

Systematic Review

The Antitumor Efficacy of *Astragalus membranaceus* and Its Active Constituents: A Systematic Review of Preclinical Evidence

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Abstract

Backgrounds: *Astragalus membranaceus* (AM), a traditional Chinese medicinal herb, has garnered interest for its potential in anticancer therapy. Preclinical evidence suggests that AM inhibits tumor growth and could mitigate the adverse effects associated with conventional treatments. However, a comprehensive review of its efficacy across various cancer types is lacking. **Objectives:** This systematic review evaluates the preclinical evidence for the antitumor efficacy of AM and its active components to inform future clinical translation. **Methods:** A systematic literature search was conducted in PubMed, EMBASE, and Web of Science from their earliest records to February 2026 to identify relevant studies. Studies reporting on the antitumor effects of AM or its constituents in murine models were included. **Results:** Seventy-six studies met the inclusion criteria. The most frequently investigated compounds were formononetin (21 studies), Astragaloside IV (20 studies), and Astragalus polysaccharide (16 studies). The evidence indicates that these compounds, both as monotherapies and in combination with standard chemotherapy, can inhibit tumor growth and potentiate antitumor efficacy. **Conclusions:** AM and its bioactive constituents exhibit promising anticancer effects against solid tumors, including breast, lung, hepatocellular, and colorectal carcinomas in preclinical models. Clinical investigation is warranted to confirm the utility of AM for cancer therapy.

Keywords: *Astragalus membranaceus* Bunge; Huang Qi; cancer; astragaloside; calycosin; formononetin; systematic review

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1. Introduction

Cancer, defined by the National Cancer Institute (2021) as a disease characterized by the uncontrolled growth and spread of the body's cells, remains a paramount global health challenge. It is a leading cause of premature mortality, ranking first or second in 134 countries [1]. Global statistics for 2022 revealed approximately 20 million new cases and nearly 18 million deaths, accounting for almost one in four deaths from noncommunicable diseases worldwide [2]. With an estimated annual cost of cancer care reaching US\$1.16 trillion, the disease undeniably constitutes a critical public health priority [3].

Conventional cancer treatments, including surgical resection, radiotherapy, and chemotherapy, remain foundational to oncology but are fraught with significant challenges. A major limitation of chemotherapy is the development of drug resistance, wherein initially responsive cancer cells acquire evasion mechanisms. This process, driven by

genetic alterations, cancer stem cells, and tumor microenvironment interactions, leads to intratumoral heterogeneity and ultimately, treatment failure [4]. Furthermore, these therapies often induce severe side effects (such as peripheral neuropathy, oral mucositis, and psychological distress including anxiety, depression, and sleep disturbances), many of which are inadequately managed and can diminish patient adherence to treatment regimens [5].

Traditional Chinese medicine (TCM) represents a renowned source of bioactive compounds, such as polysaccharides, alkaloids, flavonoids, and terpenes, which possess demonstrated anticancer and anti-inflammatory properties [6]. Due to its favorable safety profile and low toxicity, TCM has been used as a supportive therapy to alleviate many side effects of conventional cancer treatments, including nausea, vomiting, anorexia, polyneuropathy, pain, and fatigue [5]. Moreover, in vitro and in vivo studies have revealed that these compounds can directly and indirectly influence cancer immunity, modulate the tumor microenvironment, and enhance chemotherapeutic efficacy [7]. Consequently, TCM presents a promising adjunct to chemotherapy, with the potential to reverse multidrug resistance and improve therapeutic outcomes.

Astragali radix (Huang Qi), derived from the dried roots of *Astragalus membranaceus* (Fisch.) (AM) Bunge and its variant *A. membranaceus* var. *mongholicus* (Bge.) Hsiao, is a fundamental herb in TCM. According to World Flora Online (www.worldfloraonline.org), the name *Astragalus membranaceus* is widely accepted as a scientific synonym for *Astragalus mongholicus* Bunge. Traditionally employed as a Qi-invigorating tonic, it is used to enhance stamina, strength, and vitality, often in combination with other herbs. Its medicinal use was first documented in *Shennong's Classic of Materia Medica*, the earliest complete pharmacopoeia of China [8]. In TCM theory, AM is believed to fortify the spleen and lung, with the spleen considered a vital immune organ essential for sustaining life [9]. Renowned as an adaptogenic herb, AM is credited with vital energy tonifying, skin reinforcing, diuretic, abscess-draining, and tissue-regenerative actions, which collectively help defend the body and maintain physiological equilibrium.

Phytochemical analyses have identified over 200 bioactive compounds in *Astragalus* species, including flavonoids, triterpenoids, and polysaccharides. Among them, the isoflavones (calycosin, calycosin-7-glucoside, formononetin), the triterpenoid saponin astragaloside IV, and astragalus polysaccharides (APS) have been extensively studied. These constituents were shown to exhibit a broad spectrum of pharmacological activities, such as antioxidant, anti-inflammatory, anti-diabetic, cardioprotective, immunomodulating and antitumor effects in various in vitro and in vivo studies [10–12]. Notably, formononetin, astragaloside IV, and APS demonstrate remarkable antineoplastic properties. Their mechanisms of action include inhibiting tumor cell proliferation, inducing apoptosis, suppressing metastasis and angiogenesis, and exerting immunostimulant and immunomodulatory effects [4,13,14].

Despite compelling preclinical evidence supporting the antitumor potential of AM and its constituents, their clinical application in oncology remains limited. A comprehensive evaluation of its efficacy in established tumor models is also lacking. Therefore, we conducted this systematic review to examine the direct antineoplastic and chemosensitizing effects of AM and its bioactive compounds in animal models in vivo, with the aim to inform future translational research and therapeutic development.

2. Results

2.1. Literature Search and Study Selection

After removing 1736 duplicates, we screened 10,260 records by title and abstract, of which 400 were retained for full-text review. Following this assessment, 324 studies were

excluded based on predefined criteria. The primary reasons for exclusion were: not being an *in vivo* animal study ($n = 154$), investigating an indirect mechanistic relationship ($n = 67$), or focusing on the mitigation of chemotherapy-related side effects ($n = 34$). Other reasons included the use of TCM formulas, chemically modified constituents, or advanced drug delivery systems ($n = 26$); absence of a tumor model ($n = 15$); inaccessibility of the full text ($n = 7$); being a pharmacokinetic study ($n = 7$); involving surgical or radiotherapy interventions ($n = 8$); examining phytoestrogenic effects ($n = 4$); and missing relevant results ($n = 2$). Consequently, 76 studies were deemed eligible for inclusion in the final analysis. The study selection process is detailed in the PRISMA flow diagram (Figure 1), which was conducted in close adherence to the PRISMA guidelines [15].

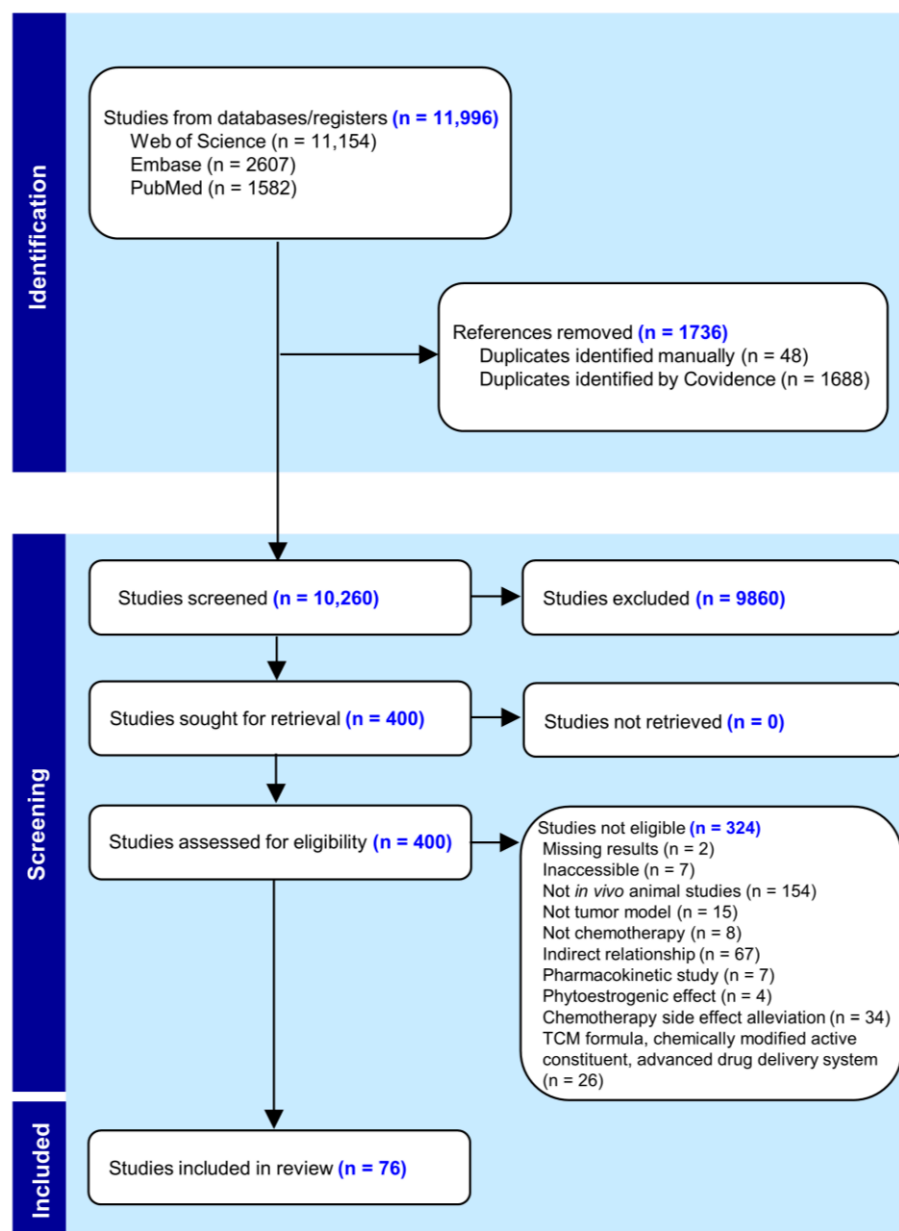


Figure 1. PRISMA flow diagram of study searching and selection.

2.2. Characteristics of Included Studies

The characteristics of the 76 included preclinical studies are summarized in Supplementary Table S1. The studies exhibited considerable diversity in the animal models, routes of administration, and cancer types investigated. BALB/c mice were the

most frequently used strain ($n = 49$, 64.5%), and the intraperitoneal route was the most common method of administration ($n = 31$, 40.8%). The predominant constituents of *A. membranaceus* evaluated were formononetin (28.0%), Astragaloside IV (26.7%), and *Astragalus* polysaccharides (21.3%). The chemical structures of these active constituents are illustrated in Figure 2. Regarding cancer types (Figure 3), the most prevalent models were breast cancer ($n = 13$, 17.1%), colorectal cancer ($n = 11$, 14.4%), hepatocellular carcinoma ($n = 11$, 14.4%), and non-small cell lung cancer ($n = 10$, 13.2%). Less frequently represented cancers included cervical cancer ($n = 5$, 6.6%), melanoma ($n = 5$, 6.6%), osteosarcoma ($n = 4$, 5.3%), nasopharyngeal cancer ($n = 3$, 4.0%), prostate cancer ($n = 3$, 4.0%), stomach cancer ($n = 3$, 3.9%), myeloma ($n = 2$, 2.6%), ovarian cancer ($n = 1$, 1.3%), thyroid cancer ($n = 1$, 1.3%), sarcoma ($n = 1$, 1.3%), and lymphoma ($n = 1$, 1.3%).

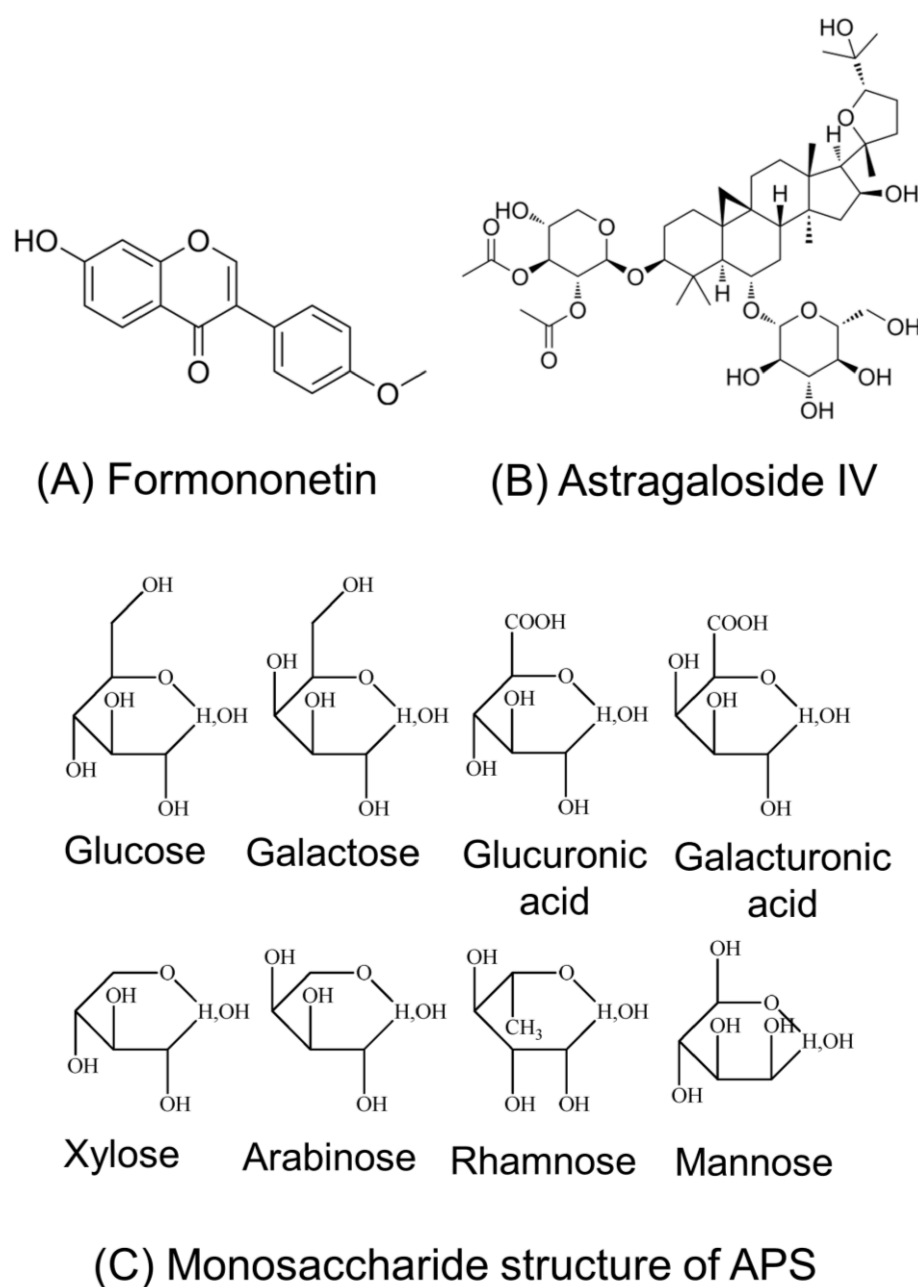


Figure 2. Chemical structures of *Astragalus membranaceus* active constituents: (A) Formononetin (FMN); (B) Astragaloside IV (AS-IV); and (C) Monosaccharides of *Astragalus* polysaccharides (APS).

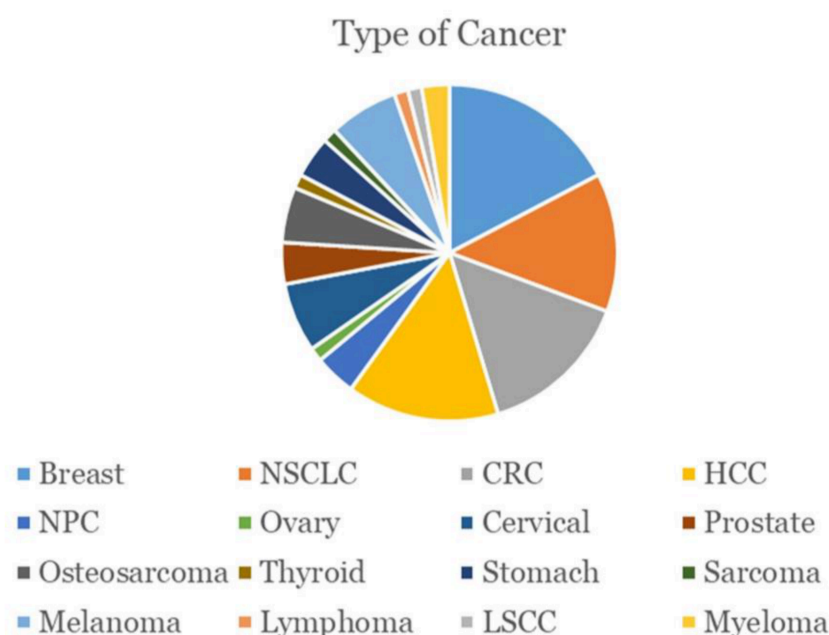


Figure 3. Cancer type of the animal models evaluated in the included studies. Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; LSCC, lung squamous cell carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer.

2.3. Risk of Bias and Quality Assessment

The methodological quality of the 76 included studies was assessed using the SYRCLE risk of bias tool. The results of this assessment are detailed in Figures 4 and S2. A significant finding was the consistent lack of reporting on key methodological safeguards. No studies described the method of random sequence generation or allocation concealment. Also, information on blinding of caregivers and outcome assessors was universally absent. On the other hand, reporting was robust for other domains, including baseline characteristics, random outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Most studies confirmed that experimental groups were similar at baseline. One study was flagged with a high risk of bias due to an unreported number of animals, affecting the domains of outcome assessment and data completeness. Overall, the included studies demonstrated a low to moderate level of methodological quality. The risk of bias scores ranged from 2 to 6 out of a possible 10, with a mean score of 4.92 ± 1.12 .

2.4. Results of Individual Studies

2.4.1. *Astragalus membranaceus* Extract

Extraction Methods

The studies employed different extract protocols. Three studies used methanol [10,16,17], two of which added 2% KOH to methanol to facilitate the extraction process [10,17]. Four studies used aqueous extraction [17–19], two of which performed further extraction using ethanol [18], and another one performed further extraction with ethyl acetate [19]. The final extracts were typically dried and reconstituted in an aqueous solution for experiments. One study did not report the extraction method [20]. Only in one study, the amount of total flavonoids in the extract was quantified by LC-MS and was found to be 40–60% [19].

Antitumor Efficacy of AM Extract Versus Control

The crude extract demonstrated superior antitumor activity compared to the control groups. All three studies evaluating tumor weight as the end-point reported significant

reductions by AM extract (250–500 mg/kg) [16,17,19]. Similarly, all four groups assessing tumor volume (100–500 mg/kg) found a significant reduction [10,16–18].

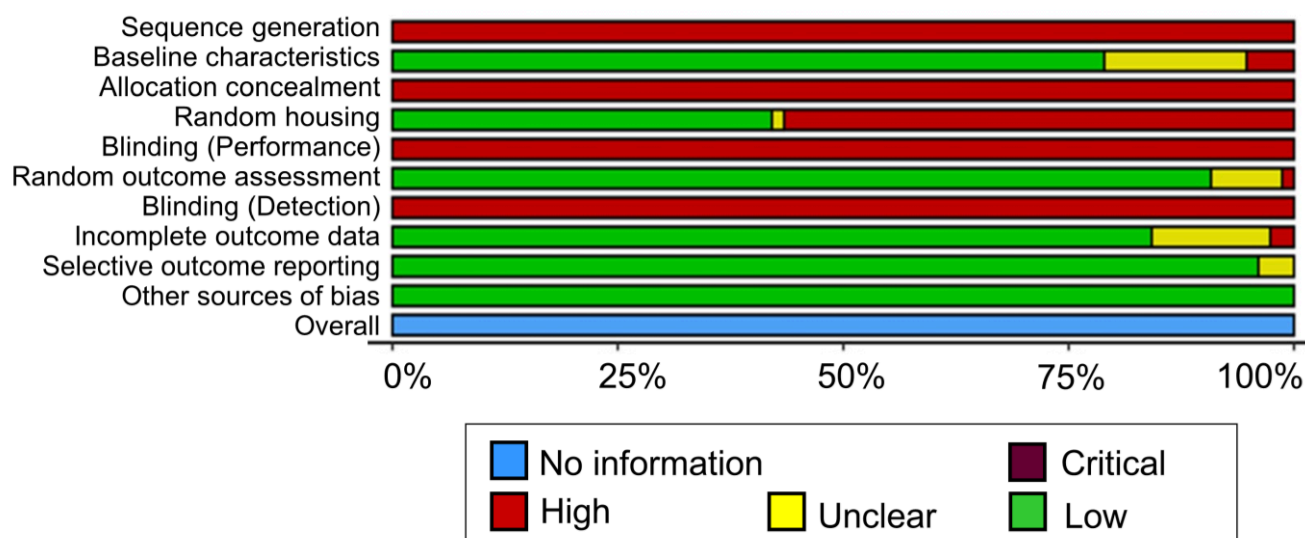


Figure 4. Methodological quality assessment of the 76 included animal studies. Quality was evaluated using the SYRCLE risk of bias tool. The tool assesses 10 domains of potential bias: (i) sequence generation, (ii) baseline characteristics, (iii) allocation concealment, (iv) random housing, (v) blinding of investigators, (vi) random outcome assessment, (vii) blinding of assessors, (viii) incomplete outcome data, (ix) selective outcome reporting, and (x) other sources of bias. For each domain, studies were judged as having “low”, “high”, or “unclear” risk of bias. The graph depicts the percentage of studies judged to be low, high, or unclear risk for each domain across all included studies.

Dose–Response Relationship

Evidence for a dose–response relationship was limited. Only one study compared AM extract at two dose levels (100 mg/kg and 200 mg/kg), and it found no significant difference in tumor volume reduction between the two doses [19].

Antitumor Efficacy of AM Extract Versus Standard Anticancer Therapy

The available evidence suggests the crude extract is not effective as a monotherapy alternative to standard treatment. One study found that a dose of 48 mg/kg was less effective than cisplatin in reducing tumor weight [19]. Another study found that AM extracts (100 or 200 mg/kg) were less effective than 5-FU in reducing tumor volume [16].

Antitumor Efficacy of AM Extract-Containing Drug Combination

Results from two studies suggest potential for combination therapy, though the results were mixed. In one study, the combination of AM extract (48 mg/kg) and cisplatin (1 mg/kg) was found to produce significant tumor weight reduction compared to cisplatin treatment alone [19]. In another study, while the combination of AM extract (100 mg/kg) and 5-FU showed a significant reduction in tumor volume compared to 5-FU treatment alone, it is less effective than the 5-FU + oxaliplatin combination [16].

Antitumor Mechanisms of AM Extract

Based on the existing literature, AM extract produced an antitumor effect primarily by potentiating antitumor immunity (through increasing CD3(+) CD4(+) T-lymphocytes), enhancing the cytostatic activities of macrophages, or activating dendritic cells [10,17,20].

2.4.2. Formononetin (FMN)

FMN, a phytoestrogen isoflavonoid, was investigated in 21 studies [21–41] (Supplementary Table S2). The most frequently reported efficacy metrics were tumor weight ($n = 16$, 76.2%) [21–36] and tumor volume ($n = 15$, 71.4%) [22,23,26,27,29–34,37–41]. Other assessed outcomes included tumor reduction ($n = 5$, 23.8%) [22,24,29,30,42], body weight ($n = 9$, 42.9%) [21–28,38,39], and metastasis ($n = 1$, 4.8%) [42].

Antitumor Efficacy of FMN Versus Control

FMN demonstrated consistent antitumor activity against control groups. A significant reduction in tumor weight was reported in 14 of 16 studies (87.5%), at doses ranging from 5 to 100 mg/kg (median: 20 mg/kg; mode: 10 mg/kg) [21,22,24–35]. Similarly, a significant reduction in tumor volume was observed in 13 of 15 groups (86.7%), with effective doses between 10 and 100 mg/kg [22,23,26,27,30–34,37–40].

Dose–Response Relationship

All seven studies that tested escalated doses (5–100 mg/kg) confirmed a dose-dependent antitumor effect [21,25–28,31]. Higher doses (20–100 mg/kg) consistently produced a greater reduction in tumor weight than lower doses (5–25 mg/kg). The dose–response curve reached a plateau at intraperitoneal doses between 60 and 80 mg/kg.

Antitumor Efficacy of FMN Versus Standard Anticancer Therapy

Nine studies compared FMN monotherapy (10–75 mg/kg) against various chemotherapeutic agents (e.g., 5-FU, cisplatin, paclitaxel, tamoxifen, everolimus, osimertinib, bortezomib) [24,25,30,31,34,35,41–44]. FMN showed similar antitumor efficacy to standard therapy in a subset of the studies. Tumor weight was measured in eight studies. Only one study (12.5%) reported comparable tumor weight reduction (10 mg/kg FMN versus osimertinib in a drug-resistant tumor xenograft model) [35]. Tumor volume was assessed in all nine studies. Four studies (40.4%) reported a non-inferior tumor volume reduction by FMN treatment (10–75 mg/kg) against chemotherapeutic agents including osimertinib (25 mg/kg), paclitaxel (50 mg/kg), and 5-FU (48 mg/kg) [35,41,43]. A key finding was FMN's superior tolerability. All six studies that monitored animal body weight found that FMN treatment resulted in significantly less weight loss compared to standard anticancer agents [24,25,30,31,34,44].

Antitumor Efficacy of FMN-Containing Drug Combination

Three studies evaluated FMN (20–50 mg/kg) in combination with paclitaxel, everolimus, or bortezomib [30,41]. The combinations consistently enhanced antitumor efficacy. One study showed that adding 20 mg/kg FMN to a low dose of bortezomib (0.25 mg/kg) significantly reduced tumor weight versus bortezomib alone [30]. Moreover, all three studies assessing tumor volume reported significant reductions for the combination therapies compared to single-agent treatment.

Antitumor Mechanisms of FMN

FMN elicits antitumorigenic properties *in vivo* primarily by modulating key signaling pathways to induce cell apoptosis via intrinsic pathways, which includes Bax, Bcl-2, caspase-3/-8 [25,28]; trigger cell cycle arrest (by regulating mediators like cyclin A, or cyclin B1, and cyclin D1) [24]; suppress cell proliferation (by activation of STAT, the PI3K/AKT, and MAPK signaling pathways) [35]; and inhibit cell invasion (by inhibiting TGF- β 1-mediated PI3K and MAPK activation, and suppressing MMP-2 and MMP-9 expression) [33,41].

2.4.3. Astragaloside IV (AS-IV)

Astragaloside IV (AS-IV) was evaluated in 19 studies (Supplementary Table S2) [45–63]. Tumor volume was the most frequently reported metric ($n = 17$, 89.5%) [48–64], followed by tumor weight ($n = 13$, 68.4%) [47–61]. A minority of studies reported on body weight ($n = 2$) [47,62], survival ($n = 1$) [62], or metastasis ($n = 1$) [62].

Antitumor Efficacy of AS-IV Versus Control

AS-IV showed a moderate antitumor effect compared to control groups. A significant reduction in tumor weight was reported in 7 of 13 studies (53.8%) [52,54,56–58,60,61], with effective doses ranging from 15 to 150 mg/kg (median: 45 mg/kg; mode: 40 mg/kg). Similarly, 10 of 17 studies (58.8%) reported a significant reduction in tumor volume at doses of 15 to 150 mg/kg (median: 40 mg/kg; mode: 20 and 40 mg/kg) [45–47,49,51,52,55–57,59].

Dose–Response Relationship

In all three studies investigating a dose-dependent effect of AS-IV (12.5–150 mg/kg) [47,52,59], higher doses (80–150 mg/kg) were found to be more effective than lower doses (20–100 mg/kg). This was consistent for both tumor volume (two out of three studies, 66.7%) [52,59] and tumor weight (two out of two studies) [52,59]. The antitumor effect reached a plateau at 80 mg/kg.

Antitumor Efficacy of AS-IV Versus Standard Anticancer Therapy

In 10 studies comparing AS-IV monotherapy (12.5–120 mg/kg) against various agents (e.g., cisplatin, carboplatin, paclitaxel, imipenem, anti-mPD-1 antibody) [52,55,59], AS-IV was not found to be effective as a monotherapy alternative. None of the seven groups evaluating tumor weight or the nine groups evaluating tumor volume reported efficacy equivalent to the anticancer therapy alone.

Antitumor Efficacy of AS-IV-Containing Drug Combination

AS-IV demonstrated strong synergistic potential when combined with anticancer agents. Across nine studies using doses of 20–120 mg/kg, the combination regimens were highly effective. Of the eight studies that evaluated tumor volume, seven (87.5%) found a significant reduction compared to anticancer therapy alone [58,62,63].

Antitumor Mechanisms of AS-IV

AS-IV, a primary active triterpenoid saponin, has shown significant antitumor activity *in vivo* via modulation of various signaling pathways. The suppression of tumor growth by AS-IV was associated with modulation of a few microRNA-mediated pathways (including miR-489-3p/EIF4A and miR-873-50/lasp1) [49,61]; conversion of M2 macrophage polarization to the tumor-killing M1 phenotype (by inhibiting TLR4/NF- κ B/STAT3 signaling) [54]; and induction of autophagy [64]. AS-IV also inhibits invasion and metastasis by blocking TGF- β or MAPK signaling pathways [45,65]. Moreover, AS-IV attenuated cancer stemness by inhibiting TGF- β and hedgehog signaling [58].

2.4.4. *Astragalus* Polysaccharides (APS)

APS was investigated in 16 studies (Supplementary Table S2) [66–81]. The most common efficacy metrics were tumor weight (nine studies, 56.3%) [66–74] and tumor volume (seven studies, 43.8%) [71–77]. A smaller number of studies reported on body weight ($n = 3$) [78–80] and survival ($n = 1$) [81].

Antitumor Efficacy of APS Versus Control

APS demonstrated a strong and dose-dependent reduction in tumor weight compared to controls. Of the 13 studies that evaluated tumor weight, 12 (92.3%) reported a significant reduction by APS, with effective doses ranging from 100 to 500 mg/kg (median: 200 mg/kg; mode: 100 and 200 mg/kg) [66–74]. The effect on tumor volume was less consistent, with only 4 of 11 studies (36.4%) showing a significant reduction by APS at doses of 100–400 mg/kg [68,71,75,76].

Dose–Response Relationship

All six studies investigating dose-dependent effects (10–400 mg/kg) indicated that higher doses were more effective. Two of three studies evaluating tumor weight reported a significantly greater tumor weight reduction by APS at higher doses (300–400 mg/kg versus 100–200 mg/kg) [67,69]. On the other hand, one study assessed metastasis following APS treatment [62]. A higher dose of APS (160 mg/kg) was significantly more effective than lower doses (10 and 40 mg/kg) at slowing metastasis in an A549 tumor xenograft model.

Antitumor Efficacy of APS Versus Standard Anticancer Therapy

Eight studies compared APS monotherapy (3–200 mg/kg; median = 50 mg/kg, mode = 50 mg/kg) against agents including cisplatin, doxorubicin, 5-fluorouracil, and anti-PD-1/PD-L1 antibodies [72,74,76,78,79,82–84]. The results showed potential for non-inferior efficacy in specific contexts: four of six studies (66.7%) reported non-inferior tumor volume reduction compared to cisplatin (2.5 mg/kg) or anti-PD-1 (20 mg/kg) therapy [72,74,76,82]. However, only one of five studies (using 200 mg/kg APS) showed comparable tumor weight reduction to cisplatin in a resistant model [82]. APS was notable for its superior tolerability. Seven of nine studies (77.8%) reported better preservation of body weight compared to anticancer therapy alone [78,79,84].

Antitumor Efficacy of APS-Containing Drug Combination

Nine studies evaluated APS-containing drug combination. The combination of APS (3–200 mg/kg) with anticancer agents (cisplatin, doxorubicin, or anti-PD1/PD-L1 antibody) consistently enhanced efficacy [72,74,76,82–85]. In all of the six studies that assessed tumor weight, APS drug combination produced a significant tumor weight reduction compared to the antitumor drug alone [72,74,76,82,85].

Antitumor Mechanisms of APS

APS acts primarily as an immunomodulator *in vivo*, enhancing antitumor immunity rather than directly killing cancer cells. Key mechanisms include activating macrophages (M1 polarization) [78], attenuating PD-L1-mediated immunosuppression [71,76], enhancing dendritic cell maturation, and increasing T lymphocyte cytotoxicity while suppressing Treg activity [17,80,82].

3. Discussion

We evaluated 76 preclinical *in vivo* studies for the antitumor efficacy of AM and its active components. FMN dose-dependently reduced tumor weight and volume, with a plateau observed at 60–80 mg/kg. As a monotherapy, FMN produced weaker antitumor effects than standard chemotherapeutic drugs, but co-administration enhanced the activity of these conventional agents. For AS-IV and APS, tumor reduction was variable across experiments, though reports of synergistic activity with other treatments were frequent. Mechanistically, FMN and AS-IV inhibited tumor growth, induced apoptosis, and arrested the cell cycle through multiple signaling pathways. In contrast, APS and

crude AM extracts appeared to act primarily by stimulating antitumor immune responses (Supplementary Table S2). These outcomes are broadly consistent with those of recent narrative reviews [86,87]. The evidence overall indicates that AM constituents could complement existing anticancer therapies. The poor methodological quality of the included studies, however, substantially limits the certainty of this conclusion.

3.1. Methodological and Reporting Limitations

The SYRCLE's risk of bias assessment revealed significant limitations in the methodological quality of the included studies. Among the 76 studies, 45 (59.2%) scored below 5 out of 10, indicating an overall low study quality (Figure 4). Key flaws included: (1) Animal randomization: While some studies mentioned random assignment, none detailed the specific randomization method. (2) Animal husbandry: Most studies failed to report the housing conditions of the laboratory animals during experiments. (3) Blinding: No study reported blinding of investigators or outcome assessors. These shortcomings, coupled with the potential for publication bias in preclinical research, may have led to an overestimation of the antitumor effects of AM and its constituents.

3.2. Implications for Further Research and Clinical Translation

3.2.1. Consistency in the Preparation of Crude Extract

Eight out of the 76 included studies (10.5%) utilized a crude extract of *Radix astragali* as the intervention. These studies generally required higher doses (250–500 mg/kg) to achieve antitumor effects comparable to those of single-agent constituents. Unlike chemically synthesized compounds, AM extract faces challenges of batch-to-batch variation. The phytochemical profile and quality of the herb are significantly influenced by geographical location, cultivation techniques, and climatic conditions. To ensure the translational relevance of preclinical findings, the chemical consistency of AM extracts must be standardized to generate replicable results in a clinical setting.

3.2.2. Contribution by Immunomodulatory Effects

AM is recognized for its broad immunomodulatory activities, largely attributed to APS. As summarized by Zheng et al. (2020), APS regulates immune function by promoting immune cell proliferation, stimulating cytokine release, and affecting immunoglobulin secretion and immune signal transduction [14]. However, it is critical to distinguish the general immune-stimulatory effect of AM from its direct and/or specific antitumor effect. Several excluded studies reported the detailed immunological effects of AM, which did not seem to link with the antitumor outcomes. This lack of specificity could imply that other immune stimulants might yield similar results. Future research should, therefore, explicitly investigate and delineate the causal relationship between the immunomodulatory properties of AM and its observed antitumor efficacy.

3.2.3. Mitigation of Chemotherapy Adverse Effects

A key rationale for combining AM with standard therapy is not only to enhance efficacy but also to mitigate chemotherapy-induced side effects. Among the 76 included studies, cisplatin ($n = 14$, 18.4%) and paclitaxel ($n = 7$, 9.2%) were the most frequently combined chemotherapeutic agents. Notably, a few excluded studies specifically investigated AM's role in ameliorating toxicities such as doxorubicin-induced cardiotoxicity and cyclophosphamide-induced nephrotoxicity [88–93]. This pattern of combination likely stems from the severe side-effect profiles of these chemotherapeutics and the documented protective effects of AM constituents, particularly AS-IV. Given that cyclophosphamide, doxorubicin, and paclitaxel are mainstays in breast cancer regimens, where cardiotoxicity, nephrotoxicity, and immunosuppression are common dose-limiting toxicities, AS-IV

presents a promising candidate for clinical trials aimed at improving patient performance status and treatment tolerance.

3.2.4. Phytoestrogenic Effects of AM Constituents

FMN and calycosin are isoflavones with known phytoestrogenic activity, capable of binding estrogen receptors [13]. Evidence suggests a concentration-dependent dual effect, particularly for FMN, where low doses may stimulate and high doses inhibit angiogenesis and breast cancer growth [94]. Although their proliferative effect on breast cancer cells is weaker than that of 17 β -estradiol (E2), they may still interfere with hormonal therapies. For instance, a low-dose isoflavone diet was shown to promote mammary tumor development in tamoxifen-treated mice [95]. This interaction is clinically concerning for hormone-sensitive cancers (e.g., breast, ovarian, prostate). While the antitumor efficacy of FMN had been compared to tamoxifen [21], the potential pharmacodynamic interaction between them remains uninvestigated, leaving open the possibility that co-administration could reduce the efficacy of anti-estrogen therapies.

3.2.5. Bridging the Gap to Clinical Studies

Clinical evidence supporting AM as a monotherapy for cancer is absent. Our screening identified multiple clinical trials of TCM formulas containing AM, but we excluded them due to their multi-herb compositions. Assessing the interactions among constituents in these formulas demands further investigation at the chemical, cellular, and physiological levels, and is complicated by the difficulty of standardizing multi-component interventions. Thus, a substantial gap remains between the data on single herbs and the clinically used TMC formulas drawn from the classical literature.

Although AM constituents have improved chemotherapy efficacy in animal models, their potential for herb–drug interactions, specifically with hormonal therapies and P-glycoprotein substrates, is not well characterized. Several AM-based injections, including Shenqi Fuzheng Injection, Aidi, PG2, are approved as chemotherapy adjuvants in East Asia [96–98]. Whether the observed adjuvant effects stem from the whole formula or from individual AM compounds remains unresolved. Future trials that directly compare purified AM constituents with established combination products are required to define AM's specific therapeutic contributions. To date, only one Phase 1 clinical trial has been conducted to investigate the pharmacokinetic profile of AS-IV in healthy adult volunteers (NCT04026321).

4. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] (Supplementary Figure S1: PRISMA 2020 checklist [15]). The protocol for this systematic review was registered on the Open Science Framework (OSF) and is available at <https://osf.io/ykts7> (accessed on 22 June 2026).

4.1. Database and Search Strategies

A comprehensive search was performed on three electronic databases, PubMed, EM-BASE, and Web of Science, spanning from the earliest available record to 30 March 2026. The following combinations of keywords and their corresponding Medical Subject Headings (MeSH) with Boolean operators were employed:

- a. Neoplasms: cancer, malignancy, neoplasm, oncology, tumor;
- b. *Astragalus membranaceus*:

- i. *Astragalus membranaceus*, *Astragalus mongholicus*, Huang Qi, milk vetch root, *Radix astragali*;
- ii. astragaloside, calycosin-7-o- β -d-glucoside, cycloastragenol, formononetin.

4.2. Eligibility Criteria

The inclusion and exclusion criteria were established in accordance with the PICO (Population, Intervention, Comparison and Outcome) framework [99]. The criteria were as follows:

- a. Populations: Animal models adapting experimental cancer cell models or experimental murine models of tumors. In vitro cell line study, network pharmacology, molecular docking, or bioinformatics analysis studies without in vivo validation were excluded.
- b. Intervention: Treated with *Astragalus membranaceus*, or its active constituents alone or combined with any anticancer therapy, i.e., cytotoxic, immunotherapy and targeted therapy. TCM formula with *Astragalus membranaceus*, active constituents modified chemically, novel active constituents, formulated as an advanced drug delivery system, surgical or radiotherapy were excluded.
- c. Outcome: The primary outcome measures should be indicative of effects of AM and its active component or altering drug efficacy in animal tumor models, including tumor volume, tumor weight, tumor reduction and survival. A mechanistically causative relationship between AM and antitumor efficacy should be demonstrated. Indirect relationships, e.g., immunological effect via macrophage, T-cells, gut microbiome; change in marker genes, proteins or biomarker without direct evidence of altering drug efficacy; phytoestrogenic effect; pharmacokinetic study; and chemotherapy-related side effect mitigation (e.g., cisplatin-induced nephrotoxicity, doxorubicin-induced cardiotoxicity) were excluded.

The studies were included if they fulfilled the additional criteria: (1) published in a peer-reviewed journal; (2) written in English; (3) original research studies. In addition, systematic reviews, meta-analyses, conference abstracts, book chapters, and editorials were excluded; articles where their full text or key data are not available were also excluded.

4.3. Selection Process

After the retrieval, a web-based systematic review tool, Covidence (www.covidence.org), was used for title and abstract screening and full-text screening. Duplicate studies were removed when search results were imported into Covidence. The full manuscripts of the selected papers were obtained and those that appeared to meet the inclusion criteria were reviewed. Finally, after the exclusion of irrelevant papers, all eligible studies were formally assessed and included in this systematic review. The systematic review was conducted by two independent investigators (CY and KT). CY screened studies from PubMed and the Web of Science whereas KT resolved disagreements when necessary.

4.4. Data Extraction and Classification

Information from each included paper were extracted utilizing a predefined form. The extraction of data encompassed the following details: (1) the basic information about included study comprising the primary author and the date of publication; (2) the traits including the species, gender, weight, and age; (3) details on the experiment/control group, which consist of the specific model used for modeling, the cell line and type of tumor, the route of administration, dose, length of treatment, and the number of animals in each group; (4) the outcome indicators, including tumor weight, tumor volume, tumor reduction and survival.

4.5. Quality Assessment and Risk of Bias

The risk of bias and methodological quality in individual animal intervention studies were assessed using the SYRCLE's risk of bias tool [100], which comprises 10 domains covering six specific areas of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain was labeled with reviewer assessment as "yes," "no," or "unclear." "Yes" indicates a low bias risk, "no" indicates a high risk of bias, and "unclear" denotes that the necessary information was not reported.

5. Conclusions

In summary, this systematic review found that AM and its bioactive constituents, notably FMN and AS-IV, produce antitumor effects in preclinical animal models of several cancer types. To our knowledge, this work represents the most comprehensive systematic review of animal studies across different cancer types investigating the antitumor efficacy of AM constituents. A most recent related systematic review by Li et al. covered only hepatocellular carcinoma models [101]. The observed outcomes, including reduced tumor weight and volume, preserved body weight, extended survival, and suppressed metastasis, point to a potential therapeutic role of AM in solid malignancies (including breast, lung, colorectal, and hepatocellular carcinoma). Nevertheless, the reliability of these conclusions is constrained by methodological shortcomings and the heterogeneous quality of the primary studies included. Clinical evidence of AM-containing formulas does not resolve the efficacy of individual AM constituents. Direct comparison of purified AM constituents against defined combination products is required.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/ddc5030042/s1>. Table S1: General information about the 76 included studies. Table S2: Summary of major findings from individual studies. Figure S1: PRISMA 2020 Checklist. Figure S2: Risk of bias assessment for individual studies using the SYRCLE RoB tool (Traffic-Light Plot). Detailed judgements for each of the 10 domains of the SYRCLE risk of bias tool are presented per included study (rows). Domains (columns) are: (D1) sequence generation, (D2) baseline characteristics, (D3) allocation concealment, (D4) random housing, (D5) blinding of investigators, (D6) random outcome assessment, (D7) blinding of assessors, (D8) incomplete outcome data, (D9) selective outcome reporting, and (D10) other sources of bias. Judgements are color-coded: Green (+) indicates low risk of bias, Red (x) indicates high risk of bias, and Yellow (-) indicates unclear risk of bias (insufficient information reported). The rightmost column provides an overall summary of study-level concerns.

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