Astragalin: A promising herbal compound with broad anticancer potential (Review)

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Abstract. In recent years, compounds that are active ingredients in herbal medicines have been investigated for their ability to treat cancer. Astragalin may exert anticancer effects through anti-inflammatory, anti-glycosylation, anti-adipogenesis, antioxidant and neuroprotective effects; however, there has been no literature review on the specific mechanism of action of astragalin in cancer, to the best of our knowledge. Therefore, the present review searched and reviewed the literature related to astragalin and cancer, and summarized the possible mechanisms. The results revealed that astragalin affects the proliferation, invasion and angiogenesis of cancer cells through participating in signaling pathways, regulating apoptotic proteins, inactivating oncogenes and suppressor genes, as well as the tumor microenvironment, angiogenesis and other mechanisms of action. In turn, this exerts antitumor effects and reverses chemotherapy resistance. Astragalin is expected to serve a greater role in the prevention and treatment of malignant tumors in the future due to its availability, safety and economy, thus providing new hope for global cancer treatment.

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Abbreviations: AHA, astragalin heptaacetate; Bcl-2, B-cell lymphoma-2; CE, Cyperus *exaltatus* var. *iwasakii*; DLBCL, diffuse large B-cell lymphoma; GLUT5, glucose transporter protein 5; HER2, human epidermal growth factor receptor-2; HIF-1α, hypoxia inducible factor-1α; LLF, lotus leaf flavonoid; mCRPC, metastatic castration resistant prostate cancer; MMP, matrix metalloproteinase; MSK1, mitogen- and stress-activated protein kinase 1; NB, neuroblastoma

Key words: astragalin, Chinese herbal medicine, neoplasms, apoptosis, mortality, broad-spectrum anti-cancer

Contents

1. Introduction

In the past decades, the application of certain new research methods and technologies have led to the proposal of new treatments for cancer, mainly neoadjuvant chemotherapy and targeted immunotherapy. Whilst they have often shown improved efficacy in the initial clinical application, they are associated with drug resistance and side effects (1). Therefore, seeking complementary and alternative treatments from traditional herbal medicine has become one new approach in the treatment of cancer. For example, astragalin has attracted widespread attention due to its wide availability, affordable cost, potent anticancer activity and high safety profile. Moreover, astragalin and its derivatives are considered to have definite cytotoxicity (2).

Astragalin, also known as kaempferol-3-O-glucoside (Fig. 1), is a flavonoid compound found in a number of medicinal plants such as *Astragalus*, *Apocynum venetum* leaves, *Rosaceae*, safflower, cassia seed and edible plants such as green tea, legumes, *Allium ursinum* and *Allium victorialis* (3). It has been reported to have anti-inflammatory (4), anti-glycemic, anti-adipogenic (5,6), antioxidant (7) and neuroprotective effects (8,9). Modern pharmacological studies have also reported that astragalin and its derivatives have several biological effects on the cardiovascular system (10,11), the endocrine system (12) and cancer (13,14). Furthermore, it has been reported to be associated with the inhibition of proliferation, migration and invasion of tumor cells, induction of apoptosis and inhibition of angiogenesis (3,15).

Regarding the anticancer effects of astragalin, previous studies have reported effects of astragalin on specific cancers through *in vitro* and *ex vivo* experiments, or network pharmacological analyses (16-18). However, unlike previous literature reports on this topic, the present paper summarizes

the anticancer effects of the natural compound Astragalin in several types of cancers, systematically outlining the specific mechanisms of the cancer-inhibiting effects of Astragalin, and suggesting future research directions for Astragalin. The present paper presents a comprehensive and systematic review of the mechanism of action of astragalin and its derivatives in several cancers, with an in-depth exploration to elucidate the potential and possibilities of astragalin for anticancer use. Table I summarizes the mechanism of action of astragalin on several cancers and Fig. 2 presents the specific types of anticancer mechanisms of astragalin.

2. Search and selection criteria

The PubMed (https://pubmed.ncbi.nlm.nih.gov/.), Web of Science (https://www.webofscience.com/) and China Knowledge (https://www.cnki.net/) databases were used for data mining using the following search terms: ['astragalin' in the Mesh database (title/abstract) or all its synonyms (kaempferol-3-O-glucoside glycoside)] and ['Neoplasms' or all its synonyms (cancer) in the Mesh database (title/abstract)]. Articles published between the creation of the database and April 1, 2025, were imported into Zetero 6.0 (https://www.zotero.org/blog/zotero-6/). A total of 89 papers were obtained after removing duplicates.

The inclusion criteria were as follows: i) *In vivo* and *in vitro* experiments with astragalin in the treatment of different types of cancer; ii) preclinical trials of astragalin in different types of cancer; iii) clinical trials of astragalin combined with other drugs; and iv) clinical trials of astragalin for different types of cancer. Articles such as meta-analyses, reviews, abstracts, letters and case reports were not included in the present review. The exclusion criteria were as follows: i) Repeated literature and research; ii) irrelevant articles, defined as articles that did not examine the anticancer mechanism of astragalin; and iii) investigation of the anticancer mechanism of a complex that does not contain astragalin in its composition.

3. Astragalin and several cancers

Astragalin and lung cancer. Lung cancer poses a serious health and economic burden to the global population, with the number of new lung cancer cases expected to reach ~3.8 million by 2050 (19). Issues with current lung cancer treatment include high morbidity and mortality rates, late diagnosis, limited therapeutic options, restrictions on targeted therapies, economic and resource constraints, tumor heterogeneity and drug resistance (20), nutritional and quality of life issues (21), and research and clinical translational challenges (22). Therefore, the option of developing novel therapeutic agents with high safety margins may improve this situation.

Among the existing herbal medicine developments, astragalin is expected to be a safe and reliable novel ingredient due to its potent potency to inhibit the activity of lung cancer cells, impede cell migration, proliferation, invasion and induce apoptosis. Astragalin belongs to the class of lotus leaf flavonoids (LLF), and *in vitro* studies (23,24) have reported that high concentrations (500 μg/ml) of LLF can notably induce apoptosis in human lung cancer A549 cells (25). LLF increases the content of reactive oxygen species and the level of the oxidative end-product malondialdehyde, and at the same time, reduces superoxide dismutase activity. It upregulates several apoptotic factors including caspase-3 and caspase-9, and inhibits the expression of related factors [such as B-cell lymphoma-2 (Bcl-2) and nuclear factor erythroid 2-related factor 2], thereby achieving an anti-lung cancer effect (25). Astragalin acts on the JAK/STAT pathway to regulate the expression of apoptotic factors and related genes in a dose-dependent manner, causing damage to cellular DNA and augmenting reactive oxygen species to promote apoptosis and inhibit migration and invasion (26). Moreover, *in vivo* studies (27,28) have reported that astragalin may induce cell death via the aspartase, ERK-1/2, AKT and NF-κB signaling pathways, a process that may be associated with an increased Bax:Bcl-2 ratio (29). Network pharmacological studies (30,31) have also reported that astragalin treatment of lung adenocarcinoma may exert its unique inhibitory effects on cell proliferation, migration and apoptosis through the microRNA (miRNA/miR)-140-3p/3-phosphoinositide dependent protein kinase 1 axis (32). Finally, astragalin has been reported to act on the lung cancer A549 cell line with potent cytotoxicity, activating effector caspase-3 and inducing apoptosis (33).

Astragalin and ovarian cancer. In 2022, ovarian cancer was associated with ~3 million deaths worldwide (34). Whilst current standard treatment regimens have improved patient survival to a certain extent, overall survival remains low due to issues of drug resistance and relapse (35). For example, whilst offering hope for patients with breast cancer gene mutations, poly (ADP-ribose) polymerase inhibitors have limited efficacy, prolonging survival by only a few months, and are associated with resistance (36,37). This has led to the need for the research and development of new treatment modalities and novel drugs. In this process, the active components of traditional Chinese herbs have received attention.

Astragalin has been reported to inhibit cell proliferation and migration and induce apoptosis in ovarian cancer cells by regulating signaling pathways, affecting the expression of specific cytokines and inhibiting the glycolytic pathway. This effect is associated with the upregulation of prolyl hydroxylase domain-containing protein 2 (PHD2) expression and inhibition of hypoxia-inducible factor 1α (HIF-1α) (38,39). PHD2 can act as an oxygen sensor and improve perfusion and oxidization of tumor cells (40), and participates in the programming of macrophage glycolysis (41). HIF-1α is stabilized by binding to hypoxia-responsive element in the anaerobic state, activating key enzymes such as pyruvate dehydrogenase kinase 1 (PDK1) and pyruvate kinase type M2, and inhibiting the tricarboxylic acid cycle, thus shifting glucose metabolism from oxidative phosphorylation to anaerobic glycolysis (42-44). This metabolic reprogramming enhances cell survival. Astragalin inhibits the phosphorylation of related proteins, whereas 3-methyladenine or bafilomycin A1, which act as autophagy inhibitors, can reverse this process. Astragalin can also regulate cellular autophagy by targeting the PI3K/AKT/mTOR signaling pathway (45), a classic signaling pathway in ovarian cancer tumorigenesis, proliferation and progression (46). Thus, astragalin may exert its unique biological effects on ovarian cancer cells.

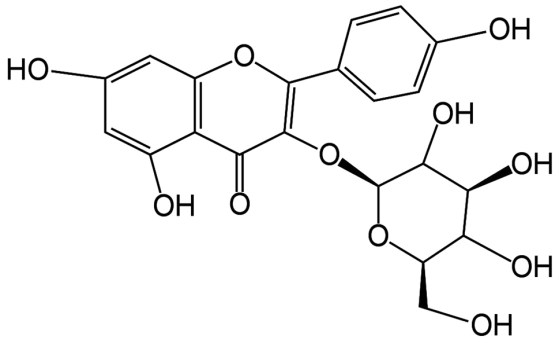

Figure 1. Molecular structural formula of astragalin. Astragalin is also known as kaempferol 3-O-β-D-glucoside, where kaempferol binds to a glucose unit at the 3-position hydroxyl group and exhibits typical flavonoid glycoside bioactivity. The figure was drawn using the KingDraw platform (version v3.6.5; https://www.kingdraw.com/).

Astragalin and cervical cancer. Cervical cancer ranks second among malignant neoplastic diseases in women and has a high mortality rate (47). Due to the high resistance to platinum-based chemical drugs, this disease is now often treated with radiotherapy (48); however, this can cause damage to the mucosa of the vagina and urinary tract, which can affect patient quality of life (49). Therefore, it is necessary to explore new therapeutic methods with low toxicity and high safety.

It is conceivable that if astragalin is applied in conjunction with radiotherapy drugs, it may be able to exert neuroprotective effects locally, reduce the discomfort of vaginal and urinary tract mucosa, and improve the quality of life of patients. Astragalin inhibits cell proliferation and accelerates the process of apoptosis in cervical cancer cells by regulating signaling pathways and cellular oxygenation (50). Network pharmacological analysis has reported that, in HeLa cells, astragalin can exert regulatory effects on signaling proteins such as EGFR, STAT3 and cyclin D1, affecting the ErbB and forkhead box protein O signaling pathways. This induces an increase in reactive oxygen species and notably inhibits the proliferation and promoting apoptosis in a manner that is linearly associated with concentration (51). Moreover, astragalin, has been reported to exhibit clear anti-cervical cancer activity (52).

Astragalin and gastric cancer. Gastric cancer is a great challenge to global public health with the fifth highest global incidence rate, the third highest mortality rate and a high rate of metastasis (53). The molecular and phenotypic heterogeneity of gastric cancer is particularly high (54), and >70% of patients with gastric cancer are diagnosed at an intermediate-to-advanced stage, missing the optimal time for treatment, with limited efficacy of chemotherapy, targeted therapies and immunotherapy, and issues of drug resistance and side effects (55,56).

Astragalin has been reported to act as a gastroprotective component (57), demonstrating satisfactory results in inhibiting gastric cancer cell activity and suppressing cell proliferation (58,59). Astragalin may be used in the treatment of undifferentiated gastric cancer as it can inhibit the EGFR/PDK/AKT signaling pathway, arrest the cell cycle at pre-G1 stage, induce apoptosis by upregulating the transcription of BAX and BAD genes whilst downregulating PDK1 and BCL-2, and reduce the expression of PI3K and AKT proteins (59). Astragalin inhibits the PI3K/AKT signaling pathway and induces an increase in the level of apoptosis-related proteins, thereby effectively suppressing the viability of gastric cancer cells and inhibiting the escape of cancer cells (17). The inhibitory effect of astragalin on mucin 1 mRNA was reported to be the strongest among the related proteins, reducing the expression of ppGalNAcT2 mRNA and fucosyltransferase 4 mRNA, and controlling tumor growth and proliferation (58). Similar to in lung cancer A549 cells, astragalin can also act on the gastric cancer AGS cell line through the same mechanism of action (33). Persistent *Helicobacter pylori* infection is also associated with the development of gastric cancer (60), and astragalin has been reported to bind to potential protein targets and exhibit unique antibacterial activity, preventing gastric cancer by eradicating persistent infection by this bacterium (61).

Astragalin and colorectal cancer. In 2022, the global number of colorectal cancer deaths was ~900,000 (34,62). Conventional treatments have limited success in advanced or metastatic colorectal cancer, and chemotherapeutic agents such as 5-fluorouracil, oxaliplatin and irinotecan are widely used but have notable side effects (63). Advanced technologies and new therapeutic ideas [including targeted drugs, immunotherapy and nanotechnology (64,65)] are not yet available for clinical treatment (66). However, herbs may exert anticancer effects by affecting the intestinal flora and improving the intestinal microenvironment (67). For example, astragalin may weaken the activity of colorectal cancer cells, inhibit their proliferation and induce apoptosis through several mechanisms (16,68).

In vitro and *in vivo* studies have reported that astragalin targets the NF-κB pathway in a dose-dependent manner to reduce the number of colorectal cancer cells, inhibit their growth, induce apoptosis and block their escape (16,27). Its molecular mechanism includes the following: Increasing the level of pro-apoptotic protein factors caspase 6, 7 and 8, whilst inhibiting the expression of Bcl-2; and inhibiting the concentration of CDK2, CDK4 and cell cycle protein D1, increasing the concentration of P21 and P27, so as to cause stalling of the cell growth cycle and promote the cell death (16). Previous research reported that with increasing time and astragalin concentration, the value-added rate and IC_{50} value of HCT116 cells decreased (16). Moreover, the ability of astragalin to disrupt cell membranes is proportional to its concentration (68). Molecular docking experiments have also reported that astragalin has a high affinity for amino acid targets in the PI3K/AKT/mTOR pathway and is able to retard the growth of cancer foci (69). Novel biological silver nanoparticles combined with astragalin can precisely target carbonic anhydrase IX enzyme and promote anticancer activity (14). Furthermore, the antiproliferative activity of astragalin may be associated with the inhibition of ERK1/2 phosphorylation (70).

Astragalin and breast cancer. In 2022, there were ~2 million women with breast cancer worldwide (34). Moreover, the incidence of male breast cancer is increasing every year by an average of 1.1% per year, which has been associated with unregulated levels of estrogen receptors (71). Chemotherapy,

Table I. Biological effects of astragalin and its derivatives on several cancers.

A, Lung cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	0, 2.5, 5, 10, 20, 40 μg/ml	6, 12, 18 and 24 h	*In vitro*	A549 and H1299 cells	Caspase-3 upregulated, caspase-9 upregulated, PI3K downregulated,	Inhibits cell growth and promotes apoptosis	Chen *et al*, 2017 (29)
	20 or 50 mg/kg	21 days	*In vivo*	Athymic nude mice	AKT downregulated, NF-κB downregulated and Fas downregulated	Suppressed tumor growth	
	0-500 μg/ml	48 h	*In vitro*	A549 and SCLC-H466 cells	p38 MAPK upregulated, caspase-3 upregulated, caspase-9 upregulated, Bax upregulated, Nrf2 downregulated, NQO1 downregulated, Bcl-2 down-regulated and SOD downregulated	Inhibits proliferation, induces apoptosis and non-cytotoxic to normal cells	Jia *et al*, 2021 (25)
	0, 5, 25, 75 and 150 μM	12 and 24 h	*In vitro*	A549 cells	Caspase-3 upregulated, caspase-9 upregulated, Bax upregulated, Bak upregulated, XIAP downregulated and Bcl-xL downregulated	Inhibits cell migration, invasion and induces apoptosis	Xu *et al*, 2021 (26)
	$151x10^{-3}$ g/l	24 h	*In vitro*	A549 cells	Caspase-3 upregulated	Induction of apoptosis	Ribeiro *et al*, 2021 (33)

B, Ovarian cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	20 and 40 mg/kg	8 days	*In vivo*	APP/PS1 mice	LC3BII/LC3BI upregulated, Beclin-1 upregulated, ATG5 upregulated, ATG12 upregulated, LAMP-1 upregulated and p62 downregulated	Reversal of autophagy or autophagic flux dysfunction	Yang *et al*, 2023 (45)
	100 μM	24 h	*In vitro*	OVCAR-8 and SKOV3 cells	HIF-1α downregulated, PCNA down-regulated, MMP-2 downregulated and MMP-9 downregulated	Inhibition of glycolytic pathways, proliferation and invasion in ovarian cancer cells	Song and Fu, 2018 (38) and Song and Fu, 2019 (39)

C, Gastric cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	-	-	*In vitro*	HGC-27 cells	Bax upregulated, Bad upregulated, PI3K downregulated and AKT downregulated	Inhibits cell proliferation, induces apoptosis, and blocks the cell cycle	Chu *et al*, 2022 (59)

Table I. Continued.

C, Gastric cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
	0, 20, 40 and 80 μM	12 h	*In vitro*	MGC-803, HGC-27, MKN28 cells	Bcl-2 downregulated, Bim upregulated, PI3K downregulated and AKT downregulated	Inhibits cell proliferation and migration, induces apoptosis	Wang *et al*, 2021 (17)
	25 and 50 mg/kg	21 days	*In vivo*	Xenograft mouse		Reduce tumor size and inhibit tumor growth	
	80 and 160 μM	24 h	*In vitro*	AGS cells	ppGalNAcT2 downregulated, C1GalT1 downregulated and NF-κB downregulated	Weakens cell viability and induces apoptosis	Radziejewska *et al*, 2022 (58)
	151x10^{-3} g/l	24 h	*In vitro*	AGS cells	Caspase-3 upregulated	Induction of apoptosis	Ribeiro *et al*, 2021 (33)

D, Colorectal cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	20, 40 and 80 μg/ml	4, 8, 24, 48 and 72 h	*In vitro*	HCT116 cells	Caspase-3 upregulated, caspase-9 upregulated, Bax upregulated, p53 upregulated, G_0/G_1 upregulated, CDK2 downregulated, CDK4 downregulated, TNF-α downregulated and NF-κB	Inhibits cell growth, migration and proliferation, induces apoptosis, induces cell cycle arrest and inhibits transcription	Yang *et al*, 2021 (16)
	0, 25, 50 or 75 mg/kg	18 days	*In vivo*	Xenograft nude mouse	P65 downregulated	Reduce the size and volume of the tumor	
	25-250 μg/ml	48 h	*In vitro*	LS180 cells	Caspase-8 upregulated, Bax up-regulated; MAPK downregulated, p53 downregulated, PI3K-AKT downregulated and TGF-β downregulated	Inhibits cell proliferation and metabolic activity, and induces apoptosis	Augustynowicz *et al*, 2022 (68)
	0, 15.63, 31.25 and 62.5 μg/ml	24 h	*In vitro*	HCT-116 and HT-29 cells	mTOR downregulated, PI3K down-regulated and AKT downregulated	Inhibits cell cloning and promotes apoptosis	Zhai *et al*, 2022 (69)
	120 mg/kg	22 days	*In vivo*	HCT-116 xenograft nude mice		Delays tumor growth	
	0, 1, 5, 10, 25 and 50 μg/ml	24 and 48 h	*In vitro*	HCT-116 cells	NF-κB downregulated, AKT downregulated and ERK1/2 downregulated	Inhibits cell growth and proliferation	Tragulpakseerojn *et al*, 2017 (70)

Table I. Continued.

E, Breast cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	20 and 40 μg/ml	24 h	*In vitro*	MDA-MB-231 cells	GLUT-1 downregulated, LDH-A downregulated, HK-2 downregulated, mTOR downregulated and AMPK upregulated	Inhibits aerobic glycolysis and cell proliferation	Zeb *et al*, 2024 (77)
	5 and 10 μg/ml	8 h	*In vitro*	MDA-MB-231 cells	MMP-9 downregulated and NF-κB downregulated	Inhibits cell invasion and reduces cell metastasis	Ahn *et al*, 2019 (82) and Shin *et al*, 2016 (83)
	10 mg/kg	8 days	*In vivo*	Balb/c mice		Inhibition of cellular lung metastasis	

F, Kidney cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	10, 20 and 40 μM	24 h	*In vitro*	A498 cells	Caspase 3 upregulated, caspase 9 upregulated, Bax upregulated, Bcl-2 downregulated, G_2/M upregulated and miR-203 upregulated	Inhibits cell growth, induces apoptosis and blocks the cell cycle	Zhu *et al*, 2019 (89)

G, Melanoma

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	0, 25, 50, and 100 μM	24, 48, and 72 h	*In vitro*	A375P and SK-MEL-2 cells	Caspase 3 upregulated, caspase 9 upregulated, Bax upregulated, cyclin D1 downregulated, Mcl-1 downregulated and SOX10 downregulated	Inhibits cell growth and induces apoptosis	You *et al*, 2017 (96)

H, Prostate cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	200, 400 and 800 mg/kg	21 days	*In vivo*	Xenograft mice	G_0/G_1 upregulated, p38 MAPK upregulated, MMP-9 downregulated, CDK4 downregulated, cyclin D1 downregulated and cyclin E	Inhibits tumor growth and reduces tumor weight	Kim *et al*, 2023 (104)

Table I. Continued.

H, Prostate cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
	0, 200, 400 and 800 μg/ml	24 h	*In vitro*	DU145 and LNCaP cells	downregulated	Induces cell cycle arrest and inhibits cell proliferation and migration	
	0-200 μg/ml	24 h	*In vitro*	DU-145 cells	Caspase 3 upregulated, caspase 8 upregulated, caspase 9 upregulated, TP53 upregulated and Bax upregulated	Destroys organelles, inhibits cell proliferation and promotes cell death	Koyuncu *et al*, 2024 (103)

I, Liver cancer

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	0, 11 and 33 μM	24, 48 and 72 h	*In vitro*	HCC cells	miR-125b upregulated, HK-2 downregulated and ROS upregulated	Inhibits cell proliferation and induces cell cycle arrest and apoptosis	Li *et al*, 2017 (109)
	0, 10 and 20 mg/kg	0, 5, 10, 15 and 20 days	*in vivo*	Nude mice		Inhibits tumor growth, Inhibits tumor cell proliferation *in vivo*	
	5-100 μg/ml	22 h	*In vitro*	HepG2 and L-929 cells	Bcl-2 downregulated	Inhibits cell viability and resists cell proliferation	Pirvu *et al*, 2018 (111)
	10-100 μg/ml	24 and 48 h	*In vitro*	HepG2 cells	TC downregulated, ROS downregulated, SOD upregulated, GSH, upregulated PI3K upregulated and p-AKT upregulated	Reduces cell viability, regulates redox, regulates cellular glucose and lipid metabolism, and improves insulin resistance	Zhou *et al*, 2024 (113)

J, Leukemia

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Heptaacetyl derivative of astragalin	0, 3, 10, 30 and 100 μM	0, 6, 12 and 24 h	*In vitro*	HL-60 cells	Caspase 3 upregulated, Bcl-2 downregulated, Bax upregulated, ERK1/2 upregulated and JNK/SAPK upregulated	Inhibition of cell proliferation and induction of apoptosis	Burmistrova *et al*, 2011 (117)

Table I. Continued.

K, Neuroblastoma

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	25, 50, 100 and 200 μg/ml	24 h	*In vitro*	SK-N-SH cells	MAPK downregulated, ROS downregulated, HO-1 upregulated, CAT upregulated and SOD2 upregulated	Reduces oxidative stress, exerts neuroprotective effects and induces apoptosis in tumor cells	Chung *et al*, 2016 (128)

L, Diffuse large B-cell lymphoma

Agent	Concentration	Time	Research type	Cell lines/animal	Target	Mechanism	First author/s, year (Refs.)
Astragalin	0, 1, 5, 25 and 125 μg/l	0, 24, 48 and 72 h	*In vitro*	OCI-LY8 cells	p53 upregulated, caspase-3 upregulated, Bax upregulated, Bcl-2 downregulated, JAK1 downregulated, JAK2-downregulated and STAT3 downregulated	Inhibits cell viability, inhibits cell growth and induces apoptosis	Lu *et al*, 2017 (143)

Bcl-2, B-cell lymphoma-2; Nrf2, nuclear factor erythroid 2-related factor 2; NQO1, NAD (P)H quinone dehydrogenase 1; SOD, super oxide dismutase; Bak, BCL2-antagonist/killer; XIAP, X-linked inhibitor of apoptosis protein; ATG5, recombinant autophagy related protein 5; ATG12, recombinant autophagy related protein 12; LAMP-1, lysosomal associated membrane protein 1; p62, sequestosome 1; HIF-1α, hypoxia inducible factor-1α; PCNA, proliferating cell nuclear antigen; MMP, matrix metalloproteinase; GLUT-1, glucose transporter protein 1; LDH-A, lactate dehydrogenase A; HK-2, hexokinase 2; Mcl-1, myeloid cell leukemia sequence 1; ROS, reactive oxygen species; GSH, glutathione; HO-1, heme oxygenase 1; CAT, catalase; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; AMPK, AMP-activated protein kinase; C1GalT1, core 1 synthase, glycoprotein-N-acetylgalactosamine 3-β-galactosyltransferase 1; miR, microRNA; p-, phosphorylated; SAPK, stress-activated protein kinase; TC, total cholesterol.

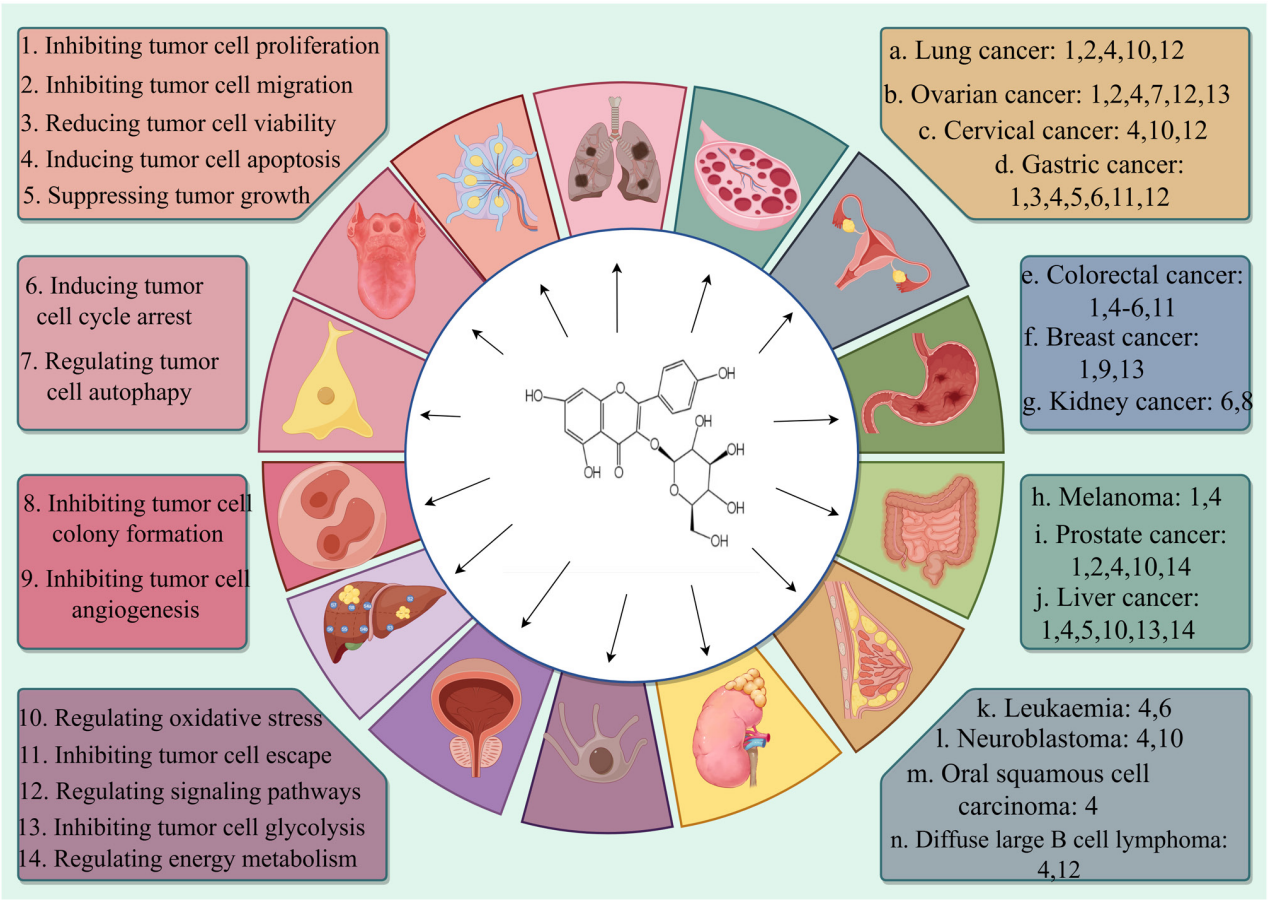

Figure 2. Astragalin exerts anticancer effects through various mechanisms. The numbers shown for each type of cancer on the right correspond to the mechanism numbers shown on the left. The figure was drawn using Figdraw (version 2.0; https://www.figdraw.com/static/index.html#/).

radiotherapy and endocrine therapy, although effective, are often accompanied by serious side effects, such as nausea, vomiting and bone marrow suppression (72-74). In addition, issues such as lymphoedema and chronic arm complications after breast cancer treatment also seriously affect patient quality of life (75).

Astragalin inhibits the activity of the drug metabolizing enzyme cytochrome P450 family 1 subfamily B member 1 and, *in vivo*, it inhibits estradiolation to produce the carcinogenic metabolite 4-hydroxy-estradiol (76). Furthermore, astragalin inhibits breast cancer cell activity and proliferation and angiogenesis (18,77). Astragalin can act on AKT, zinc finger E-box binding homeobox 1, VEGF and matrix metallopeptidase (MMP)9 targets to inhibit cell motility and exert anti-angiogenic effects (18). It downregulates the protein expression levels of glucose transporter protein (GLUT)-1, lactate dehydrogenase A and hexokinase 2, activates AMP-activated protein kinase (AMPK) and inhibits mTOR activity, reduces glucose uptake, inhibits glycolysis, and inhibits cell proliferation through the AMPK/mTOR pathway (77). Activation of the estrogen receptor is associated with the development of >50% of invasive breast cancers (78), and astragalin, which exerts therapeutic effects comparable with those of hormones with a high margin of safety, may offer new hope for clinical application (79). Moreover, astragalin may mainly interact with human estrogen receptor α receptors to exert anticancer effects (80), and it can also bind to human epidermal growth factor receptor-2 (HER2) and become a potential inhibitor of HER2 (81). Astragalin may also be an effective therapeutic agent for metastasized advanced breast cancer, and this biological effect may be achieved by reducing the expression of TNF-α, which impairs the expression of MMP-9 (82,83).

Astragalin and kidney cancer. The incidence and mortality of renal cell carcinoma is increasing annually (84). By contrast, conventional therapies including surgery, ablation and radiation face notable challenges, including more extensive surgery, nephrotoxicity and suboptimal therapeutic range (85). Patients undergoing kidney transplant have a markedly increased risk of new cancers due to the use of potent immunosuppressants (86). Furthermore, dysregulated miRNA expression is associated with cancer cell emergence, growth and cellular drug resistance (87). As a renoprotective drug (88), lower doses of astragalin have been reported to upregulate miRNAs in renal cancer cells to impede tumor cell growth, affect the cell cycle and promote apoptosis in renal cancer cells (89). Previous research reported that 20-50 μM astragalin was cytotoxic to all renal cancer cells, especially the A498 cell line, and the therapeutic index value of astragalin treatment for renal cancer was high. It upregulated the RNA levels of tumor suppressor genes, causing cancer cells to stagnate at the G2/M stage. It also upregulated the expression of apoptotic proteins and inhibited the colony formation of renal cancer cells, which was positively associated with the dosage of astragalin (89).

Astragalin and melanoma. Melanoma is an aggressive metastatic cancer, with a 5-year survival rate of only 4.6% (90). Global melanoma incidence and mortality in 2040 will be >150% of what it was in 2020 (91). In recent years, immunotherapy and targeted therapies have achieved a certain degree of efficacy as the first-line recommended drugs (92); however, there is a substantial risk of toxicity and drug resistance (93).

Astragalin is cytotoxic and capable of inducing apoptosis. Mitogen- and stress-activated protein kinase 1 (MSK1) is an enzyme involved in several cancer processes, and in melanoma, high levels of MSK1 are often accompanied by high expression of CREB, and increased activity of the MSK1-CREB pathway promotes cell proliferation and metastasis (94). Astragalin directly binds to and inhibits p38 MAPK activity, antagonizing MSK1 phosphorylation and high levels of γ-H2AX in a time- and dose-dependent manner, thereby reducing precancerous skin lesions (95). Astragalin has also been reported to exert toxic effects on melanocytic tumor A375P and SK-MEL-2 cells, increasing the levels of positive cells and sub-G1 populations, activating cleaved poly(ADP-ribose) polymerase, inhibiting SRY-box transcription factor 10 signaling, acting on cell cycle-related proteins and promoting apoptosis (96). Moreover, astragalin has been reported to upregulate the expression of superoxide dismutase and exhibit skin protection effects (97).

Astragalin and prostate cancer. Prostate cancer ranks second among malignancies in men (34), and it has a high degree of homogeneous lesion heterogeneity, with common point mutations in <30% of the same surgically resected specimen (98). Androgen deprivation therapy is widely used in metastatic hormone-sensitive prostate cancer and improves the quality of life of patients with advanced disease; however, it also affects their cardiovascular health (99). With disease progression, it can further develop into metastatic castration resistant prostate cancer (mCRPC). Docetaxel can prolong the overall survival of patients with mCRPC (100); however, adverse effects, such as neutropenia and neurotoxicity, can occur (101,102).

Astragalin has been reported to have notable biological effects for the treatment of prostate cancer by inhibiting cell proliferation, migration and invasion, and inducing apoptosis (103). Astragaloside, the most abundant component of *Cyperus exaltatus* var. *iwasakii* (CE) secondary metabolites, modulates transcription factors and inhibits the expression of MMP-9, thereby inhibiting invasion, migration and proliferation of prostate cancer cells. *In vivo* studies have also reported that in an allogeneic model, CE inhibits tumor loading (104). Moreover, *Jurinea mesopotamica* Hand.-Mazz. contains high levels of astragalin, which can destroy cell organelles, promote the generation of reactive oxygen species, increase apoptotic gene expression and transcription, regulate energy metabolism, inhibit cell proliferation and induce cell death (103).

Astragalin and liver cancer. Liver cancer is a common primary cancer and a high-risk site for cancer metastasis (105). Emerging Yttrium 90 microsphere therapy has been reported to have notable efficacy in patients with advanced, non-surgical liver cancer (106); however, this method requires strict pre-operative screening, is relatively expensive and requires a high level of expertise to perform the surgery (107). By contrast, it is advantageous to explore the development of Traditional Chinese Medicine herbal active ingredients. For example, astragalin has been reported to inhibit the activity of hepatocellular carcinoma cells, suppressing their proliferation and inducing apoptosis through several mechanisms (108-110).

In vitro and *in vivo* experiments have reported that astragalin can promote miR-125b expression, inhibit hexokinase 2 and shrink allogeneic tumors. It can also promote the oxidative phosphorylation of hepatocellular carcinoma cells, reduce glycolysis, generate reactive oxygen species and antagonize apoptotic proteins to serve an anti-cell proliferation role (109,111). Previous research reported that astragalin reduced Bcl-2 levels, promoted Bax expression, cleaved caspase 3, 8 and 9, and exerted anti-hepatocellular carcinoma activity by regulating apoptosis pathway (110). Astragalin has also been reported to inhibit the activity of HepG2 cells (112), as well as serve as a potential complementary treatment for insulin resistance in patients with hepatocellular carcinoma. Its mechanism of action may include activation of insulin receptor substrate 1, PI3K and AKT, and the regulation of glycolipid metabolism and oxidative stress in cancer cells to a certain extent (113).

Astragalin derivatives and leukemia. With 58,903 deaths, China had the highest number of leukemia deaths in the world in 2021 (114). Personalized treatment approaches for leukemia have been developed; however, there are issues of treatment resistance, long-term side effects and quality of life (115). Several studies have reported that Chinese herbal medicine has satisfactory therapeutic effects on myelosuppression (116). For example, astragalin has been reported to inhibit growth and induce apoptosis in leukemia cells (117).

Certain researchers have isolated drug components with anticancer activity and clarified that astragalin is its main antileukemia component (118). The flavonoid derivative astragalin heptaacetate (AHA) can induce cell death through non-specific caspases. AHA has been reported to concentrate and cleave cell chromatin under aerobic conditions, block the cell cycle in the G0-G1 phase and affect the mitochondrial membrane potential. It also has been reported to regulate cytokine expression, activate MAPK, exhibit notable cytotoxicity and induce apoptosis at the organelle level (117).

Astragalin and neuroblastoma (NB). The development of NB may be associated with the neural spine during embryonic development (119). The disease is highly malignant (120), with >50% of patients presenting with high-risk phenotypes (121) and a 5-year survival rate of <50% (122). The immune microenvironment of NB is complex, with low immunogenicity of tumor-associated antigens and immunosuppressive factors (such as TGF-β and IL-10), hindering the effectiveness of immunotherapy (123). Moreover, the high clinical behavioral heterogeneity of NB makes it more difficult to develop standardized treatment protocols (124,125).

Previous research has reported that mutations associated with the RAS/MAPK pathway are present in the majority of recurrent NBs (126,127). Astragalin exhibits biological effects on this pathway, inhibiting cell activity and inducing apoptosis (128). Furthermore, astragalin pretreatment reverses the cytoprotective effect, which is associated with the inhibition

of oxidative stress and phosphorylation of MAPK, as shown by a reduction in the levels of extracellular protein-regulated protein kinases, p38 and c-Jun N-terminal kinase, exerting their cytotoxic effects and inducing apoptosis in NB SK-N-SH cells (128).

Astragalin and oral squamous cell carcinoma (OSCC). Oral cavity cancer accounts for ~90% of oral malignancies (129). Risk factors for the disease include smoking, alcohol consumption and betel nut consumption (130), and human papillomavirus has also been reported to have an association (131). The disadvantages of traditional treatments include systemic damage, limited efficacy and drug resistance (132). Emerging therapies, such as transoral laser surgery and intensity modulated radiation therapy show potential; however, the popularization and application of these therapies still face technical and economic challenges (133,134). By contrast, herbal medicines have advantages in improving survival, enhancing immune function and reducing the toxicity of chemotherapy (135-137).

Research has demonstrated that the Chinese herbal formulation, FFBZL, composed of *Scutellaria barbata* D. Don, *Astragalus membranaceus* and *Ligusticum chuanxiong* Hort, may be used in the treatment of OSCC; therefore, its molecular mechanisms warrant in-depth exploration. As a crucial component, *Astragalus membranaceus* exhibits marked antitumor activity in laryngeal squamous cell carcinoma through its extract, total flavonoids of Astragalus, suggesting the potential of its active ingredients (138). Astragalin, one of the key active components of *Astragalus membranaceus*, currently lacks direct data demonstrating its inhibitory effect on OSCC; however, network pharmacology combined with bioinformatics analysis has revealed that six key ingredients of FFBZL (including components from *Astragalus membranaceus*) may interact with 820 potential target genes. These targets intersect with OSCC-related target genes, generating 151 common targets (139).

Astragalin and diffuse large B-cell lymphoma (DLBCL). DLBCL is a common aggressive non-Hodgkin's lymphoma that accounts for 30-40% of all non-Hodgkin's lymphomas (140). The R-CHOP regimen (rituximab + cyclophosphamide + adriamycin + vincristine + prednisone) is the first-line standard of care for DLBCL. However, certain patients still relapse after treatment or transition to refractory cases (141).

Astragalin has been reported to induce apoptosis in DLBCL cells by modulating cytokines (142). A previous study reported that astragalin inhibits DLBCL OCI-LY8 cell viability and disrupts the nucleus to promote the emergence of apoptotic vesicles by affecting the JAK/STAT signaling pathway, upregulating the levels of p53, caspase-3 and Bax, and inhibiting Bcl-2 expression (142).

4. Discussion

Anticancer mechanisms. Astragalin has notable anticancer effects in several types of cancer. It also scavenges free radicals in the body (143). Furthermore, overexpression of GLUT5 has been reported to lead to marked changes in glucose metabolism and enhance glycolysis, which is a prominent manifestation of cancer cells. This protein is expected to be used as a biomarker for the diagnosis of cancer and as a therapeutic target (144). A derivative of astragalin, astragalin-6-glucoside, has been reported to inhibit GLUT5 (145). Certain studies suggest that it is associated with glycolysis; however, the exact mechanism of action is not clear (146).

Based on a review of the mechanisms of astragalin and its derivatives against several malignant tumors, the anticancer mechanisms of astragalin are summarized as follows: i) Regulation of signaling pathways: Astragalin can regulate the PI3K/AKT, MAPKs, JAK/STAT and NF-κB signaling pathways, miRNA expression and the Notch1 pathway (27,147), which inhibits tumor cell growth and survival (148); ii) induction of apoptosis: Astragalin can cause loss of caspase activity, mutation of p53 gene and imbalance in the regulation of Bcl2 protein, leading to reduced activity and programmed death of cancer cells (149). It also affects mitochondrial function, reduces mitochondrial membrane potential and increases the Bax/Bcl-2 ratio (150). Notably, a study reported that astragalin ameliorated testicular germ cell apoptosis in rats with varicocele by reducing the expression of caspase 3 and the Bax/Bcl-2 ratio (151). Moreover, astragalin reduced intracellular oxidative stress, activated caspase 3, 7 and 9, and promoted programmed cell death in cancer cells, whilst protecting normal cells from oxidative damage, suggesting that it has a dual effect on the human body (7); iii) inhibition of cell proliferation and migration: Astragalin is closely associated with several angiogenesis-related factors (such as prostaglandin-endoperoxide synthase 2, kinase insert domain receptor and MMP9), revealing potential biological effects with angiogenesis and suggesting new ideas for the treatment of tumors in terms of reducing the number of blood vessels (152). Astragalin downregulates the expression of specific protein factors, regulates miRNAs and induces cell cycle arrest (26); and iv) enhancement of drug sensitivity: In a previous study, astragalin was administered with carboplatin and cisplatin over a range of concentrations, and the results demonstrated that astragalin was associated with an improved combined effect in OVCAR-8 and SKOV-3 cells compared with carboplatin or cisplatin alone (39). This indicates that astragalin could enhance the accumulation of chemotherapeutic drugs in tumor cells and reverse resistance to chemotherapeutic drugs.

Advantages for cancer treatment. Astragalin has a wide range of advantages in cancer treatment, especially in the process of cooperating with chemotherapeutic drugs to reduce toxicity and increase efficiency.

Range of effects of astragalin. For different cancer types, astragalin has varied anticancer mechanisms of action, but there are also cross-overlapping mechanisms of effect. In general, they include reducing the growth activity of tumor cells, inhibiting tumor cell angiogenesis, inducing apoptosis, blocking the cell growth cycle, and reprogramming the metabolic process of tumor cells, affecting the proliferation, migration and invasion of tumor cells (58). Moreover, several studies have reported that astragalin does not cause harm to normal human cells (8,153).

Role of astragalin in cancer. Astragalin has shown promising results in different types of cancer. For example,

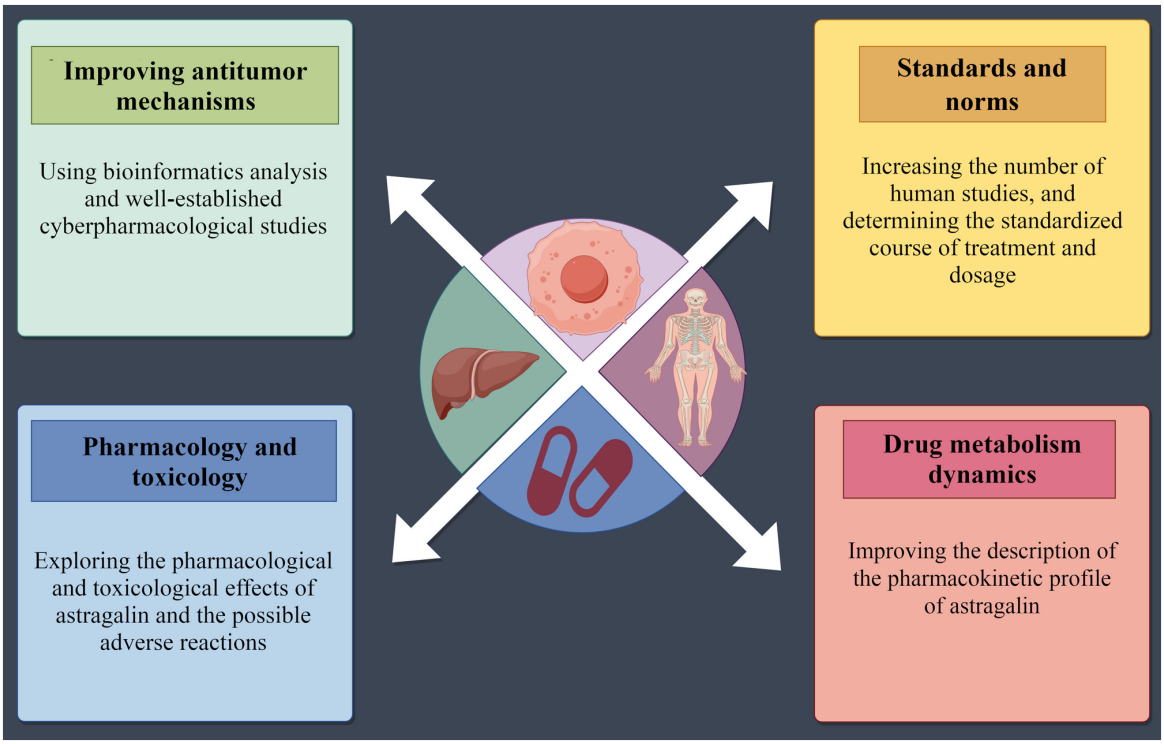

Figure 3. Future research directions of astragalin for cancer treatment. The figure was drawn using Figdraw (version 2.0; https://www.figdraw.com/static/index.html#/).

radiotherapy may lead to neurotoxicity (154), cancer-caused fatigue (155) and gastrointestinal impairment, and other therapeutic adverse effects (156,157). However, previous research has suggested that if astragalin is used in combination with chemotherapeutic drugs, the neuroprotective, anti-inflammatory, antioxidant (158,159) and antibacterial effects of astragalin could assist the action of the chemotherapeutic drugs (160). Moreover, research has reported that astragalin is involved in targeting cellular resistance factors (89): It can enhance the accumulation of chemotherapeutic drugs in cells and increase the sensitivity of cells to the drugs, thus reversing cellular resistance (39). However, at present, there is a lack of direct research data on the application of astragalin and chemotherapeutic agents in other cancers. Based on the collection of existing literature, we hypothesize that astragalin can serve a direct inhibitory and blocking role in the growth and metabolism of tumor cells, hindering cell growth, proliferation, invasion and migration, and inducing apoptosis through several mechanisms. At the same time, we hypothesize that it can serve a unique toxicity-reducing and synergistic effect in the standardized radiotherapy process. This gives it the potential to be used as a complementary or alternative treatment to first-line chemotherapeutic agents.

Safety and cost-effectiveness. Absorption, distribution, metabolism, excretion and toxicity model predictions have reported that astragalin is not susceptible to acute hazards or systemic toxicity and, meeting drug safety requirements, may reduce accumulation toxicity to normal tissues through exocytosis mechanisms (153). In A549 lung cancer cells, astragalin had an IC_{50} of 150 μM (after 72 h treatment) and inhibited 85% of lung cancer cells; however, to the best of our knowledge, at this dose, there is no evidence of toxicity to normal lung bronchial epithelial cells and cell survival was markedly higher compared with that of cancer cells (26). Moreover, the IC_{50} was 20-50 μM in A498 renal carcinoma cells and ≤110 μM in normal renal cells, indicating that the toxicity to normal cells was notably lower than that to cancer cells (89). Additionally, the IC_{50} of astragalin-containing extract of *Citrus* x *aurantium* was 23.26 μg/ml in colon cancer HCT-116 cells; however, the toxicity in normal lung fibroblasts (WI-38) was low, with no marked IC_{50} value reported. This suggests that astragalin may have a selective effect on cancer and normal cells (161). Moreover, the aforementioned findings indicate that astragalin has a wide therapeutic window and exhibits notable anticancer activity with a high safety profile for normal cells.

In summary, astragalin has potent antitumor biological effects with little or no toxic effects on normal tissues; however, this needs to be supported by further evidence from numerous future clinical trials.

Shortcomings and prospects. Previous research reported that the absolute oral bioavailability of astragalin in rats was <5% (162). This is mainly due to its molecular structure (higher molecular weight and worse water solubility) (163) and its easy conversion by metabolic enzymes [such as uridine diphosphate-glucuronosyltransferases (UGTs)] in the liver and intestine, which is characterized by rapid absorption and clearance (8). However, improved processing or structural optimization may enhance gastric absorption and delay metabolism, thereby increasing bioavailability (164,165). UGT enzymes have been reported to be key metabolizing enzymes of astragalin *in vivo*. They include CtUGT3 (166) and AtUGT78D2 (167). Moreover, astragalin is distributed in several organs, with the highest concentration in the gastrointestinal tract. It can also cross the

blood-brain barrier (168) and can be detected in the liver, lungs and kidneys (169). However, although there are studies that investigated the pharmacokinetics of astragalin (8,170,171), there is a lack of clinical pharmacokinetic validation, and the pharmacological properties of the metabolites, lower bioavailability and stability enhancement need to be further optimized.

Most of the literature included in the present review involved *in vivo* or *in vitro* experiments, which largely fail to provide a comprehensive and systematic picture of the drug effects of astragalin within the complex human environment when used in combination or alone. The lack of clinical data, drug metabolism and pharmacokinetics hinders the development of standardized therapeutic protocols for astragalin. Therefore, before the approval of the marketing of this Chinese medicine monomer and its use in large quantities in patients with cancer, several studies are needed: i) Further elucidation of the antitumor mechanism of astragalin through bioinformatics analyses and well-established cyberpharmacological studies; ii) several human studies on the antitumor effect of astragalin and determination of the standardized course of treatment and dosage; iii) exploration of the pharmacological and toxicological effects of astragalin and the possible adverse reactions; and iv) improvement of the description of the pharmacokinetic profile of astragalin. This will aid in the systematic investigation of the different targets of astragalin in several cancer types and promote the discovery and development of new drugs (Fig. 3). At the same time, treatment protocols that maximize anticancer effects should be assessed for different types of cancer to enhance efficacy and reduce toxic side effects. By analyzing the outcomes of treating different types of patients, the differences in the effects of astragalin on different types of cancers can be explored, and the treatment plan can be refined.

Therefore, future in-depth studies on astragalin should focus on the advancement of data on the real drug environment in the clinic, as well as data associated with drug metabolism pathways and pharmacokinetics in a standardized manner, with a view to providing an objective basis for the development of new drugs and the update of therapeutic regimens.

5. Summary

In the research of malignant tumors, the development and utilization of herbal medicines has become a major topic. The results of the present review indicate that astragalin, with its wide and natural sources, strong anticancer activity, high safety value and low cost, has potential to be an alternative drug with considerable efficacy in the prevention and treatment of malignant tumors; however, further research is required. Although astragalin has demonstrated promising antitumor effects, its pharmacokinetic profile is incompletely defined, and its low oral bioavailability limits its potential clinical application. Future studies should investigate the bioavailability of astragalin through systematic *in vitro* and animal experiments, and the optimization of formulation processes for novel drug delivery systems. With further research, astragalin has the potential to become an alternative drug for cancer treatment in the future.

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Availability of data and materials

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Authors' contributions

YFZ retrieved the data and participated in the conceptualization and design of the article as well as the data analysis; YQF wrote the original manuscript and made several revisions with the assistance and editing of CL, DND and FYL. FJH was involved in the design of the manuscript and the interpretation of the data. Data authentication is not applicable. All authors contributed to the article and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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