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Research Progress on Active Constituents of Astragalus Membranaceus and Its Compatibility in Traditional Chinese Medicine for Oncology Therapy

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Abstract: ***Malignant neoplasms remain a significant threat to human health, with continually rising incidence, mortality, and metastasis rates in recent epidemiological data. The treatment of various malignancies persists as a global research priority. Clinical applications of Traditional Chinese Medicine (TCM) have demonstrated the antitumor efficacy of Astragalus membranaceus, which has been empirically validated and preserved through generations of medical practice. Modern pharmacological studies have identified its primary active antitumor constituents, including Astragalus polysaccharides (APS), flavonoids, and astragalosides, all exhibiting well-documented oncostatic effects. Given the distinctive therapeutic approach of TCM compared to contemporary molecular-targeted therapies, researchers have investigated its compatibility with other medicinal agents. These studies reveal that formula combinations based on TCM theory (including principle-method-formula-herb systematics) demonstrate enhanced therapeutic outcomes in clinical practice.This review synthesizes decade-long research on bioactive constituents of Astragalus membranaceus and its Traditional Chinese Medicine compatibility in oncotherapy, aiming to provide references for subsequent antitumor component analysis and novel drug development. Furthermore, it proposes new research directions for investigating the interventional effects of complex macromolecules formed through herb-herb interactions on neoplastic processes.***

Keywords: Astragalus membranaceus, Tumors, Traditional Chinese Medicine Compatibility, Astragalus Polysaccharides (APS), Astragalosides.

1. Introduction

Malignant tumors are characterized by high incidence, metastasis, and mortality rates, along with low cure rates, posing significant threats to human health. The treatment of malignancies remains a major focus in both clinical and basic medical research. Conventional therapies—including surgical resection, radiotherapy, chemotherapy, targeted therapy, and immunotherapy—have long been the mainstay of clinical oncology due to their cost-effectiveness and efficacy. Emerging approaches such as gene therapy and nanomedicine, as well as adjuvant treatments, are increasingly being translated into clinical practice. However, these interventions often induce marked adverse effects, including inflammatory responses, oxidative stress, immune dysregulation, and microbiota imbalance [1]. Additionally, patient drug resistance and psychological factors frequently compromise therapeutic outcomes, leading to poor prognoses. Consequently, novel agents and innovative treatment strategies represent a critical direction in oncology research.

Traditional Chinese Medicine, with its millennia of empirical knowledge, offers unique advantages in cancer management. Astragalus membranaceus (Huangqi), a classical herbal medicine, has demonstrated broad therapeutic potential [2–4]. Pharmacologically characterized as sweet in taste and mildly warm in nature, this non-toxic herb is revered as the "sovereign of tonics" in TCM. Its documented functions include replenishing qi, fortifying the spleen, elevating yang, promoting diuresis, draining pus, healing wounds, consolidating the defensive exterior, nourishing blood, and relieving stagnation [5]. Clinically, it has been applied to treat consumptive disorders, jaundice, arthralgia syndromes, and constipation, earning its place as a cornerstone herb across dynasties.

Notably, Astragalus exhibits remarkable efficacy in oncology when combined with other herbs—exemplified by its classic pairing with Curcuma phaeocaulis (Ezhu). Modern pharmacological studies confirm its antitumor, immunomodulatory, and cardioprotective properties [6], underpinning its widespread clinical use. TCM formulations containing Astragalus demonstrate significant synergies with surgery, radiation, and chemotherapy, positioning them as a hotspot for novel anticancer drug development [7].

This review synthesizes current evidence on the antitumor components of Astragalus and its TCM-based combinatorial strategies, elucidates its therapeutic principles in oncology, and provides insights for future drug discovery and mechanistic exploration.

2. Component Analysis of Astragalus Membranaceus

2.1 Active Components and Safety of Astragalus Membranaceus

Astragalus membranaceus mainly contains astragalus polysaccharides, saponins, flavonoids, amino acids, and alkaloids [6]. Among these, astragalus polysaccharides show the strongest activity. Recent studies on its antitumor components have confirmed that astragalus polysaccharides, saponins, and flavonoids have good immunomodulatory, antitumor, and antimetastatic effects. As an adjuvant to chemotherapy, Astragalus membranaceus can inhibit tumor progression, reduce toxic side effects, enhance immune function, and improve quality of life [8].

2.2 Astragalus Polysaccharides

Astragalus polysaccharides (APS) are the most abundant and bioactive antitumor components in Astragalus membranaceus, primarily composed of glucans and heteropolysaccharides [9]. The composition of APS varies slightly depending on the geographical origin of the plant. Recent studies have confirmed that APS can regulate the cell cycle and induce early apoptosis in tumor cells [10]. Research demonstrates that APS suppresses the proliferation and metastasis of lung adenocarcinoma in mice by reducing EMT markers and inhibiting the PI3K/Akt pathway and EMT process [11], while also enhancing the efficacy of cisplatin [12]. APS modulates macrophage M2 polarization and CD8+ T-cell exhaustion via the PI3K/AKT/FoxO1 axis, inhibiting bladder cancer progression and increasing cisplatin (DDP) sensitivity [13]. Additionally, APS upregulates autophagy-related proteins to regulate tumor cell autophagy [14]. APS enhances cisplatin's therapeutic effect on triple-negative breast cancer by promoting tumor cell apoptosis, inhibiting epithelial-mesenchymal transition (EMT), and inducing CD8+ T-cell infiltration [15]. It also induces ferroptosis in ovarian adenocarcinoma cells via the Nrf2/SLC7A11/GPX4 signaling pathway [16]. In clinical applications, APS combined with S-1 (tegafur-gimeracil-oteracil potassium) improves short-term efficacy and long-term survival rates in pancreatic cancer patients while alleviating chemotherapy-induced immunosuppression and adverse effects [17]. Furthermore, APS enhances the antitumor effect of CD8 CAR-T cells by promoting the formation and tumor migration of CD122/CXCR3/PD-1 memory T cells [18]. APS regulates the immune microenvironment in tumor-bearing animals [19], targeting tumor-associated macrophages (TAMs) and T cells to restore immune balance and inhibit tumor proliferation and metastasis. Toxicity studies confirm that APS is non-toxic, with no pathological abnormalities or mutagenic effects observed in animal experiments. In conclusion, APS exerts antitumor effects by modulating immune cells in the tumor microenvironment, restoring immune equilibrium, and suppressing tumor growth and metastasis.

2.3 Flavonoids

The flavonoid components of Astragalus membranaceus include formononetin, calycosin, and neobavaisoflavone, all exhibiting antitumor activity. Formononetin inhibits tumor cell proliferation and metastasis by promoting PI3K/AKT pathway inactivation and arresting the tumor cell cycle [20]. Calycosin demonstrates significant inhibitory effects against female-prevalent malignancies including gastric, breast, adenocarcinoma, cervical, ovarian, hepatic, and colorectal cancers [21, 22]. Flavonoids also show therapeutic efficacy in cardiovascular, hepatic, and neurological disorders. Bioactivity analysis of Astragalus total flavonoids reveals antioxidant, immunomodulatory, antitumor, cardioprotective, and antidiabetic properties [23, 24].

2.4 Astragalosides

Astragalosides serve as qualitative and quantitative markers for Astragalus membranaceus and represent important antitumor components [25]. Major astragaloside constituents include astragaloside, isoastragaloside, acetylastragaloside, cycloastragaloside, and soyasaponin. Astragaloside IV regulates tumor-related signaling pathways, inhibiting proliferation and metastasis of gastric cancer cells, vulvar squamous carcinoma cells, and human osteosarcoma cells, while inducing autophagy in lung cancer cells [26, 27]. Astragaloside III (AS-III) suppresses lung cancer metastasis and angiogenesis while inducing apoptosis by inhibiting macrophage M2 polarization and promoting M1 phenotype transformation [28]. Astragaloside IV (AS-IV) inhibits nasopharyngeal carcinoma progression by downregulating SATB2 and suppressing Wnt pathway activation [29]. Astragalosides also promote ferroptosis in gastric cancer cells via SIRT3 upregulation [30]. AS-IV enhances autophagy through AMPK and AKT/mTOR pathway modulation, suppressing oral cancer cell proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) [31]. Astragaloside II activates T lymphocytes, promotes Th1 cytokine release, and enhances immunity in H22 liver cancer metastasis mouse models [32].

The antitumor mechanisms of Astragalus membranaceus are complex and multifaceted, involving multiple bioactive components that collectively regulate the cell cycle, modulate tumor-related signaling pathways, induce early autophagy in tumor cells, inhibit angiogenesis, restore the tumor microenvironment, suppress tumor proliferation and metastasis, and enhance immune function. Current research on the antitumor effects of Astragalus membranaceus requires further elucidation of its specific regulatory mechanisms.

3. Compatibility analysis of Astragalus Membranaceus

3.1 Classical Inheritance

The earliest records of tumors date back to the Shang Dynasty. Astragalus membranaceus has the effects of tonifying qi and strengthening the spleen, raising yang to lift collapse, promoting diuresis to reduce swelling, expelling pus, astringing sores to promote tissue regeneration, reinforcing the defensive exterior, nourishing blood and promoting fluid production, and moving stagnation to unblock obstruction. Honey-fried Astragalus enhances its qi-tonifying and middle-jiao-fortifying effects. In advanced-stage tumors, when vital qi is deficient and cancer toxins prevail, clinical treatments often focus on replenishing qi to consolidate the root while activating blood circulation to resolve stasis.

Qing Dynasty physician Zhang Xichun proposed that combining Astragalus membranaceus with Curcuma phaeocaulis enhances their stasis-breaking effects. Experts like Zhu Liangchun have demonstrated this combination's efficacy in treating hepatic, biliary, and pancreatic tumors, improving patients' quality of life and prolonging survival. Clinically, Astragalus membranaceus is frequently combined with Curcuma phaeocaulis, Salvia miltiorrhiza, and Angelica sinensis for treating tumors at various sites, with the Astragalus-Curcuma pairing being most common. Modern practitioners have developed injectable Astragalus preparations and compound oral solutions by integrating classical formulas with contemporary medicine.

3.2 Compatibility of Astragalus Membranaceus and Curcuma Zedoaria

Zhang Xichun of the Qing Dynasty proposed that this combination allows Astragalus to tonify primordial qi without causing stagnation, while Curcuma's mass-resolving effects are enhanced by Astragalus. Together, they resolve blood stasis when present and prevent stagnation when absent. The pairing demonstrates synergistic effects with 5-FU in colorectal cancer treatment [33]. Zhu Liangchun recommended adjusting their ratio based on presentation: increasing Astragalus for pronounced qi deficiency, or emphasizing Curcuma for dominant blood stasis. His clinical applications in hepatobiliary and pancreatic tumors showed improved quality of life. Professor Pang Jingsan developed an herbal cluster (Astragalus-Codonopsis-Sparganium-Curcuma) from Li Chong Tang, creating effective base prescriptions for ovarian cysts and uterine fibroids. He applied this to qi deficiency/ stagnation with blood stasis patterns, extending to esophageal/gastric cancer post-chemoradiotherapy. Professor Dou Yongqi employed Astragalus-Curcuma as a foundational qi-tonifying and blood-activating pair for post-treatment patients. His "Fuzheng Sanjie" formula adapted for various tumors improved constitution and quality of life while inhibiting metastasis. Xu Chengyong [13] demonstrated this pair's anti-angiogenic effects against lung cancer, with optimal 3:1 ratio suppressing tumor microvessels and preserving immune organ function in murine models.

Yang Qi et al. demonstrated through in vitro and in vivo experiments that the Astragalus-Curcuma combination inhibits proliferation, migration, and invasion while inducing apoptosis in colon cancer HT-29 cells, and suppresses subcutaneous tumor growth while improving epithelial-mesenchymal transition (EMT) in nude mice [34]. Network pharmacological analysis identified several key targets for gastric cancer treatment and optimal docking combinations, revealing that certain active components regulate major gastric cancer targets through PI3K-AKT, MAPK, and P53 signaling pathways, influencing tumor cell apoptosis and proliferation [35]. Comparative studies show superior anti-cancer efficacy of the Astragalus-Curcuma combination over individual herbs, achieved by suppressing EGFR, AKT, and VEGF protein expression and mRNA transcription in the EGFR/PI3K/AKT and HIF-1α/VEGF pathways to inhibit lung cancer angiogenesis [36]. Liang Li et al. [37] reported enhanced colon cancer suppression when combining Astragalus-Curcuma with 5-fluorouracil through downregulation of specific mRNA and protein expression, outperforming single-agent treatments. Liu Tiantian et al. [38] found the Astragalus-Curcuma-Paris combination reduces vascular permeability in the colon by modulating ZO-1 expression via RhoA/ROCK pathway inhibition, thereby preventing vascular metastasis. Liang Yan et al. [39] demonstrated through animal studies that this triple combination significantly reduces primary tumor volume and hepatic metastases by activating PI3K-AKT and MAPK signaling pathways. Gu Junfei et al. [40] employed molecular docking and in vivo experiments to show Astragalus-Curcuma may regulate SDF-1/CXCR4/NF-κB pathway components to inhibit colon cancer progression. Sun Ruolan et al. [41] identified a 2:1 ratio as optimal for colon cancer intervention in tumor-bearing mice, consistent with clinical practice. Some studies suggest this herb pair suppresses human breast cancer cell proliferation by upregulating PTEN to directly inhibit AKT protein levels. The Astragalus-Curcuma combination exhibits multi-organ, multi-target, and multi-pathway anti-tumor effects, negatively regulating tumor angiogenesis, growth, and metastasis through various cancer-related signaling pathways and factor expression, with applications in liver, colorectal, gastric, and gynecological cancers. As a quintessential Qi-invigorating and blood-activating pair in contemporary TCM oncology, Astragalus-Curcuma represents an important bridge between traditional knowledge and modern research with promising clinical prospects.

3.3 Compatibility of Astragalus Membranaceus with other Chinese Medicinal Herbs

In addition to the combination of Astragalus-Curcuma, Astragalus-Angelica sinensis (Huangqi-Danggui) represents another frequently used herb pair in cancer treatment, with both herbs demonstrating qi-tonifying and blood-nourishing properties that enhance immune function, protect vascular endothelium, and exert anti-inflammatory and antitumor effects. The classic formula Danggui Buxue Tang, composed primarily of Astragalus and Angelica in a 5:1 ratio, exhibits efficacy enhancement and toxicity reduction in malignant tumors while providing immunoprotective benefits. The compound SH003, derived from Astragalus, Angelica, and Trichosanthes, has been shown to reverse epithelial-mesenchymal transition (EMT), thereby reducing migration and invasion capabilities in oral cancer cells [2], with additional inhibitory effects observed in non-small cell lung cancer (NSCLC) and colorectal cancer [42,43]. The polysaccharide AAPS-1a from the Astragalus- Angelica combination significantly inhibits proliferation and induces apoptosis in HCT116 colorectal cancer cells [44]. Danggui Buxue Tang may suppress sarcoma growth in S18 tumor-bearing mice by elevating serum IL-2 levels [45]. The active antitumor components in the Astragalus-Angelica pair function through multiple mechanisms including inhibition of tumor cell metastasis, anti-inflammatory activity, and anti-apoptotic effects, while also enhancing immune function, mitigating adverse reactions to radiotherapy and chemotherapy, and improving patient quality of life [46]. This herb combination reduces IL-10 and TGF-β1 secretion by tumor tissue, normalizes abnormalities in peripheral blood lymphocytes and basophils, and decreases pulmonary metastases, thereby demonstrating partial efficacy against breast cancer. Wang Xuezhen et al. [47] reported that Danggui Buxue Tang not only induces tumor cell apoptosis, inhibits proliferation and metastasis, and enhances chemosensitivity, but also addresses certain adverse effects following malignant tumor surgery or chemoradiotherapy, such as myelosuppression. Among the various antitumor components in Danggui Buxue Tang, astraschrysoside A and isorhamnetin exhibit favorable stability warranting further investigation. Additionally, the Astragalus-Hedyotis diffusa (AH) combination inhibits proliferation of A549 lung adenocarcinoma (LUAD) cells through the miR-582-3p-p27 signaling pathway [48].

Astragalus injection has been shown to inhibit osteosarcoma growth by activating cytotoxic T lymphocytes and targeting

CTSL [49]. The combination of Astragalus membranaceus and turmeric suppresses tumor metastasis by inhibiting HIF-1α nuclear translocation and promoting tumor vascular normalization [50]. Shenqi Fuzheng injection effectively reduces the release of inflammatory factors, enhances immune factor levels, improves microcirculation, and promotes tumor cell apoptosis. It also mitigates cisplatin-induced apoptosis and mitochondrial DNA damage while improving cisplatin-related mitochondrial dysfunction [51]. The combined use of low-concentration Astragalus injection and Salvia miltiorrhiza injection significantly inhibits the proliferation of lung tumor cells and induces apoptosis. Astragalus Qi-tonifying decoction extract exhibits inhibitory effects on certain tumor cell proliferation, with enhanced suppression at higher concentrations and prolonged exposure, though sensitivity varies across different tumor cell types, indicating potential for further development. Astragalus-Cinnamon Twig Five Substances Decoction reduces chemotherapy-induced adverse effects such as myelosuppression and nausea/vomiting. When combined with chemotherapy for advanced gastric cancer, it effectively alleviates the negative impact of chemotherapy on immune function. Studies suggest that Astragalus Center-Fortifying Decoction repairs damaged gastric mucosa, prevents precancerous lesions, and suppresses cancer cell progression, demonstrating significant efficacy in chronic gastritis and gastric cancer treatment [52]. Astragalus Four Gentlemen Decoction improves symptoms such as abdominal pain, fatigue, and pale lips/nails in mid-to-late-stage primary hepatocellular carcinoma (HCC) patients with qi-blood deficiency, while enhancing immune function. Research on Modified Astragalus Center-Fortifying Decoction reveals that it inhibits tumor growth and metastasis in spleen-qi-deficient lung cancer models by suppressing tumor-associated macrophage (TAM) infiltration. This formulation strengthens the spleen and tonifies qi, correcting the abnormal tumor microenvironment caused by spleen-qi deficiency, thereby suppressing tumor proliferation and migration.

4. Application of Astragalus in Integrated Chinese and Western Medicine Therapy

Astragalus membranaceus is commonly used in the treatment of malignant tumors including hepatocellular carcinoma, colorectal cancer, gastric cancer, breast cancer, and endometrial carcinoma [53, 54]. Furthermore, its combination with radiotherapy and chemotherapy effectively prevents and manages treatment-related side effects [15], while also demonstrating favorable clinical outcomes for certain tumor complications. Consequently, the integration of Astragalus and its related formulations with surgical intervention, radiotherapy, chemotherapy, and immunotherapy presents promising clinical prospects in contemporary oncology practice.

Astragalus injection enhances Fas receptor expression in post-chemotherapy patients, inducing apoptosis in hepatocellular carcinoma cells and improving chemotherapeutic efficacy. Astragalus total flavonoids protect normal cells from radiation damage while promoting apoptosis in liver cancer cells. Zang Wenhua et al. [55] demonstrated through animal experiments that the combination of Astragalus, Curcuma, and cisplatin downregulates specific protein and mRNA expression, inhibiting tumor angiogenesis and enhancing therapeutic effects. The apoptosis-inducing effect on human hepatocellular carcinoma HepG2 cells shows dose-dependent correlation with the combination therapy [56].

Colorectal cancer, encompassing both colon and rectal carcinoma, shows increasing incidence rates with frequent late-stage diagnosis. Current research explores numerous integrated Chinese-Western therapeutic approaches [57, 58]. Pre-chemotherapy administration of Astragalus polysaccharides effectively mitigates chemotherapy-induced leukopenia in colorectal cancer patients. As an adjuvant during chemotherapy, it reduces gastrointestinal adverse effects while enhancing efficacy and reducing toxicity [59]. In addition to hepatocellular carcinoma and colorectal cancer, Astragalus membranaceus has also been clinically applied in combination with radiotherapy and chemotherapy for endometrial carcinoma and gastric cancer, as explored by numerous medical experts, which will not be elaborated here.

5. Conclusion and Perspectives

Current multidisciplinary approaches to cancer treatment have become a research focus. However, the known antitumor components of Astragalus membranaceus remain relatively nonspecific and require further refinement. Most studies have focused on signaling pathways, related factors, mRNA, and proteins without clearly elucidating the mechanisms of action or providing definitive evidence, necessitating further investigation into its antitumor mechanisms. Due to the unique principles of TCM pattern differentiation and treatment, herb combinations vary among patients. Identifying consistent patterns and optimal compatibility ratios requires deeper clinical research. While Astragalus demonstrates efficacy against various tumors, its precise mechanisms in specific cancer types and the refinement of its therapeutic scope warrant further study. Although Astragalus is widely used in integrative oncology, it is primarily employed as an adjuvant therapy for advanced-stage cancers. Exploring its potential for preventive use in reducing precancerous lesions could be a valuable research direction. Leveraging modern molecular biology, immunology, and pharmacokinetics may enable deeper understanding of Astragalus-based combination therapies, clarifying their efficacy-enhancing and toxicity-reducing mechanisms, and facilitating the development of novel antitumor drugs and targeted comprehensive therapies.

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