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Review

Multi-Targeted Anti-Tumor Effects of Huaier: A Comprehensive Review of Molecular Mechanisms and Clinical Applications

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Abstract

Cancer remains a major global health challenge, necessitating the development of low-toxicity therapeutic agents. Huaier (*Trametes robiniophila* Murr.), a traditional Chinese medicinal fungus, has demonstrated significant multi-target anti-cancer potential. This review summarizes recent advances in understanding the molecular mechanisms and clinical applications of Huaier. Mechanistically, Huaier inhibits tumor cell proliferation, survival, and metastasis by modulating key signaling pathways, including Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and Wnt/β-catenin, thereby inducing apoptosis, autophagy, and ferroptosis. Huaier has also been reported to suppress epithelial–mesenchymal transition (EMT) through pathways including G protein-coupled receptor 30 (GPR30)/PI3K/AKT and syntenin/STAT3. Furthermore, Huaier remodels the tumor microenvironment by regulating the gut microbiota, polarizing macrophages, enhancing $CD8^+$ T cell infiltration, and inducing immunogenic cell death (ICD). Interestingly, Huaier also reverses chemoresistance and acts synergistically with chemotherapy, targeted therapy, and immunotherapy. Clinically, as an adjuvant treatment, Huaier has been shown to significantly improve overall survival and disease-free survival in patients with hepatocellular carcinoma, gastric cancer, and breast cancer, while reducing recurrence and improving quality of life. Nonetheless, despite the promising results, future research requires large-scale clinical trials and further exploration of the multi-component synergistic mechanisms of Huaier to fully elucidate the associated therapeutic potential.

Keywords: trametes; medicine, Chinese traditional; antineoplastic agents; drug resistance, neoplasm; neoplasms; molecular mechanisms of pharmacological action

1. Introduction

Cancer remains a formidable global public health challenge and a leading cause of death worldwide [1]. The uncontrolled proliferation and metastatic potential of malignant cells not only severely threaten patient survival but also impose a substantial socioeconomic burden. Current mainstream therapeutic modalities, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have significantly improved outcomes, yet their efficacy is often limited by severe toxicity, acquired drug resistance, and unsatisfactory prognosis [2,3]. There is, therefore, an urgent and ongoing need to develop novel anti-tumor agents with low toxicity and the ability to overcome drug resistance.

In this context, traditional Chinese medicine (TCM) has attracted increasing attention for its multi-targeting characteristics, favorable safety profile, and low cost [4–6]. Growing evidence suggests that integrating TCM as an adjuvant to conventional therapy can help mitigate adverse effects, enhance clinical efficacy, and improve patient quality of life. Consequently, exploring the TCM repository for new anti-cancer drug candidates holds considerable promise.

Huaier (scientific name: Trametes robiniophila Murr.), a medicinal fungus with a history of use spanning over 1600 years, has emerged as a particularly promising candidate. It grows predominantly on the trunks of trees such as locust and acacia. Bioactive components isolated from Huaier, including polysaccharides, steroids, and alkaloids, have been shown to exert broad anti-tumor activities, such as inducing apoptosis, inhibiting cell migration and inducing autophagy, modulating immune cell function, reversing chemoresistance, and sensitizing cancer cells to conventional drugs [7–10]. These pleiotropic effects underscore Huaier's considerable potential as an anti-cancer agent and have stimulated extensive research into its underlying molecular mechanisms and clinical translation.

This review comprehensively summarizes recent advances (over the past five years) in elucidating the multifaceted anti-tumor mechanisms and clinical utility of Huaier across a range of cancers. We systematically outline its modulation of key oncogenic signaling pathways, related epigenetic regulation, and remodeling of the tumor microenvironment. Furthermore, we highlight clinical evidence demonstrating that Huaier granules, as an adjuvant therapy, can significantly prolong overall survival and disease-free survival in patients with liver, gastric, and

breast cancers, and synergize with chemotherapy, targeted therapy, and immunotherapy. Overall, this review aims to provide a deeper understanding of the multi-target anti-tumor profile and clinical translation value of Huaier, while offering insights to guide future anti-tumor drug development and combination strategy optimization.

2. Various Mechanisms of Huaier in Cancer Prevention and Treatment

Numerous studies have shown that Huaier modulates a variety of cell signaling pathways, thereby affecting key biological processes in malignancies, as shown in Table 1 (Ref. [11–41]).

2.1 Gastric Cancer

Gastric cancer (GC) ranks among the most prevalent malignancies worldwide [42]. Despite considerable advances in its treatment, the prognosis for GC patients remains poor, primarily attributed to the fact that approximately two-thirds are diagnosed at an advanced, inoperable stage. Moreover, even after curative resection, over 70% of early-stage patients experience recurrence or metastasis.

2.1.1 GPR30/PI3K/AKT Signaling Pathway

Epithelial-mesenchymal transition (EMT) is a key process that drives tumor cell invasion and metastasis [43]. In GC, GPR30 has been identified as a critical regulator of EMT, activating downstream pathways including intracellular calcium mobilization, epidermal growth factor receptor (EGFR) transactivation, and the PI3K/AKT signaling cascade. GPR30 is significantly overexpressed in GC tissues compared to adjacent non-cancerous tissues, and its elevated expression correlates with poor patient prognosis. Experimental studies have reported that Huaier effectively suppresses the proliferation, migration, and invasion of GC cells in a concentration-dependent manner by inhibiting the GPR30-mediated PI3K/AKT pathway [11].

2.1.2 Syntenin/STAT3 Signaling Pathway

Aberrant activation of the STAT3 pathway is a well-established driver of tumor metastasis [12]. Research has demonstrated that Huaier exerts its anti-metastatic effects by downregulating syntenin expression and inhibiting STAT3 phosphorylation at the Y705 site. Concurrently, Huaier reduces the expression of EMT-related proteins (N-cadherin, vimentin) and upregulates E-cadherin. Furthermore, syntenin knockout enhances Huaier's inhibitory effect on both the syntenin/STAT3 pathway and EMT, underscoring syntenin's pivotal role in gastric cancer metastasis. These findings indicate that Huaier primarily inhibits GC metastasis by modulating the syntenin/STAT3 signaling pathway [13].

2.1.3 c-Myc-Bmi1 Signaling Pathway

Bmi1 is a core regulator of tumor stem cell stemness, cell cycle progression, and senescence inhibition. An experimental study confirmed that Huaier reduces Bmi1 expression by downregulating c-Myc. Notably, exogenous Bmi1 overexpression significantly reversed Huaier-mediated suppression of gastric cancer cell growth and metastasis [14]. Taken together, these results suggest that Huaier inhibits gastric cancer progression by targeting the c-Myc-Bmi1 pathway, providing a mechanistic basis for its development as a potential therapeutic adjuvant.

2.1.4 JAK2/STAT3 Signaling Pathway

In both *in vitro* and *in vivo* experiments, Huaier has been demonstrated to target the JAK2/STAT3 pathway, inhibiting proliferation, migration, and invasion while inducing apoptosis in gastrointestinal stromal tumor (GIST) cells (GIST-T1 and GIST-882). These effects resulted in significant suppression of cell viability and proliferation [15], suggesting Huaier's potential as an adjuvant therapy for GIST.

2.2 Lung Cancer

Lung cancer, the leading cause of global cancer incidence and mortality [44], is pathologically classified into non-small cell lung cancer (NSCLC, ~85% of cases) and small cell lung cancer (SCLC). Major NSCLC subtypes include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

2.2.1 EGFR Inhibitor

Dysregulated EGFR signaling reportedly promotes the growth, invasion, metastasis, and angiogenesis of malignant tumors, making it a key therapeutic target [16]. A study has indicated that EGFR is a potential target of Huaier, which significantly inhibits NSCLC growth by suppressing EGFR expression and its downstream signaling, offering a natural product-based strategy for EGFR-targeted therapy [17].

2.2.2 The DLEU2/miR-212-5p/ELF3 Axis

Long non-coding RNAs (lncRNAs) can function as oncogenes or tumor suppressors [45,46]. Widespread lncRNA dysregulation has been identified in lung cancer via high-throughput sequencing [47]. Huaier was shown to downregulate the oncogenic lncRNA *DLEU2*, thereby alleviating its sequestration of miR-212-5p. This allows miR-212-5p to more effectively inhibit its target gene, ELF3, ultimately suppressing the proliferation, migration, and invasion of NSCLC cells [18].

2.2.3 Induction of Ferroptosis

Huaier induces ferroptosis in lung cancer cells through a dual mechanism: it downregulates key antioxidant proteins (SLC7A11, GPX4), thereby impairing clearance of lipid peroxides. Concurrently, Huaier promotes NCOA4-

Table 1. Molecular targets of Huaier in cancer.

Experimental model	Biological response	Involved genes/pathway	Reference
Gastric cancer cells	↓ Proliferation ↓ Migration ↓ Invasion	↓ GPR30/PI3K/AKT	[11]
Gastric cancer cells	↓ Metastasis ↓ EMT progression	↓ syntenin/STAT3 ↓ EMT-related proteins	[12,13]
Gastric cancer cells	↓ Proliferation ↓ Metastasis	↓ c-Myc/Bmi1	[14]
GIST-T1 GIST-882 xenograft mouse model	↓ Proliferation ↓ Migration ↓ Invasion ↑ Apoptosis	↓ JAK2/STAT3	[15]
Non-small cell lung cancer	↓ Proliferation	↓ EGFR	[16,17]
NSCLC cells	↓ Proliferation ↓ Migration ↓ Invasion	↓ DLEU2 ↑ miR-212-5p ↓ ELF3	[18]
Lung cancer cells	↑ Ferroptosis	↓ SLC7A11/GPX4 ↑ ferritinophagy	[19]
Lung cancer cells	↑ Sensitivity to cisplatin	↓ JNK/JUN/IL-8	[20]
Lung cancer cells	↓ Glucose transport ↓ Lactic acid accumulation	↓ PI3K/AKT/HIF-1α	[21]
Lung cancer cells	↓ Migration ↓ EMT progression ↑ Apoptosis ↑ Ferroptosis	↓ MAPK ↓ Bcl-2 ↑ ROS	[22]
Mice models of liver cancer	↓ M2 phenotypic differentiation ↑ M1 transformation	unknown	[23]
H22-bearing mice of liver cancer	↑ Infiltration of $CD8^+$ T cells ↓ Formation of tumor blood vessels	↑ PD-L1 ↓ VEGFA	[24]
Liver cancer cells	↓ Proliferation ↑ Apoptosis ↑ Autophagy	↓ mTOR	[25]
Tumor-bearing mouse model of triple-negative breast cancer	↓ Formation of myoCAFs	↓ TGF-β/SMAD	[26]
Breast cancer cells tumor-bearing mouse model	↓ Invasion ↓ Migration ↓ EMT progression ↑ Autophagy	↓ Snail	[27]
Breast cancer xenograft mouse model	↑ Infiltration of cytotoxic $CD8^+$ T cells	unknown	[28]
Triple-negative breast cancer cells	↑ Immunogenic cell death	↑ CircCLASP1/PKR/eIF2α	[29]
Pancreatic cancer cells	↑ Ferroptosis ↑ Autophagy	↓ GSH-GPX4 antioxidant system	[30]
Pancreatic cancer cells and xenograft model	↑ Sensitivity to gemcitabine	↓ FoxM1	[31,32]
Pancreatic cancer cells and xenograft model	↓ Proliferation ↑ Apoptosis ↓ EMT progression	↓ Wnt/β-catenin	[33]
Cholangiocarcinoma cells	↓ Proliferation ↓ Metastasis	↓ TWIST1 ↑ FBP1 ↓ Wnt/β-catenin	[34]

Table 1. Continued.

Experimental model	Biological response	Involved genes/pathway	Reference
Cholangiocarcinoma cells	↑ Cell cycle arrest ↑ Apoptosis ↓ Proliferation ↓ Migration ↓ Invasion	↓ PI3K/AKT/mTOR ↑ p53 ↑ BECN1 ↑ ATG7 ↑ DRAM1	[35]
Colon cancer cells	↑ Autophagy ↑ Sensitivity to oxaliplatin	↓ Wnt/β -catenin	[36]
Colon cancer cells	↑ Infiltration and function of $CD8^+$ T cells	↑ STAT1-MHC-I	[37]
Colorectal cancer cells	↓ Mitochondrial autophagy	↓ PINK1/Parkin	[38]
Colorectal cancer cells	↑ Autophagy ↑ Sensitivity to oxaliplatin	↓ METTL3 ↓ Wnt/β-catenin ↓ P-gp resistance protein	[39]
Leukemia cells	↑ Apoptosis ↓ Proliferation	↓ Bcl-2 ↑ BAX ↑ caspase-3	[40]
Leukemia cells	↓ Autophagy ↑ Apoptosis ↓ Proliferation	↓ SIRT1	[41]

"↑" denotes increase/upregulation, and "↓" denotes decrease/downregulation. GPR30/PI3K/AKT, G protein-coupled receptor 30/phosphoinositide 3-kinase/protein kinase B; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; c-Myc/Bmi1, cellular myelocytomatosis oncogene/B-cell-specific Moloney murine leukemia virus integration site 1; JAK2, Janus kinase 2; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; DLEU2, deleted in lymphocytic leukemia 2; ELF3, E74-like factor 3; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; JNK, c-Jun N-terminal kinase; HIF-1α, hypoxia-inducible factor 1-alpha; MAPK, mitogen-activated protein kinase; Bcl-2, B-cell lymphoma 2; ROS, reactive oxygen species; PD-L1, programmed death-ligand 1; VEGFA, vascular endothelial growth factor; mTOR, mammalian target of rapamycin; myoCAFs, myofibroblast-like cancer-associated fibroblasts; TGF-β, transforming growth factor-beta; SMAD, mothers against decapentaplegic homolog; ICD, immunogenic cell death; circCLASP1, circular RNA CLASP1; PKR, protein kinase R; eIF2α, eukaryotic initiation factor 2 alpha; GSH, glutathione; FoxM1, forkhead box M1; TWIST1, twist family bHLH transcription factor 1; FBP1, fructose-1,6-bisphosphatase 1; BECN1, beclin 1; ATG7, autophagy-related protein 7; DRAM1, DNA damage-regulated autophagy modulator 1; MHC-I, major histocompatibility complex class I; PINK1, PTEN-induced putative kinase 1; Parkin, parkin RBR E3 ubiquitin-protein ligase; METTL3, methyltransferase-like 3; P-gp, P-glycoprotein; BAX, Bcl-2-associated X protein; SIRT1, sirtuin 1.

mediated ferritinophagy, leading to degradation of the iron-storage protein ferritin heavy chain 1 (FTH1). The accumulated iron then catalyzes massive lipid peroxide production via the Fenton reaction [19].

2.2.4 The JNK/JUN/IL-8 Signaling Axis

Kaempferol, a key bioactive compound in Huaier, directly binds to and inhibits JNK kinase activity, preventing downstream phosphorylation and activation of the proto-oncogene c-Jun. This ultimately suppresses the entire JNK/JUN/IL-8 signaling axis [20], providing a rationale for developing Huaier as an adjuvant to reverse cisplatin resistance in lung cancer.

2.2.5 The PI3K/AKT/HIF-1α Signaling Pathway

Current evidence suggests that Huaier inhibits the PI3K/AKT/HIF-1α pathway. Since HIF-1α is a master regulator of glycolytic genes, this inhibition suppresses aerobic glycolysis, glucose transport, and lactate accumulation in tumor cells, effectively "starving" them of energy [21]. This reveals a novel anti-tumor mechanism of Huaier targeting cancer metabolism.

2.2.6 Targeting the MAPK/Bcl-2/ROS Axis

Huaier suppresses EMT by inhibiting MAPK signaling, thereby reducing cancer cell migration. Simultaneously, it synergistically induces caspase-dependent apoptosis and ferroptosis by downregulating the anti-apoptotic protein Bcl-2 and increasing intracellular reactive oxygen species (ROS) levels [22]. This multi-targeted action allows Huaier to inhibit NSCLC proliferation, survival, and metastasis through multiple signaling axes.

2.3 Liver Cancer

Primary liver cancer (PLC), a major cause of cancer-related death globally, ranking as the fourth most fatal malignancy [44]. Patient prognosis is poor, with a very low five-year survival rate and most cases are diagnosed at an intermediate or advanced stage. Histologically, hepatocellular carcinoma (HCC) represents the predominant subtype (70–85%), followed by intrahepatic cholangiocarcinoma (ICC).

2.3.1 Intestinal Microbiota-Mediated Macrophage Polarization

Huaier remodels the gut microbiota and its metabolic profile, particularly by increasing key metabolites such as chenodeoxycholic acid (CDCA). These gut-derived signals modulate macrophage polarization within the tumor microenvironment, inhibiting pro-tumor M2 polarization while promoting anti-tumor M1 polarization and the secretion of pro-inflammatory factors. This immune reprogramming reverses the immunosuppressive microenvironment, indirectly inhibiting liver cancer growth [23].

2.3.2 Huaier Upregulates PD-L1 Expression in the TME and Inhibits Angiogenesis Through VEGFA Suppression and Reduced Microvessel Density

Huaier promotes the infiltration and cytotoxicity of $CD8^+$ T cells while upregulating PD-L1 expression in the tumor microenvironment, creating a rationale for synergy with anti-PD-L1 therapy. Besides, it inhibits angiogenesis by suppressing vascular endothelial growth factor (VEGFA) expression and reducing microvessel density (MVD) [24]. These mechanisms highlight the promising synergistic potential of Huaier combined with immune checkpoint inhibitors in HCC.

2.3.3 Targeting mTOR to Induce Autophagic Cell Death

The combination of Huaier and sorafenib (SOR) synergistically inhibits HCC cell proliferation, promotes apoptosis, and induces autophagy by suppressing the mTOR pathway, evidenced by decreased p-mTOR, p-p70S6K, and p62, and increased Beclin-1 and LC3B-II. The mTOR activator MHY1485 reverses this effect, confirming that Huaier sensitizes liver cancer cells to SOR by inducing mTOR-mediated autophagic cell death [25].

2.4 Breast Cancer

Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer death in women worldwide [44]. Its prognosis varies by subtype and stage, with unsatisfactory five-year survival rates in advanced stages. Hormone receptor-positive (HR+)/HER2-negative breast cancer is the most common subtype (60–70%), followed by HER2-positive and triple-negative breast cancer (TNBC).

2.4.1 TGF-β/SMAD Signaling Pathway

Myofibroblast-like cancer-associated fibroblasts (myoCAFs) promote tumor progression, immunosuppression, and fibrosis. Huaier significantly inhibits myoCAF formation by attenuating the TGF-β/SMAD pathway, thereby converting the immune microenvironment from immunosuppressive to immunoactivating [26]. This suggests Huaier may enhance response to immunotherapy and synergize with PD-1 inhibitors.

2.4.2 Autophagy-Mediated Degradation of Snail

In TNBC, the Huaier polysaccharide PS-T was found to inhibit metastasis by activating an autophagy-dependent mechanism. Experimental evidence demonstrates that PS-T induces autophagy, which subsequently targets the transcription factor Snail for degradation. This degradation suppresses the EMT, leading to a significant reduction in TNBC cell invasion and migration, both *in vitro* and *in vivo*. This effect was reversed by autophagy inhibitors (LY294002, ATG5 knockout) or Snail overexpression [27]. Accordingly, the autophagy-Snail-EMT axis has been identified as a mechanism for PS-T's anti-metastatic effect in TNBC.

2.4.3 Remodeling the Intestinal Flora

The CDK4/6 inhibitor palbociclib inhibits tumor cell proliferation. Oral administration of Huaier reportedly reshapes the host gut microbiota, significantly increasing the abundance of Akkermansia. The microbial metabolite butyrate synergizes with palbociclib to promote the infiltration and granzyme B expression of cytotoxic $CD8^+$ T cells, enhancing anti-tumor immunity [28]. Building upon these findings, it can be inferred that Huaier augments palbociclib's efficacy via the "gut microbiota-immune axis".

2.4.4 The circCLASP1/PKR/eIF2α Signaling Pathway

Huaier upregulates circCLASP1, thereby stabilizing and activating the downstream PKR/eIF2α pathway, inducing endoplasmic reticulum stress. This promotes calreticulin (CRT) exposure and the release of ATP and HMGB1, culminating in immunogenic cell death (ICD). The released "danger signals" promote dendritic cell maturation and T-cell activation. In mouse models, Huaier significantly increased tumor-infiltrating lymphocytes and inhibited tumor growth in a T-cell-dependent manner [29], demonstrating that Huaier induces ICD via the circCLASP1/PKR/eIF2α axis to suppress TNBC.

2.5 Pancreatic Cancer

Pancreatic cancer is a highly malignant tumor of the digestive system [48]. Over half of the cases arise in the pancreatic head, and approximately 90% are pancreatic ductal adenocarcinomas. The incidence and mortality rates of pancreatic cancer continue to rise, while patient prognosis remains persistently poor. This is largely due to the

absence of specific early symptoms, resulting in frequent late-stage diagnosis. Consequently, the overall diagnosis rate is low, mortality is high, and curative potential is extremely limited.

2.5.1 Ferroptosis

Huaier induces ferroptosis in pancreatic cancer cells by inhibiting the intracellular glutathione-GPX4 antioxidant axis, resulting in the accumulation of reactive oxygen species and iron ions, and subsequent lipid peroxidation. This process is morphologically characterized by hallmark features of ferroptosis, including mitochondrial shrinkage, reduced cristae, and increased autophagosomes. The autophagy inhibitor Wortmannin attenuates Huaier-induced ferroptosis, confirming its dependence on autophagic activation [30]. Collectively, these findings indicate that Huaier exerts anti-pancreatic cancer effects by activating the "autophagy-ferroptosis" regulatory axis.

2.5.2 FoxM1 Signaling Pathway

Huaier enhances the efficacy of gemcitabine in pancreatic cancer by targeting the FoxM1 pathway. It downregulates FoxM1 protein expression and inhibits its nuclear translocation, thereby blocking its transcriptional activity. Concurrently, Huaier reverses gemcitabine-induced tumor stemness, as evidenced by reduced sphere-forming capacity and stem cell marker expression, ultimately restoring tumor cell sensitivity to gemcitabine [31]. Both *in vivo* and *in vitro* studies have confirmed that the combination of Huaier and gemcitabine significantly suppresses pancreatic cancer growth, an effect directly associated with FoxM1 inhibition and stemness downregulation. Another study demonstrated that this combination synergistically inhibits viability, migration, and invasion, while promoting apoptosis in pancreatic cancer PaTu8988 cells. The core mechanism involves Huaier increasing tumor sensitivity to gemcitabine and reversing chemoresistance, thereby enhancing its cytotoxic effects [32].

2.5.3 Wnt/β-catenin Signaling Pathway

Research employing both *in vivo* and *in vitro* models has established that Huaier extract targets the Wnt/β-catenin pathway, diminishing β-catenin expression to inhibit EMT and cell proliferation while promoting apoptosis in pancreatic cancer [33].

2.6 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a malignant tumor originating from the bile duct epithelium, exhibiting histopathological characteristics of biliary differentiation [49]. Its incidence is second only to hepatocellular carcinoma among primary liver malignancies [50]. Over the past four decades, the global incidence and mortality of CCA have continued to rise. CCA is anatomically classified into hilar (~50%), distal (~42%), and intrahepatic (~8%) types. The disease often has an insidious onset, is frequently chemoresistant, and typically becomes symptomatic only at advanced stages, making radical cure highly challenging.

2.6.1 TWIST1-FBP1-Wnt/β-catenin Signaling

Current evidence suggests that Huaier downregulates the transcription factor TWIST1, which is highly expressed in CCA tissues. This alleviates TWIST1-mediated transcriptional repression of FBP1, increasing FBP1 expression and, in turn, inhibiting Wnt/β-catenin pathway activity [34]. By targeting the TWIST1-FBP1-Wnt/β-catenin axis, Huaier exerts multi-dimensional anti-tumor effects at both transcriptional and signaling levels, suggesting a potential new strategy for CCA treatment.

2.6.2 Multi-target Synergy

Huaier inhibits CCA progression through a multi-target synergistic mechanism: (1) It inhibits the PI3K/AKT/mTOR pathway, downregulating phosphorylated AKT and ribosomal protein S6, thereby blocking survival and proliferation signals; (2) It activates the p53 tumor suppressor pathway, upregulating p53 and its phosphorylated forms, inducing cell cycle arrest and apoptosis; (3) It modulates the expression of core autophagy molecules (BECN1, ATG7, DRAM1), interfering with autophagosome formation and the crosstalk between autophagy and apoptosis [35]. These mechanisms collectively mediate the multi-faceted inhibition of CCA cell proliferation, migration, and invasion, and promote apoptosis, highlighting Huaier's multi-pathway anti-tumor characteristics.

2.7 Colorectal Cancer

Colorectal cancer (CRC) is one of the most common malignancies of the digestive system globally, ranking third in incidence [51]. Adenocarcinoma is the predominant pathological type (90–95%), originating from colonic glandular epithelial cells. Other types include mucinous adenocarcinoma (~10%) and signet-ring cell carcinoma (~1%). CRC is highly invasive, and due to the frequent absence of typical early symptoms, most patients are diagnosed at intermediate or advanced stages.

2.7.1 Autophagy and the Wnt/β-catenin Signaling Pathway

Huaier significantly reverses oxaliplatin resistance in HCT-8/L colon cancer cells by inhibiting the Wnt/β-catenin pathway and modulating cellular autophagy activity. This mechanism was further validated using Wnt agonists and autophagy inhibitors, demonstrating that Huaier synergistically suppresses the Wnt pathway and regulates autophagy to restore chemosensitivity in resistant cells [36].

2.7.2 Activation of MHC-I and $CD8^+$ T Cells

Huaier enhances tumor antigen presentation by activating the STAT1-MHC-I pathway, thereby remodeling the immune microenvironment. It significantly promotes the infiltration and function of $CD8^+$ T cells while effectively depleting immunosuppressive Treg cells [37]. This mechanism provides a foundation for the synergistic effect between Huaier and anti-PD-1 therapy, offering a feasible translational strategy to improve immunotherapy efficacy in CRC.

2.7.3 Mitochondrial Damage and the PINK1/Parkin Pathway

Huaier induces oxidative stress and mitochondrial damage while concurrently inhibiting PINK1/Parkin-mediated mitophagy. This dual effect leads to the accumulation of damaged mitochondria, resulting in efficient activation of the mitochondrial apoptotic pathway and inhibition of growth in CRC cells (HCT116, SW480) [38]. These results suggest Huaier's potential as an anti-CRC agent and provide an important theoretical basis for its further development.

2.7.4 Wnt/β-catenin Signaling Pathway

Huaier exerts anti-CRC effects through a multi-target mechanism. It downregulates METTL3 expression, inhibits the Wnt/β-catenin pathway, and reduces P-glycoprotein (P-gp) expression, thereby reversing oxaliplatin resistance and enhancing chemosensitivity [39]. This dual mechanism enables Huaier to directly induce cancer cell apoptosis while effectively overcoming chemotherapy resistance.

2.8 Leukemia

Acute myeloid leukemia (AML) is a malignant clonal disease originating from hematopoietic stem cells in the bone marrow and represents a major global health burden [52]. Its core pathology involves dysregulated self-renewal of leukemia stem cells. This malignant proliferation can infiltrate the spleen, causing structural remodeling and hyperfunction, clinically manifesting as splenomegaly and associated impaired immune function.

2.8.1 Bcl-2/BAX/caspase-3 Apoptotic Pathway

A study has confirmed that Huaier, in combination with conventional chemotherapeutic agents (vincristine/VCR, daunorubicin/DNR, asparaginase/L-Asp), exhibits significant anti-tumor effects in acute lymphoblastic leukemia (ALL) cell lines (Nalm-6, Sup-B15), demonstrating synergistic or additive effects. The combination groups showed significantly higher inhibition of proliferation and apoptosis than the single-agent groups (combination index $q \geq 0.85$). Mechanistically, the Huaier/VCR combination synergistically downregulated Bcl-2, upregulated BAX, and activated caspase-3. The Huaier/DNR combination enhanced Bcl-2 downregulation and caspase-3 activation without significantly affecting BAX. Although the Huaier/L-Asp combination showed no significant synergistic protein-level changes, it still enhanced proliferation inhibition and apoptosis induction [40]. Taken together, these results indicate that Huaier enhances the inhibitory and lethal effects on leukemia cells by synergistically regulating the Bcl-2/BAX/caspase-3 apoptotic pathway in conjunction with chemotherapy drugs.

2.8.2 Regulation of the SIRT1-Autophagy Axis

Huaier inhibits protective autophagy by downregulating the deacetylase sirtuin 1 (SIRT1), resulting in reduced expression of key autophagy proteins (ATG7, Beclin-1) and increased accumulation of the autophagy substrate p62. Concurrently, it activates the mitochondrial apoptotic pathway, promoting cytochrome c release, activating caspase-3, cleaving PARP, and upregulating p53 protein expression. This leads to synergistic inhibition of proliferation and induction of apoptosis in T-cell acute lymphoblastic leukemia (T-ALL) cells [41]. These findings suggest Huaier's potential as a novel agent or adjuvant therapeutic for the treatment of ALL.

3. Clinical Evidence for Huaier in the Prevention and Treatment of Cancers

3.1 Liver Cancer

A retrospective analysis from The First Affiliated Hospital of Harbin Medical University involving 243 patients with high-risk factors following complete liver cancer resection demonstrated that adjuvant Huaier Granules monotherapy prolonged both overall survival (OS) and disease-free survival (DFS), effectively delaying recurrence. Furthermore, the combination of Huaier Granules with lenvatinib was more effective than either agent alone, with the combination group exhibiting significantly greater improvements in OS and DFS, suggesting a synergistic effect. Multivariate analysis confirmed that the lenvatinib-Huaier combination reduced the risk of death and recurrence by approximately 22.3% and 24.7%, respectively, and its efficacy was independent of other clinical factors [53]. These findings establish Huaier Granules as an effective adjuvant anti-liver cancer drug, that not only reduces recurrence and prolongs survival as a single agent but, more importantly, synergizes with modern targeted therapies, such as lenvatinib, offering a promising integrated traditional Chinese and Western medicine strategy for preventing postoperative recurrence.

An updated systematic review and meta-analysis indicated that, for primary liver cancer, combining Huaier Granules with conventional therapy reduced the recurrence rate by 35% and the one-year mortality risk by 21% (both $p < 0.05$), with 95% confidence intervals that excluded 1 [54]. Besides, Huaier Granules were found to improve patients' quality of life, significantly reduce alpha-

Table 2. Clinical trials for the treatment of various types of cancers using Huaier Granules.

ClinicalTrials.gov identifier	Cancer type	Phase of study	Primary purpose of the study
NCT02796820	Colorectal Cancer	Phase 3	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in colorectal cancer patients after radical surgery.
NCT02785146	High-risk Stage II, Stage III Colorectal Cancer	Phase 3	To investigate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in colorectal cancer patients after radical surgery.
NCT07197853	Non-small Cell Lung Cancer	Phase 3	To evaluate the efficacy and safety of microwave ablation (MWA) combined with Huaier Granules in patients with inoperable stage IA non-small cell lung cancer.
NCT01770431	Hepatic Carcinoma	Phase 4	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in hepatocellular carcinoma patients after radical hepatectomy.
NCT05871437	Breast Cancer	Phase 4	To compare the rate of tumor marker normalization between breast cancer patients treated with Huaier Granules and the control group.
NCT05860907	Breast Cancer	Phase 4	To evaluate the efficacy and safety of Huaier Granules in patients with advanced breast cancer without visceral metastasis.
NCT06665334	Colorectal Cancer	Phase 4	To explore the effect of Huaier Granules on the conversion rate of elevated CEA levels in patients after colorectal cancer surgery.
NCT06387368	Pancreatic Cancer	Phase 4	To evaluate the efficacy and safety of Huaier Granules combined with capecitabine in patients with unresectable pancreatic cancer.
NCT04790305	Triple-negative Breast Cancer	Phase 4	To evaluate the safety of long-term use of Huaier Granules as postoperative adjuvant therapy and the associated changes in quality of life scores in patients with high-risk, early-stage triple-negative breast cancer.
NCT06090994	Colorectal Cancer	Phase 4	To evaluate the efficacy of Huaier Granules in preventing recurrence and metastasis after radical resection of colorectal cancer.
NCT02615457	Triple Negative Breast Cancer	Phase 4	To evaluate the efficacy and safety of Huaier Granules in women with surgically resected triple-negative breast cancer.
NCT06368063	Pancreatic Cancer	Phase 4	To evaluate the efficacy and safety of Huaier Granules as postoperative adjuvant therapy for resectable pancreatic cancer.
NCT05498766	Gastric Cancer	Phase 4	To evaluate the efficacy and safety of Huaier Granules versus the SOX regimen as postoperative adjuvant therapy for resectable stage II–III gastric cancer.
NCT01760616	Hepatic Carcinoma	Phase 4	To evaluate the efficacy and safety of Huaier Granules in preventing disease progression in hepatocellular carcinoma patients after non-radical hepatectomy.
NCT02627248	Breast Cancer	Phase 4	To evaluate the effects of Huaier Granules in managing locally advanced breast cancer in combination with neoadjuvant chemotherapy.

Table 2. Continued.

ClinicalTrials.gov identifier	Cancer type	Phase of study	Primary purpose of the study
NCT03356236	Hepatocellular Carcinoma	Not applicable	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in hepatocellular carcinoma patients following local ablation.
NCT05749211	Ovarian Cancer	Not applicable	To evaluate the efficacy and safety of Huaier Granules combined with immunotargeted agents in postoperative ovarian cancer patients.
NCT05660213	Hepatocellular Carcinoma	Not applicable	To evaluate the efficacy of different treatment regimens for unresectable stage III hepatocellular carcinoma.
NCT06109454	Non-small Cell Lung Cancer	Not applicable	To explore whether the 3-year disease-free survival (DFS) with Huaier Granules is non-inferior to standard platinum-based doublet chemotherapy.
NCT03349762	Colorectal Cancer	Not applicable	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in colorectal cancer patients after radical surgery.
NCT03198117	Non-small Cell Lung Cancer	Not applicable	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in stage II/III non-small cell lung cancer (NSCLC) patients after postoperative adjuvant chemotherapy.
NCT02975661	Gastrointestinal Cancer	Not applicable	To evaluate the efficacy and safety of Huaier Granules in preventing recurrence and metastasis in gastrointestinal cancer patients after radical surgery.
NCT05792254	Primary Ovarian Cancer Fallopian Tube Cancer Peritoneal Cancer	Not applicable	To explore the efficacy of Huaier Granules in patients with stage II–IV primary ovarian, fallopian tube, or peritoneal cancer after satisfactory tumor cytoreduction (R0/R1).

CEA, carcinoembryonic antigen; SOX, S-1 + oxaliplatin.

fetoprotein levels, and enhance immune function by modulating T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$) and the $CD4^+/CD8^+$ ratio [54].

In a study evaluating adjuvant Huaier Granules following thermal ablation for hepatocellular carcinoma, the most notable benefit was the prolongation of progression-free survival (PFS). The median PFS was significantly longer in the combination group than in the ablation-alone group (24 months vs. 12.5 months), with superior 1-, 3-, and 5-year PFS rates (Hazard Ratio [HR] = 0.67). Huaier also significantly inhibited extrahepatic metastasis (HR = 0.49). Although the difference in OS was not statistically significant ($p = 0.110$), a positive trend was observed, with a longer median OS in the combination group (35 vs. 31 months; HR = 0.76) [55]. These results indicate that Huaier Granules reduced the risk of recurrence/progression, extrahepatic metastasis, and death by 33%, 51%, and 24%, respectively. The regimen was well-tolerated, with a slightly higher but non-significant incidence of mild and manageable nausea and vomiting.

3.2 Gastric Cancer

Postoperative adjuvant therapy with Huaier Granules plus Tegafur (Teggio) Capsules significantly improved survival outcomes in patients with stage IIb gastric cancer. The combination group achieved a longer median disease-free survival (51.32 ± 2.23 months) compared to the Tegafur monotherapy group (44.19 ± 2.26 months; $p = 0.034$). Besides, overall survival was significantly extended in the combination group (56.81 ± 1.32 months vs. 51.32 ± 1.69 months; $p = 0.020$) [56]. Concurrent experimental studies have shown that Huaier polysaccharide downregulates Livin expression at both the mRNA and protein levels, thereby alleviating its suppression of apoptosis [56]. These findings not only support the clinical efficacy of Huaier Granules but also suggest a potential molecular mechanism, providing a solid theoretical foundation for its application in gastric cancer treatment.

3.3 Breast Cancer

In a clinical study involving patients with stage I–III triple-negative breast cancer (TNBC), adjuvant treatment with Huaier Granules demonstrated efficacy in pre-

venting tumor recurrence and metastasis. The Huaier group achieved superior 5-year disease-free survival (DFS: 81.3% vs. 53.8%) and overall survival (OS: 87.5% vs. 65.4%) rates compared to the control group. A subgroup analysis revealed a duration-dependent effect, with longer Huaier therapy (18 vs. 6 months) associated with reduced disease progression, highlighting the importance of sustained administration and a favorable safety profile. However, the survival benefit did not reach statistical significance in the overall stage I–III population [57].

Supporting these findings, a separate propensity score-matched study enrolled 214 patients with early aggressive breast cancer (n = 107 per group). The results showed that Huaier Granules significantly improved both 2- and 5-year DFS (HR = 0.495) and OS (HR = 0.308) compared to controls. After adjusting for confounding variables via multivariate Cox regression, Huaier treatment remained an independent prognostic protective factor for DFS (HR = 0.440) and OS (HR = 0.236) [58].

Collectively, these clinical data substantiate that Huaier Granules, as an adjuvant therapy, can significantly prolong DFS and OS in patients with early invasive breast cancer, primarily by reducing disease recurrence and metastasis. In addition to these, as shown in Table 2, several other clinical trials have examined Huaier's effectiveness in treating cancer.

4. Conclusions

This review summarizes recent advances in the molecular mechanisms and clinical applications of the traditional Chinese medicine Huaier in oncology. Substantial evidence demonstrates that the active components of Huaier exert broad anti-tumor effects through multi-target and multi-pathway mechanisms. At the molecular level, Huaier-mediated anti-tumor activities primarily include: (1) Suppressing tumor cell proliferation and survival by modulating key signaling pathways (e.g., JAK2/STAT3, MAPK), thereby inducing diverse forms of programmed cell death, including cell cycle arrest, apoptosis, autophagy, and ferroptosis; (2) Inhibiting tumor invasion and metastasis by interfering with pathways such as GPR30, syntenin/STAT3, and TGF-β/SMAD, consequently reversing the epithelial-mesenchymal transition (EMT) process; (3) Remodeling the tumor microenvironment and converting immunologically "cold" tumors into "hot" tumors via mechanisms such as reshaping gut microbiota, regulating macrophage polarization, promoting $CD8^+$ T cell infiltration and function, and inducing immunogenic cell death (ICD); (4) Enhancing the efficacy of chemotherapy, targeted therapy, and immunotherapy by inhibiting pathways like FoxM1 and Wnt/β-catenin, downregulating drug-resistant proteins such as P-gp, thereby reversing chemoresistance and generating synergistic effects with agents including PD-1/PD-L1 inhibitors, lenvatinib, and sorafenib. Huaier granules, as an adjuvant therapy, have been clinically shown to significantly improve survival outcomes, reduce recurrence, and enhance quality of life with a favorable safety profile in cancers including liver, gastric, and breast cancer.

Despite the promising findings summarized herein, it is important to acknowledge several inherent limitations in the current evidence base. Indeed, a substantial portion of the supportive clinical data is derived from retrospective analyses or single-center studies, which may introduce selection bias and limit generalizability. Besides, the consistency and comparability of mechanistic findings may be limited by heterogeneity across preclinical studies in the specific Huaier extracts or purified components (e.g., polysaccharides vs. total extract) and dosages used, potentially affecting the consistency and comparability of mechanistic findings. Furthermore, while multi-target effects are a strength, they also pose a challenge in identifying the definitive primary active compounds responsible for specific outcomes across different cancer types. These limitations underscore the necessity for the future research initiatives outlined below.

Although the anti-tumor value of Huaier has been preliminarily established, future investigations should address the following aspects: (1) Elucidating multi-component synergistic mechanisms. Current research predominantly focuses on single components; a systematic understanding of the synergistic interactions among multiple constituents and their host targets remains limited. Future studies should employ network pharmacology and systems biology approaches to decipher Huaier's "multi-component–multi-target–multi-pathway" regulatory network, ultimately clarifying the molecular basis of its synergistic anti-tumor effects. (2) Expanding clinical evidence. Most clinical evidence to date derives from retrospective analyses or small-scale trials, hindering the evaluation of Huaier's efficacy across diverse clinicopathological subtypes. There is a pressing need for large-scale, multi-center, prospective randomized controlled trials that stratify patients based on tumor stage and molecular subtypes, thereby identifying predictive biomarkers for Huaier-responsive populations. (3) Innovating drug formulations. Although Huaier polysaccharides represent key active anti-tumor components, other bioactive constituents remain incompletely characterized. Moreover, Huaier granules constitute the only available clinical formulation. Future efforts should prioritize the development of novel, targeted delivery systems based on established active ingredients to overcome current formulation limitations and broaden clinical applicability.

Author Contributions

WZ: Conceptualization, literature search and data curation, writing – original draft preparation, writing – review and editing, final approval, and agreement to be accountable for all aspects of the work. FL: Conceptualization, supervision, critical revision of the manuscript for important

intellectual content, writing – review and editing, final approval, and agreement to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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