurea* for 7 consecutive days twice a day (via ingestion) that induced the proliferation and activation of human immune cells (Brush et al. 2006). Matkovic et al. (2010) reported the alleviation of seasonal allergic rhinitis symptoms, in patients treated with 80 mg of mineral complex, containing *A. membranaceus* root extract, for 6 weeks, resulting in positive signals such as decreased rhinorrhea intensity. Improvement of immune function was reported in a clinical trial, with patients with lupus nephritis received cyclophosphamide plus *Astragalus* (20 ml, intravenous drip infusion) daily for 12 days that, after a month, showed an increase in the red blood cell count and in plasmatic albumin, and reduction in the urine protein content, infection rate, and active clinical symptoms ($P < 0.05$), indicating positive effect (Su et al. 2007).

6 Conclusions

Astragalus membranaceus is a widely used medicinal plant containing various natural bioactive compounds with therapeutic potential. For instance, *Astragalus* polysaccharides are monomeric components extracted from the plant that have been described for potential use in handling a range of diabetic complications (e.g., diabetic neuropathy, diabetic retinopathy, diabetic cardiomyopathy, diabetic foot, and infection). Among its compounds, Astragaloside-IV has been identified as one of the major constituents of its aqueous extract. It is a cycloartane-type triterpene glycoside chemical that has been described to have neuroprotective and hepatoprotective effects and can also be used as anti-cancer and anti-diabetic drug. Its antioxidant properties can also be exploited to improve neurotransmission and further neuroprotection. However, there is still a need for more comprehensive in vitro and in vivo studies, and clinical trials to determine the effective correlation between the chemical composition of this plant and the molecular targets

Table 4 Summary of clinical trials reported activities for *A. membranaceus*

Condition	Activity	Administration	Effect	References
Clinical trials	Protective effect on advanced non-small cell lung cancer	Administration of <i>Astragalus</i> once a day for a year	An improvement in the quality of life of patients by 40.1%	Zou and Liu (2003)
	Anti-fatigue	Administration of <i>Astragalus</i> extract (1.5 g) in patients with persistent fatigue twice a day for a month	A reduction in the score of fatigue severity	Cho et al. (2009)
	Anti-fatigue	Taking 2.8 g of <i>A. membranaceus</i> three times a day for 28 days	Elevated scores of global quality of life (QOL)	Liu et al. (2016)
	Anti-diabetic	Co-injection of <i>Astragalus</i> (150 ml) with 5% Sodium chloride (20 ml) once a day for two weeks	Enhanced levels of immune function, blood glucose	Zhang et al. (2018b)
	Protective effect on acute menopausal symptoms	Administration of <i>Astragalus</i> (3 g) in female patients with acute menopausal symptoms once a day for 6 months	An improvement in the frequency of mild hot flushes	Haines et al. (2008)
	Anti-proteinuria effect	Administration of <i>Astragalus</i> (15.2 g) in patients with stage 2 chronic kidney disease once a day for 24 weeks	An improvement in proteinuria with no complications	Peicheng et al. (2016)
	Anti-sudden deafness	Administration, intravenously, of Radix Astragali (10 ml) containing crude <i>Astragalus</i> (20 g) once a day for 10 days	An improvement in hearing in patients with sudden deafness	Xiong et al. (2012)
	Anti-viral effect	Administration of <i>Astragalus</i> in patients with chronic hepatitis B three times a day for two months	A prevention of hepatitis B virus replication	Tang et al. (2009)
	Anti-anorexia effect	Administration of herbal decoction in patients with anorexia in advanced cancer three times a day for three weeks	An improvement in body weight and appetite	Lee and Lee (2010)
	Protective effect on idiopathic membranous nephropathy	Daily administration of 15 g <i>A. membranaceus</i>	Reduction in the proteinuria	Ahmed et al. (2007)

that are responsible for the treatment of diseases that have been claimed, and also to draw definitive conclusions on the effects and consequences of prolonged administration of this plant. Human studies of a small number of health conditions indicate the need to use observational animal experiments for pharmacokinetic characterization. Health-promoting effects of this plant suggest its added value for potential development of new nutraceuticals as a prophylactic approach before a pharmacological treatment is needed, especially for people who are not eligible for conventional drug therapy. The quality of various chemical compositions derived from *A. membranaceus*, in particular *Astragali Radix*, is of great importance due to increasing demand of consumers. Moreover, there are needs to scientifically develop novel technologies to commercialize the plant products, such as pharmaceuticals, foods, health-promoting products, and cosmetics in integrated and multidisciplinary approach (Atanasov et al. 2021; Dwyer et al. 2021).

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Declarations

Conflict of interest The authors declare no conflict of interest.

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