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Research Progress on the Mechanisms of Active Components from Agrimonia pilosa in Intervening Colorectal Cancer

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Abstract. Colorectal cancer (CRC) is one of the most common malignancies of the digestive system worldwide, and genetic predisposition, chronic inflammation, and lifestyle habits are all believed to contribute to its development. Surgery, chemotherapy, and targeted therapy currently remain the mainstays of clinical management, however, tumor invasion and metastasis, multidrug resistance, and the adverse effects of chemoradiotherapy remain major obstacles to overall treatment efficacy. Agrimonia pilosa (Xianhecao), a widely used traditional Chinese medicine, contains a variety of bioactive constituents, including flavonoids, tannins, and polyphenols. Modern pharmacological evidence has demonstrated that these active compounds can inhibit the proliferation, invasion, and metastasis of CRC cells, reverse multidrug resistance, and modulate glycolysis, autophagy, and multiple signaling pathways such as JAK/STAT and JNK/AKT. This review summarizes the chemical basis of A. pilosa, discusses the molecular mechanisms underlying its anti-CRC activity, and reviews available clinical observational studies. It also highlights the shortcomings of current research and proposes directions for future investigation, with the aim of providing a reference for experimental and clinical research on A. pilosa against CRC.

Keywords: Agrimonia pilosa, active constituents, colorectal cancer, signaling pathways, multidrug resistance

1. Introduction

Colorectal cancer (CRC) is a highly prevalent malignancy of the digestive system, and its incidence and mortality in China have remained persistently high in recent years. Its onset is driven by the interplay of multiple risk factors, including genetic susceptibility, chronic intestinal inflammation, and dietary habits [1]. According to the Chinese Guidelines for the Diagnosis and Treatment of Colorectal Cancer (2025 Edition), surgery, chemotherapy, and targeted therapy currently constitute the mainstays of clinical care. Patients with advanced disease, however, are prone to tumor invasion and metastasis and to chemotherapy-induced multidrug resistance, and some cannot tolerate the toxicities of chemoradiotherapy, obvious bottlenecks therefore remain in clinical treatment [2]. The sustained overexpression of inflammatory cytokines is an important driver of CRC initiation and progression: the inflammatory microenvironment promotes tumor cell proliferation and epithelial–

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mesenchymal transition, thereby accelerating malignant progression [3]. Traditional Chinese medicine, with its multi-component, multi-target, and low-toxicity advantages, and low toxicity, can assist in the management of malignant tumors by modulating the tumor immune microenvironment, inducing tumor cell apoptosis, and reversing drug resistance [4,5]. *Agrimonia pilosa*, the dried aerial parts of a plant of the genus Agrimonia in the family Rosaceae, has traditionally been used to arrest bleeding, remove toxins, and tonify deficiency, and modern pharmacological studies have confirmed its pronounced antitumor activity [6, 7]. Network pharmacology analyses suggest that constituents of *A. pilosa*, including quercetin, kaempferol, and ellagic acid, can target CRC-related proteins and regulate multiple tumor signaling pathways. In parallel, in vitro, animal, and small-sample clinical studies have demonstrated that the flavonoid, tannin, and polyphenol fractions of *A. pilosa* inhibit CRC cell proliferation and migration and modulate glycolysis, the autophagy/apoptosis balance, and signaling pathways such as JAK/STAT and JNK/AKT, and related compound formulas have also shown potential as adjunctive therapy for colon cancer [8-10]. Even so, the field still faces notable gaps, including insufficient in vivo evidence for the efficacy of individual compounds, incomplete elucidation of the target network, and a scarcity of high-quality, large-sample clinical studies [11]. This review therefore synthesizes the literature on *A. pilosa* in CRC, summarizes the chemical basis of its active constituents, molecular mechanisms, and clinical evidence, and analyzes the limitations of existing studies to provide a reference for the application of *A. pilosa* in the prevention and treatment of CRC.

2. Chemical basis of the major antitumor active constituents of *Agrimonia pilosa*

The chemical composition of *A. pilosa* is complex. Its principal active components comprise flavonoids, tannins, and polyphenols, together with triterpenoids, organic acids, and other substances, and these different classes of constituents jointly participate in antitumor biological processes [12]. Through isolation and purification experiments, investigators have achieved the extraction of the polyphenolic constituents of *A. pilosa* and characterized their absorption and distribution in vivo, thereby providing an experimental basis for pharmacodynamic studies of these constituents [13].

2.1. Roles of flavonoid constituents

Flavonoids are the core active components of *A. pilosa*, with quercetin, quercitrin, and kaempferol as representative compounds. These constituents inhibit the migration and invasion of colon cancer cells and regulate the JNK and JNK/AKT signaling pathways [14]. Network pharmacology screening has identified kaempferol and quercetin as core potential active ingredients of *A. pilosa* in the treatment of colon cancer, capable of docking to key tumor targets such as TP53 and AKT1 [8]. Flavonoids are extensively involved in the regulation of multiple anti-CRC signaling pathways and intervene throughout the processes of cell proliferation, apoptosis, and invasion and metastasis [15]. In CRC, flavonoid constituents mainly regulate multiple signaling pathways and also exert combined effects, including inhibition of proliferation, induction of apoptosis, and suppression of metastasis.

2.2. Roles of tannin constituents

Tannins are likewise important antitumor constituents of *A. pilosa*, with ellagic acid as the representative compound. Animal experiments have confirmed that ellagic acid inhibits tumor

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angiogenesis and exerts inhibitory effects against solid tumors [16]. Clinical observational studies have shown that the tannins of *A. pilosa* confer certain clinical benefits as adjunctive therapy for colon cancer [10]. Related reviews summarizing the extraction techniques and antitumor pharmacological progress of the active constituents of *A. pilosa* have proposed that both tannins and flavonoids constitute its antitumor material basis and that different constituents possess synergistic antitumor potential [11, 17]. In the context of CRC, tannin constituents act mainly by inhibiting tumor angiogenesis, while also demonstrating application value at the level of clinical adjunctive therapy.

Polyphenolic constituents encompass broad classes such as flavonoid polyphenols and tannin polyphenols. Polyphenols derived from traditional Chinese medicine can interfere with tumorigenesis through epigenetic regulation, modulating DNA methylation and histone modification and thereby altering the expression status of tumor-related genes [18].

Existing studies have reviewed the chemical constituents, pharmacological activities, and clinical applications of *A. pilosa*, compiling its extraction techniques, in vitro pharmacology, and traditional uses, and thus providing a literature basis for the subsequent development of individual compounds [12]. Other studies have suggested that future work should compare total extracts with individual compounds to clarify the contribution of each constituent class to the antitumor effects [19]. With respect to CRC intervention, polyphenolic constituents not only directly inhibit tumor cells but also regulate the expression of tumor suppressors and oncogenes through epigenetic pathways, reflecting a more diversified mode of action. Taken together, flavonoids are currently the most thoroughly studied anti-CRC active constituents of *A. pilosa*: they simultaneously regulate multiple tumor signaling pathways and act on multiple aspects, including proliferation, apoptosis, and invasion and metastasis. Tannins are distinguished mainly by their inhibition of tumor angiogenesis, with small-sample clinical data already supporting their potential as adjunctive therapy. Polyphenols encompass the activities of both flavonoids and tannins and can additionally mediate epigenetic regulation, such as DNA methylation and histone modification. These constituents do not act independently but rather synergistically, jointly constituting the material basis of *A. pilosa* against CRC.

3. Molecular mechanisms of *Agrimonia pilosa* against colorectal cancer

3.1. Inhibition of cell proliferation, induction of apoptosis, and regulation of autophagy

Unrestrained proliferation of tumor cells is a core feature of CRC, and inducing tumor cell apoptosis and modulating autophagic activity represent important modes of action of antitumor drugs [20]. Studies have shown that *A. pilosa* regulates chaperone-mediated autophagy (CMA), downregulates the expression of LAMP2A and HSC70, inhibits the proliferation, migration, and invasion of CRC cells, and induces apoptosis. Xianlian Jiedu Decoction is a traditional Chinese medicine (TCM) compound formula in which *A. pilosa* is an important constituent [9]. Studies have confirmed that this decoction inhibits the proliferation of human CRC cells, interferes with the glycolytic metabolic reprogramming of tumors, reduces glucose uptake and lactate production, and cuts off the energy supply of tumor cells.

Glycolysis is a hallmark metabolic pattern of tumor cells, which preferentially generate ATP through glycolysis even under aerobic conditions, inhibition of glycolysis can substantially restrain tumor cell proliferation [7]. Early pharmacological reviews documented the in vitro antiproliferative activity of *A. pilosa* against tumor cells, laying the foundation for subsequent CRC research.

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3.2. Inhibition of invasion, metastasis, and angiogenesis

Tumor invasion and distant metastasis are the leading causes of death in patients with advanced CRC, and suppressing tumor cell migration and invasion as well as angiogenesis represents a key focus of antitumor research [21]. KEGG enrichment analysis based on network pharmacology has suggested that the potential targets of *A. pilosa* in the treatment of colon cancer are mainly enriched in signaling pathways that mediate tumor metastasis and angiogenesis, such as PI3K/Akt and HIF-1 [8]. In vitro experiments have confirmed that quercetin and quercitrin derived from *A. pilosa* suppress the migration and invasion of colon cancer cells through the JNK signaling pathway, and subsequent studies further showed that quercetin exerts anti-invasive effects on colon cancer cells by inhibiting the JNK/AKT signaling axis [14]. Reviews have noted that TCM can inhibit tumor invasion and metastasis through multiple routes while reversing tumor multidrug resistance, regulating multiple targets such as matrix metalloproteinases, epithelial–mesenchymal transition, and vascular endothelial growth factor [21]. Ellagic acid inhibits tumor angiogenesis, reduces tumor blood supply, and limits tumor proliferation and metastasis [16]. Reviews have concluded that *A. pilosa* downregulates the expression of angiogenic factors such as VEGF, thereby inhibiting tumor angiogenesis and impeding tumor metastasis [6].

3.3. Regulation of core tumor-related signaling pathways

Multiple aberrantly activated signaling pathways drive the malignant progression of CRC. Hyperphosphorylation of the JAK/STAT pathway promotes tumor proliferation, inflammation, and invasion, and this pathway therefore represents an important target of TCM against CRC [22]. Systematic reviews of TCM-mediated regulation of the JAK/STAT pathway in CRC have shown that flavonoid and polyphenolic monomers can inhibit the phosphorylation of JAK and STAT3 and downregulate downstream antiapoptotic genes, the flavonoid constituents of *A. pilosa* therefore have the potential to regulate this pathway [15]. The JNK signaling pathway is involved in multiple biological processes, including cell proliferation, stress responses, apoptosis, and migration. Quercetin and quercitrin derived from *A. pilosa* exert antimetastatic activity against colon cancer cells via the JNK pathway , and quercetin acts on both the JNK and AKT pathways to inhibit tumor invasion through multiple targets [14].

Reviews of the anti-CRC mechanisms of flavonoids have shown that flavonoid monomers can affect multiple pathways, including JAK/STAT, PI3K/Akt, and MAPK/JNK, thereby arresting tumor progression [15]. In addition, the inhibition of glycolysis in CRC by Xianlian Jiedu Decoction is essentially a regulation of metabolism-related signaling molecules such as HIF-1α, which attenuates the Warburg effect of tumor cells and achieves tumor suppression [9]. Network pharmacology predictions likewise indicate that various components of *A. pilosa* can simultaneously dock to multiple pathways, reflecting the multi-target nature of TCM [8].

4. Current status of clinical application of *Agrimonia pilosa* in colorectal cancer

Clinical research on *A. pilosa* in CRC remains relatively limited, consisting mainly of small-sample observational studies and syndrome-differentiated compound therapy, and evidence from multicenter, large-sample randomized controlled trials is still lacking [6]. One clinical observational study enrolled 60 patients who had undergone curative resection for colon cancer and divided them into an observation group and a control group, with 30 patients in each. The control group received FOLFOX4 chemotherapy combined with thymopentin, while the observation group additionally

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received 10 g of *A. pilosa* tannins orally per day, both groups completed four cycles of chemotherapy [10]. The efficacy endpoints of the study included the overall clinical response rate, peripheral blood counts (WBC, PLT, Hb), T-lymphocyte subsets ($CD4^+/CD8^+$), the tumor markers CEA and CA199, and chemotherapy-related toxicities [10]. The results showed that the observation group achieved a higher overall response rate than the control group and also exhibited greater improvements in immune parameters and blood counts, nevertheless, the small sample size and single-center design limit the strength of the evidence [10].

With regard to clinical decoction practice, when prepared slices of *A. pilosa* (yinpian) are prescribed for tumor-related diseases, the routine dose in decoctions is mostly 10–15 g, and may be increased at the clinician's discretion to 30–60 g for cancer-toxin patterns. These dose ranges, however, are largely based on clinical experience, and dose–response studies specifically addressing CRC remain lacking [11,12].

TCM compound formulas containing *A. pilosa*, such as Xianlian Jiedu Decoction, can be used clinically in combination with chemotherapy for advanced CRC to alleviate chemotherapy-related adverse reactions and improve patients' quality of life, however, the published literature on this formula is dominated by basic experimental studies, and large-sample clinical data remain insufficient [9]. Regarding safety, no serious adverse reactions attributable to *A. pilosa* have been reported in the existing small-sample clinical observations in CRC [10]. Nevertheless, clinical reports of its use in other tumors indicate that high-dose *A. pilosa* may cause gastrointestinal discomfort or allergic reactions, and potential interactions between the herb and chemotherapeutic agents warrant vigilance in patients receiving concurrent chemotherapy [12]. A systematic safety evaluation specific to the CRC population is still lacking, and clinical application therefore requires syndrome-based dose adjustment and close monitoring of patient responses [6]. Overall, *A. pilosa* and its extracts are positioned primarily as adjunctive therapy in the CRC setting, used during the postoperative or chemotherapy phase to improve immune status and alleviate treatment-related toxicities, they cannot yet serve as an independent curative modality [6]. Existing clinical studies are limited by small sample sizes, heterogeneous treatment protocols, and the lack of a standardized efficacy evaluation system, and dosage, treatment course, and eligible patient population all require further standardization [6, 10].

5. Limitations of current research on *Agrimonia pilosa* in colorectal cancer treatment

First, at the experimental level, most studies have relied on in vitro cell experiments, whereas in vivo animal studies are relatively scarce, research on extracts predominates, and in vivo pharmacokinetic and pharmacodynamic studies of individual active compounds remain insufficient [13]. Although the in vivo absorption and distribution of the polyphenolic constituents have been characterized, the tissue distribution and metabolism of tannin and flavonoid monomers in animal models of CRC remain to be determined. In addition, extracts obtained through different preparation techniques differ markedly in composition, and cross-study reproducibility remains to be improved [11]. Second, mechanistic studies have largely focused on single signaling pathways, with little attention to cross-talk among multiple pathways. Direct experimental evidence for the epigenetic regulation of CRC by polyphenols from traditional Chinese medicine remains insufficient, and most findings are confined to the level of literature reviews [18]. Third, the limitations of clinical research are conspicuous: existing clinical observations have small sample sizes, multicenter, large-sample randomized controlled trials are lacking, and unified standards for dosage and treatment course have not yet been established [6, 10]. Furthermore, the safe dose range of *A. pilosa* and its long-term toxicity require systematic evaluation [12].

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6. Conclusion

The high incidence of colorectal cancer, together with metastasis in advanced disease and chemotherapy-induced multidrug resistance, has driven growing interest in natural antitumor agents. *Agrimonia pilosa* is rich in bioactive flavonoids, tannins, and polyphenols. Existing in vitro, animal, and small-sample clinical studies suggest that this herb can inhibit CRC cell proliferation and induce apoptosis, regulate chaperone-mediated autophagy and glycolytic metabolic reprogramming, and impede tumor invasion, metastasis, and angiogenesis through pathways such as JAK/STAT and JNK/Akt, while also showing potential to reverse multidrug resistance—features that reflect the multi-component, multi-target, multi-pathway mode of action characteristic of TCM. Current research, however, still has notable gaps: in vitro studies predominate while in vivo efficacy and pharmacokinetic data are insufficient, experimental evidence on cross-talk among multiple pathways and on epigenetic regulation by polyphenols is lacking, and large-sample, multicenter randomized controlled trials are absent, with dosing regimens and safety evaluations remaining incomplete. To address these limitations, future studies should strengthen in vivo efficacy and pharmacokinetic investigations of the active compounds of *A. pilosa* in animals, elucidate the cross-regulation among multiple pathways and the epigenetic mechanisms of polyphenols, and conduct rigorous clinical trials to define the dosing regimens, efficacy, and safety of *A. pilosa*-related preparations, thereby facilitating the translation of basic research findings into adjunctive clinical therapy for CRC.

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