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REVIEW ARTICLE

Progress in the molecular mechanisms of tanshinone IIA in modulating digestive system diseases

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Abstract

Tanshinone IIA (Tan IIA), a bioactive lipophilic compound isolated from the traditional Chinese medicinal plant *Salvia miltiorrhiza*, demonstrates multitarget therapeutic effects encompassing anti-inflammatory, antioxidant, anti-fibrotic, and anti-neoplastic mechanisms, as evidenced by contemporary pharmacological research. With its unique anti-inflammatory advantages, Tan IIA has been widely used for the management of digestive disorders. This agent suppresses the overproduction of pro-inflammatory mediators and disrupts inflammatory signaling cascades, thereby effectively mitigating disease progression across inflammation-driven pathologies. In addition, Tan IIA has demonstrated strong antitumor activity. This agent suppresses the proliferation, migration, and invasion of tumor cells through interference with oncogenic signaling pathways and the activation of apoptotic pathways, demonstrating significant therapeutic potential in oncology. Such multitarget and multi-mechanism action properties make Tan IIA a promising candidate for inflammation control and tumor suppression. This review elucidates Tan IIA's mechanisms in gastric, hepatic, and intestinal pathologies, aiming to provide a scientific basis and reference for subsequent in-depth studies and clinical translation.

Keywords: Tanshinone IIA; Molecular mechanism; Tumor; Digestive system diseases; Signaling pathway

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1. Introduction

Tanshinone IIA (Tan IIA) is a principal lipophilic bioactive compound derived from the traditional Chinese medicinal plant *Salvia miltiorrhiza* Bunge (also known as *Danshen* in Chinese). Contemporary pharmacological research has established that Tan IIA exhibits a range of biological activities, encompassing antioxidant, neuroprotective, anti-inflammatory, and antitumor effects. It achieves therapeutic outcomes—such as reducing inflammation, mitigating oxidative stress, and suppressing fibrosis—through the coordinated modulation of multiple molecular signaling pathways.[1,2] In Asia, Tan IIA has been widely used in the clinical treatment of a variety of diseases, especially in the cardiovascular field, where it is regarded as a pioneering drug that has been intensively explored.[3] In addition, it has shown therapeutic potential in renal diseases (e.g., diabetic

nephropathy,[4] acute kidney injury[5]), pulmonary diseases (e.g., pulmonary fibrosis,[6] lung cancer[7]), breast diseases (e.g., breast cancer[8]), and brain diseases (e.g., cerebral ischemia,[9] Alzheimer's disease[10]).

While the efficacy of Tan IIA in diseases of the circulatory, respiratory, and musculoskeletal systems has been relatively well-documented, research focusing on its role in digestive system disorders remains limited. Although preclinical evidence confirms its therapeutic potential, comprehensive and systematic reviews are still lacking. This gap has led to limited recognition and clinical translation of its significant value in this field.

In the context of digestive system diseases, Tan IIA similarly demonstrates anti-inflammatory and antitumor effects. With respect to inflammatory conditions, it has been demonstrated to effectively alleviate inflammatory responses by modulating signaling pathways, such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), transforming growth factor-β (TGF-β)/suppressor of mother against decapentaplegic (Smad), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK). In the context of digestive system tumors, Tan IIA has been shown to possess antitumor properties through a variety of mechanisms. These mechanisms include the direct inhibition of tumor cell proliferation, the induction of apoptosis, and the suppression of migration and invasion. At the molecular level, Tan IIA induces cell cycle arrest and apoptosis by inhibiting pathways such as PI3K/Akt/mTOR and Janus kinase (JAK)/signal transducers and activators of transcription (STAT). Furthermore, it has been demonstrated that the suppression of mTOR and vascular endothelial growth factor (VEGF) is achieved through their downregulation, thus activating the MAPK kinase (MEK)/extracellular signal-regulated kinase (ERK)/mTOR pathway. This, in turn, results in the inhibition of tumor growth, angiogenesis, and metastasis.[11,12]

In addition, it has been demonstrated to reverse multidrug resistance and modulate the tumor microenvironment (TME).[13] This review aims to provide a systematic summary of the role of Tan IIA in inflammatory and neoplastic diseases of the digestive system. Specifically, the review will focus on elucidating the molecular mechanisms through which Tan IIA achieves chemopreventive and antitumor effects by regulating key signaling pathways.

2. Signaling pathway

2.1. NF-κB signaling pathway

The NF-κB signaling pathway serves as a pivotal regulatory system governing inflammatory processes and contributes to diverse disease-related mechanisms. This pathway exerts its biological influence through transcriptional modulation of over 400 gene targets, spanning inflammatory mediators, enzymatic regulators, and cellular proliferation controllers.[14] The pathway is activated through two main routes: (i) the canonical pathway facilitates the nuclear translocation of RelA/p50 heterodimers following microbial or inflammatory stimuli, driving transcriptional activation of genes encoding inflammatory cytokines or chemokines; and (ii) the non-classical pathway, which is involved in immune differentiation and tissue morphogenesis through p52/RelB heterodimers.[15,16] Notably, NF-κB demonstrates a dual regulatory function in tumor initiation and progression. Clinical data indicate a marked elevation of *NFKB1* expression in neoplastic tissues,[17] with its persistent activation contributing to tumor-promoting mechanisms through the mouse double minute 2 homolog–p53 axis. Mechanistically, this effect is linked to NF-κB's binding to the transcriptional coactivators p300/CREB-binding protein, a critical interaction for modulating downstream oncogenic pathways.[18]

2.2. TGF-β/Smad signaling pathway

The TGF-β/Smad signaling pathway is a central regulatory mechanism of tissue fibrosis.[19] The key effector molecule, TGF-β1, drives the expression of more than 60 extracellular matrix genes through the activation of Smad-dependent and Smad-independent signaling, leading to abnormal collagen deposition and fibrotic tissue formation.[20] Tan IIA demonstrates dual-axis modulation of TGF-β/Smad signaling, and NF-κB cascades through the downregulation of extracellular matrix components and pro-inflammatory cytokines, thereby exhibiting antifibrotic and anti-inflammatory therapeutic effects.[21] Previous studies have reported that Tan IIA inhibited fibroblast overproliferation and induced cell cycle arrest in its G2/M phase arrest and apoptosis by blocking TGF-β1-induced sustained Smad3 phosphorylation and upregulating Smad7 expression, with this mechanism arising from its synergistic intervention on TGF-β/Smad and MAPK/ERK pathways.[21,22]

2.3. PI3K/Akt/mTOR signaling pathway

The PI3K/Akt/mTOR cascade, a central oncogenic signaling axis frequently hyperactivated in malignancies, stimulates neoplastic growth, vascular network formation, and extracellular matrix reorganization. This pathway exerts its pro-tumorigenic effects primarily by orchestrating the activity of key mitogenic receptors, including the insulin-like growth factor 1 receptor, VEGF receptor, and epidermal growth factor receptor (EGFR) families.[23] Furthermore, this pathway critically regulates the Toll-like receptor 4/NF-κB pro-inflammatory axis while

coordinating apoptosis suppression, immune homeostasis, and anti-inflammatory mediator production.[24] Pharmacological blockade of PI3K/Akt/mTOR signaling combined with p53 activation triggers cell cycle arrest and suppresses tumor proliferation.[25] Conversely, dysregulated activation of these pathways (e.g., PI3K hyperactivation/p53 inactivation) drives chemoresistance and aggressive tumor phenotypes.[26] It is noteworthy that the decline in phosphorylated Akt levels and the upregulation of transcription factor E3 expression, induced by PI3K inhibitors, suggest the presence of a dynamic interplay mechanism between this pathway and the TME, thereby offering a scientific rationale to advance precision-targeted treatment approaches.[27]

2.4. MAPK signaling pathway

The ERK/MAPK axis, a central oncogenic driver, promotes malignant progression through cancer cell proliferation, differentiation, and metastasis. Its dysregulation further enhances tumor aggressiveness by shaping an immunosuppressive microenvironment.[28] Research has indicated that sustained activation of this pathway occurs throughout tumor evolution, promoting aberrant cell proliferation in the early stages of carcinogenesis and maintaining the malignant phenotype of tumors in the advanced stages through signaling mediated by, for example, EGFR.[29] Furthermore, Tan IIA has been reported to inhibit ERK/MAPK signaling by inducing Tribbles homolog 3 (TRIB3) protein expression, which in turn activates the apoptotic program in tumor cells.[30] Furthermore, multi-omics analysis has revealed that the compound inhibits epithelial cell pyroptosis and mitigates oxidative stress damage by modulating the MAPK signaling axis.[31] This multimodal signaling integration establishes a molecular rationale for MAPK-centric therapeutic development, enabling precision targeting of oncogenic pathway dependencies.

2.5. JAK/STAT signaling pathway

The JAK/STAT signaling axis, a critical regulator of inflammation–tumor crosstalk, modulates downstream gene expression through the JAK-mediated phosphorylation cascade of STAT proteins. This process promotes tumor proliferation and shapes the immune microenvironment.[2,32] The JAK family, which includes JAK1, JAK2, JAK3, and tyrosine kinase 2, facilitates cytokine signaling through the phosphorylation and activation of STAT proteins. Once phosphorylated, STAT proteins form dimers that translocate to the nucleus and regulate the expression of genes associated with immune and inflammatory responses.[33] Excessive activation of this cascade promotes a pro-inflammatory milieu, resulting in sustained inflammation and tissue injury.[34] Multiple cytokines—such as interferon-γ, interleukin (IL)-6, IL-12, IL-15, and IL-23—transmit signals via this pathway to influence immune activity and promote tissue damage.[35] Furthermore, Tan IIA has been shown to enhance the expression of Src homolog region 2 domain-containing phosphatase (SHP) 1 and SHP 2 through inhibition of the JAK2/STAT5 pathway. This action counteracts the functions of pro-survival proteins such as Bcl-xL, survivin, and cyclin D1, ultimately inducing apoptosis in tumor cells.[36] Figure 1 illustrates the key signaling pathways involved in the effects of Tan IIA in the context of gastric, hepatic, and intestinal diseases.

3. Inflammatory disease

3.1. Chronic gastritis (CG)

CG is a globally prevalent disease characterized by a persistent inflammatory response in the gastric mucosa, accompanied by superficial and glandular epithelial damage, affecting more than 4.4 billion people.[37,38] *Helicobacter pylori* infection serves as the main causative factor.[39]

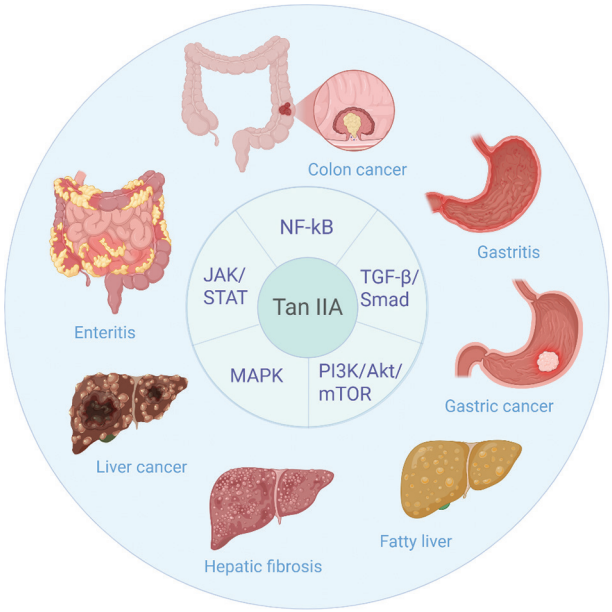


Figure 1. Tanshinone IIA modulates digestive disease pathogenesis through convergence on key signaling pathways. The figure was created using BioRender (Source: Yuke, X. (2026) https://BioRender.com/29zvq2l).

Abbreviations: Akt: Protein kinase B; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; mTOR: Mechanistic target of rapamycin; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; PI3K: Phosphoinositide 3-kinase; Smad: Mothers against decapentaplegic homolog; STAT: Signal transducer and activator of transcription; TGF-β: Transforming growth factor-β.

This pathogen drives gastric carcinogenesis through virulence factors like cytotoxin-associated GENE A and vacuolating cytotoxin A (VacA), which remodel the host TME and immune response.[40] VacA contributes to cellular injury and persistent infection by facilitating bacterial evasion of host defenses and antibiotic treatments.[41] At the molecular level, Yuan *et al.*[42] demonstrated that VacA elevates tumor necrosis factor (TNF) receptor-associated factor 1 (TRAF1) expression, subsequently triggering the NF-κB cascade through 4-1BB and thus inducing gastric epithelial cell apoptosis along with IL-8 release, outlining a novel pathogenic axis: VacA–TRAF1–NF-κB–IL-8. In a complementary study, Xiao *et al.*[43] demonstrated that VacA enhances TRAF1 protein stability by upregulating the deubiquitinase TNF-α-induced protein 3, which triggers pyroptosis and the secretion of IL-1β and IL-18, leading to gastric mucosal atrophy and promoting malignant transformation. Building on this cellular understanding, Chen *et al.*[44] performed single-cell RNA sequencing on 26,028 gastric antral cells across disease stages. They identified uridine phosphorylase 1 as a key oncogene whose expression progressively increases and is upregulated by *H. pylori* through the NF-κB pathway, further highlighting the central role of this pathway in gastric carcinogenesis.

Given the pivotal role of NF-κB signaling in *H. pylori*-associated pathogenesis, pharmacological agents targeting this pathway hold significant therapeutic promise. In this context, the principal bioactive constituent of *S. miltiorrhiza*, Tan IIA, has exhibited notable anti-inflammatory activity. Specifically, it has been found to attenuate inflammatory responses through the suppression of the NF-κB signaling pathway,[45] effectively reducing pro-inflammatory cytokine production through inhibition of the receptor for advanced glycation end products/NF-κB axis,[46] and blocking IL-1β-stimulated protein phosphorylation associated with the PI3K/AKT and NF-κB pathways.[47] These actions underscore its potential utility against the inflammatory cascade driven by *H. pylori* infection. Supporting this, a network pharmacology study demonstrated that adjunctive therapy with *S. miltiorrhiza*, identified as a hub herb, enhances clinical efficacy in chronic atrophic gastritis, with its active component Tan IIA interacting with core targets such as MAPK1/3 to modulate pathways relevant to inflammation and disease progression.[48]

The therapeutic potential of such herbal components is exemplified by formulations such as Moluodan (MLD), a multi-herb patent medicine containing *S. miltiorrhiza*. MLD is known to regulate gastrointestinal (GI) function, protect the gastric mucosa, and alleviate pain.[49] Mechanistically, Zhou *et al.*[50] utilized an integrated network pharmacology approach to delineate MLD's multitarget mode of action in chronic atrophic gastritis. Their analysis revealed that MLD's active components modulate key processes—including inflammation, cell proliferation, apoptosis, and metabolism—overlapping with conventional drug targets. Experimental validation in an N-methyl-N'-nitro-N-nitrosoguanidine-induced cell model confirmed that MLD inhibits proliferation, promotes apoptosis and differentiation, reduces inflammation, and regulates lipid metabolism. Clinical evidence from a meta-analysis of 1,143 patients indicates that MLD monotherapy significantly improves histopathological outcomes in chronic atrophic gastritis compared to folic acid or Vitamin D, while combination therapy further enhances endoscopic and symptomatic recovery.[51]

3.2. Non-alcoholic fatty liver disease

Liver diseases pose a significant global health challenge, with limited treatment efficacy and rising prevalence.[52] Non-alcoholic fatty liver disease (NAFLD), characterized by metabolically driven intrahepatic lipid accumulation,[53] currently afflicts approximately 25% of adults worldwide, ranking as the most prevalent chronic liver pathology globally.[54] The pathogenesis of NAFLD is multifactorial, involving interactions between lifestyle, dietary structure, and genetic susceptibility. The central pathophysiological link is considered to be excessive accumulation of visceral adipose tissue.[55] *S. miltiorrhiza* exhibits therapeutic efficacy against NAFLD through multitarget modulation of hepatic apoptosis, peroxisome proliferator-activated receptor (PPAR) signaling, and NF-κB-driven inflammatory cascades, as mechanistically validated in preclinical models.[56]

At the cellular level, Wang *et al.*[57] demonstrated that, using a palmitate-treated HepG2 cell model, Tan IIA alleviates hepatocyte apoptosis and reduces triglyceride accumulation by suppressing endoplasmic reticulum stress, as evidenced by the downregulation of glucose-regulated protein 78, phosphorylated eukaryotic initiation factor 2α, activating transcription factor 6, and C/EBP homologous protein, thereby mitigating hepatocyte steatosis. Gao *et al.*[58] additionally demonstrated that Tan IIA reduces de novo lipogenesis and lowers intracellular triglyceride accumulation in HepG2 cells through transcriptional suppression of sterol regulatory element-binding protein 1. Furthermore, Tan IIA alleviates NAFLD by activating the PPARα/fibroblast growth factor (FGF)-21 axis to modulate endoplasmic reticulum lipid metabolism and inhibit the unfolded protein response.[59,60] *In vivo*, using low-density lipoprotein receptor-/- mice on a high-fat diet, Zhang *et al.*[61] reported that Tan IIA ameliorates atherosclerosis and hepatic steatosis through downregulation of the

MAPKs/NF-κB pathway. This effect leads to reduced serum and hepatic lipid levels, improved liver function, and suppressed inflammatory responses. Supporting these findings, Zheng *et al.*[62] found that *S. miltiorrhiza* extract not only ameliorates hepatic steatosis in mice but also regulates serum lipid and glucose metabolism while activating lipid metabolism-related gene pathways.

Clinical studies support the translational potential of *S. miltiorrhiza*. Registered trials have shown that combinations containing it exert therapeutic effects on hepatocyte injury with minimal side effects.[63] Preclinically, Li *et al.*[64] demonstrated that a standardized *S. miltiorrhiza* formulation significantly improves dyslipidemia in hypercholesterolemic rat models. Research on herbal compounds provides further insight. You *et al.*[65] found that the Xiaozhi formula, which contains *Danshen* as a key component, alleviates NAFLD in mice by activating the AMP-activated protein kinase pathway and modulating PPARα/PPARγ expression to promote fatty acid oxidation and inhibit lipid synthesis. Similarly, Wang *et al.*[66] showed that the Compound Tiaozhi Fang (also known as *Fufang Zhenzu Tiaozhi*), another *Danshen*-containing formula, improves glycolipid metabolism and hepatic steatosis in a type 2 diabetes mellitus–NAFLD porcine model by activating the PI3K/AKT pathway and inhibiting hypoxia-inducible factor 1α (HIF-1α) signaling.

3.3. Liver fibrosis

The progression of liver injury is mechanistically linked to immune dysregulation and excessive pro-inflammatory cytokine release, a process in which chronic inflammation accelerates hepatic fibrosis, cirrhosis, and carcinogenesis.[67] Against this pathological backdrop, Tan IIA has been shown to ameliorate liver fibrosis through a spectrum of mechanisms encompassing anti-inflammation, antioxidant activity, modulation of collagen homeostasis, and prevention of tissue damage.[68]

At the molecular level, Li *et al.*[69] employed a carbon tetrachloride (CCl_4)-induced mouse model integrated with network pharmacology and demonstrated that Tan IIA suppresses fibrotic progression by inhibiting the Kirsten rat sarcoma viral oncogene homolog/PI3K/Akt and nuclear factor erythroid 2-related factor 2/heme oxygenase 1 signaling pathways and enhancing antioxidant capacity. A pivotal process in fibrosis involves the activation of hepatic stellate cells (HSCs), which then produce extracellular matrix and drive pathological collagen deposition.[70] Targeting HSC activation and proliferation is therefore critical. In this regard, Liao *et al.*[71] employed both *in vivo* (CCl_4-induced) and *in vitro* (TGFβ1-stimulated LX2/HSCT6 cells) models and demonstrated that Tan IIA alleviates liver fibrosis by regulating the ERK/cyclin D1/pSmad3L signaling axis, thereby arresting activated HSCs in the G1 phase and suppressing their proliferation. Beyond inhibiting proliferation, Tan IIA also induces apoptosis in activated HSCs, underscoring its potential as a therapeutic agent for hepatic fibrotic diseases.[72]

The anti-fibrotic activity of Tan IIA arises in part from immunomodulation, enhancing $CD4^+$ and $CD8^+$ T-cell function to enhance immune surveillance.[73] Subsequently, Shi *et al.*[74] established that Tan IIA alleviates liver injury and dysfunction through coordinated regulation of multiple pathways (MAPK, PI3K/Akt, Wnt), which collectively reduce extracellular matrix deposition and suppress HSC activation.

This multitarget profile is echoed in studies of *S. miltiorrhiza* (*Danshen*)-based formulas. You *et al.*[75] identified an epithelial membrane protein 1-labeled HSC subpopulation driving fibrosis-to-hepatocellular carcinoma (HCC) progression and four core prognostic genes (*NPY1R*, *CTHRC1*, *IGFBP3*, *ADH1B*). Network pharmacology analysis revealed *Danshen* as a potential agent targeting all four genes. Qi *et al.*[76] showed that Fuzheng Huayu formula attenuates HSC activation by suppressing α-smooth muscle actin and blocking the EGFR/ERK cascade. Research on specific compositions includes the Dan-Tao formula. Zeng *et al.*[77] predicted and validated that Dantao formula (DTF) alleviates fibrosis and portal hypertension by inhibiting endothelin-1/endothelin receptor type A/Rho-associated coiled-coil containing protein kinase signaling and activating the cyclic adenosine monophosphate/protein kinase A pathway in HSCs. In addition, Hong *et al.*[78] found that the *Gancao–Danshen* herb pair improves liver histology and reduces inflammation, with network pharmacology identifying STAT3 as a key target and quercetin as a high-affinity component. Clinical evidence indicates that *Danshen*-containing formulations can improve liver function tests and reduce serum fibrosis markers in patients with chronic liver disease, supporting their translational anti-fibrotic potential.

3.4. Inflammatory bowel disease (IBD)

IBD comprises a group of chronic immune-mediated disorders, clinically classified into Crohn's disease, ulcerative colitis (UC), and indeterminate colitis, the last of which exhibits hybrid pathologic features.[79] Its clinical presentation typically includes diarrhea, abdominal pain, and bloody stools, often accompanied by varying degrees of extraintestinal manifestations.[80] The pathogenesis of IBD is multifactorial, arising from complex interactions between host genetics, intestinal immune dysregulation, and environmental factors.[81]

Central to the inflammatory cascade in IBD are key signaling pathways. The NF-κB pathway is a master transcriptional regulator of pro-inflammatory gene expression and a critical therapeutic target. Its activation can be triggered by various stimuli, including Toll-like receptor ligands, cytokines, and bacterial products.[82] Following activation, NF-κB undergoes nuclear translocation and subsequently activates the transcription of cytokine genes, including TNF-α, IL-1β, and IL-6, thereby driving the inflammatory response in IBD.[83] In a coordinated manner, the JAK/STAT pathway transduces downstream signals from cytokines such as TNF-α, IL-6, and interferon-γ, regulating the expression of immune- and inflammation-related genes.[33] Clinically, modulation of this pathway can alleviate inflammation and promote mucosal healing in patients with IBD.[84] Research further indicates that Tan IIA exerts its therapeutic effects, at least in part, through the targeted regulation of key inflammatory pathways such as NF-κB.[16]

Supporting this mechanistic insight, experimental studies provide direct evidence. Zhu *et al*.,[85] utilizing a murine UC model combined with colon tissue metabolomic analysis (UPLC-Q-Exactive Orbitrap/MS), demonstrated that Tan IIA significantly improves the disease activity index and ameliorates colonic pathological damage. This therapeutic effect was closely associated with the regulation of serum inflammatory factors (e.g., TNF-α, IL-1β, IL-6, IL-10) and correction of dysregulated taurine and hypotaurine metabolism in the colon.

Translating these findings to the clinical setting, meta-analyses highlight the efficacy of *Danshen*-based formulations. Zhang *et al*.[86] performed a systematic review and meta-analysis covering 26 clinical trials and 11 animal studies. Their results demonstrated that combining *Danshen*-based preparations with mesalazine resulted in a significantly greater clinical response rate (risk ratio = 1.86, 95% confidence interval = 1.83–1.88) in UC patients, modulated platelet parameters, and reduced levels of inflammatory markers, including C-reactive protein, TNF-α, and IL-6. They noted that these findings should be interpreted with caution due to methodological limitations such as inadequate allocation concealment and blinding in some of the included studies. In a subsequent network meta-analysis evaluating nine Chinese patent medicines combined with 5-aminosalicylic acid, which included 70 randomized controlled trials involving 5,973 patients, Zhang *et al*.[87] found that the *S. miltiorrhiza* injection combination ranked first in reducing TNF-α levels among all compared regimens, further supporting the anti-inflammatory role of *Danshen* in UC management.

4. Cancers

Despite significant advancements in cancer treatment, this multifactorial disease continues to be a primary cause of premature death.[88] The process of tumorigenesis and subsequent progression is a multifaceted phenomenon arising from the complex interplay between cancer cells and the TME.[89] The TME is a complex ecosystem that extends beyond malignant cells to incorporate immune-inflammatory components, stromal fibroblasts, vascular networks, and a variety of chemoattractants and signaling cytokines.[90] During the formation of a tumor, cancer cells and the TME engage in continuous interaction, collectively regulating tumor progression.[18] Tan IIA exerts its antitumor effects through pleiotropic mechanisms involving apoptosis induction, proliferation suppression, angiogenesis/metastasis blockade, and TME modulation.[13,91,92] NF-κB signaling demonstrates context-dependent duality (pro-/antitumor) through genetic–microenvironmental interplay; its balance depends on differential pathway regulation in tumor–stroma interactions.[93] Furthermore, there are other mechanisms of action involving key signaling pathways such as PI3K/Akt/mTOR and MAPK, which demonstrate multitarget and multi-pathway anti-tumour potential.[2,73,94-96]

4.1. Gastric cancer (GC)

GC is a significant global health challenge among GI tract oncological diseases.[97] Despite a downward trend in morbidity and mortality rates, it remains a significant health concern, occupying the fifth position in the global cancer burden.[98] The prevailing management of GC primarily relies on surgery combined with chemotherapy. Emerging evidence highlights the therapeutic potential of *S. miltiorrhiza* in complementary GC management. Its active constituent Tan IIA demonstrates antineoplastic activity through induction of differentiation and apoptosis.[73]

The anticancer efficacy of Tan IIA stems from its ability to act on multiple molecular targets. It blocks cell surface receptors, including the EGFR and human epidermal growth factor receptor 2, thereby suppressing downstream proliferative signaling.[2] Furthermore, Tan IIA triggers cell cycle arrest and induces apoptosis in cancer cells through inhibition of key regulators in the PI3K/Akt/mTOR pathway.[99] This pathway, crucial for controlling cell proliferation and growth, is a recognized therapeutic target in cancer.[2] Notably, Tan IIA also suppresses proliferative activity in cancer cells through the JAK/STAT pathway and its downstream effectors, such as the cell cycle regulator forkhead box M1.[100] The clinical relevance of JAK/STAT signaling in GC is underscored by its distinct activity

patterns in different molecular subtypes, where specific activation signatures serve as prognostic indicators.[101]

Expanding its mechanistic repertoire, recent evidence reveals that Tan IIA potently inhibits the proliferation of GC cells (e.g., MGC803) under anaerobic conditions—a microenvironment linked to drug resistance. Proteomics and Kyoto Encyclopedia of Genes and Genomes pathway analysis demonstrated that this effect is mediated through the disruption of hypoxia-driven glycolysis. This was validated by significant reductions in glucose uptake, lactate production, ATP synthesis, and downregulation of key glycolytic enzymes, including glyceraldehyde-3-phosphate dehydrogenase and lactate dehydrogenase A.[102] These findings position Tan IIA as a potential agent against anaerobic, treatment-resistant solid tumors.

Importantly, Tan IIA exhibits synergistic effects when combined with other anticancer agents, including cisplatin, doxorubicin, TNF-related apoptosis-inducing ligand, and gefitinib, thereby enhancing their cytotoxic activity and potentially overcoming drug resistance.[2] These properties, alongside its direct antitumor mechanisms, support its potential as a combination therapy agent in oncology. The clinical study by Wu *et al.*[103] demonstrated that adjunctive use of *Danshen* injection during postoperative adjuvant chemotherapy for GC accelerated the decline of tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, significantly prolonged progression-free survival, and reduced chemotherapy-related adverse reactions, such as myelosuppression and hepatotoxicity. Together, this evidence solidifies its profile as a promising combinatorial agent. However, further research in animal models and human subjects is warranted to fully elucidate and validate these synergistic benefits.

4.2. Liver cancer

Hepatocellular carcinoma represents a major global health challenge, ranking as the sixth most common cancer worldwide and the third leading cause of cancer-related mortality (second among males), with its incidence steadily rising.[104] Among primary liver cancers, HCC and intrahepatic cholangiocarcinoma constitute the most prevalent histological types.[105]

Investigation of traditional Chinese medicine (TCM) represents a promising avenue for optimizing HCC therapeutics, particularly in advanced-stage disease. Tan IIA, a bioactive compound derived from *S. miltiorrhiza*, exhibits potent anti-HCC activity by suppressing proliferation, inducing cell cycle arrest, promoting apoptosis, and inhibiting metastasis and invasion.[106,107] These effects are mediated through the modulation of multiple oncogenic signaling pathways and contribute to the reversal of therapeutic resistance.[107]

Specifically, the pro-apoptotic effects of Tan IIA involve multiple pathways, including the activation of upstream initiator caspases, such as caspase-8 or caspase-9, with concomitant upregulation of their expression, alongside protein modulation mediated in part through the miR-30b/p53/PTPN11/SHP2 signaling pathway.[106] Furthermore, Tan IIA exerts additional antitumor effects by inhibiting cytochrome P450 in HCC cells, which not only contributes to apoptosis but also induces macrophage polarization, thereby enhancing macrophage-mediated killing of HCC.[108]

At the molecular level, Tan IIA directly targets the MAPK pathway by suppressing its expression and phosphorylation, and blocks both activation and expression of downstream MAPK cascade effectors, including ERK, JNK, and p38 MAPK. In addition, Tan IIA indirectly modulates MAPK signaling by upregulating reactive oxygen species (ROS) in cancer cells.[106] Beyond MAPK, Tan IIA inhibits HCC progression by modulating N6-methyladenosine (m6A) RNA methylation. Experimental studies demonstrate that Tan IIA suppresses HCC cell proliferation, invasion, stemness, and tumor growth in xenograft models, concomitantly downregulating the methyltransferase-like 3 (METTL3) and its target gene *TRIB3*. Mechanistically, Tan IIA attenuates METTL3-mediated m6A modification of *TRIB3* mRNA, thereby decreasing its stability and expression, identifying the METTL3/TRIB3 axis as a critical mediator of its antitumor effects.[109] Moreover, Tan IIA impedes HCC cell migration by inducing profound actin cytoskeleton remodeling, characterized by retraction of actin-based protrusions and disruption of intracellular networks. This effect is achieved through inhibition of *de novo* protein synthesis, leading to significant downregulation of actin and Rho GTPases.[110]

In addition, Tan IIA exhibits considerable potential for synergistic combination therapy with other anticancer agents. Combined administration with Adriamycin achieves a higher tumor inhibition rate (73.18%) in HepG2 xenograft models compared to monotherapy, while mitigating Adriamycin-induced hepatotoxicity. This synergy is associated with upregulation of CYP3A4 expression, and molecular docking analyses suggest that both compounds interact with the pregnane X receptor.[111]

Similarly, Tan IIA enhances the efficacy of sorafenib by normalizing tumor vasculature and alleviating hypoxia via the PI3K/AKT pathway, resulting in reduced expression of HIF-1α and HIF-2α and improvement of the TME, thereby augmenting sorafenib's antitumor and anti-metastatic effects.[92] Further studies confirm that Tan IIA suppresses

HIF-1α/HIF-2α signaling through PI3K/AKT, preserves vascular integrity, and inhibits HCC cell adhesion to the endothelium, collectively enhancing sorafenib activity.[92] Synergistic effects have also been observed with compounds such as SC-1, trans-resveratrol, and 5-fluorouracil (5-FU) in combination with sorafenib.[106]

In line with the "stasis-toxicity homeopathy" theory, the combination of *S. miltiorrhiza* with arsenic trioxide enhances tumor-killing efficacy without increasing metastatic risk, underscoring Tan IIA's promising potential as an effective and low-toxicity anticancer agent.[112] Supporting this, the Chinese medicine ShuangDan Capsules (containing *S. miltiorrhiza*) combined with sorafenib synergistically suppresses tumor growth, downregulates VEGF and Ki67, promotes caspase-3-mediated apoptosis, inhibits the PI3K/Akt/mTORC1 pathway, and reduces sorafenib-induced hepatotoxicity.[113] Collectively, these findings support Tan IIA as a promising adjunctive therapeutic agent for HCC.

4.3. Colorectal cancer (CRC)

CRC represents a major global health challenge, accounting for approximately 10.2% of all malignancies worldwide and ranking second only to lung cancer as a leading cause of cancer-related mortality.[114] Its pathogenesis involves complex interactions among genetic susceptibility, environmental factors, and chronic intestinal inflammation.[115] Notably, patients with IBD face a 2–3-fold increased risk of developing CRC, with risk correlating directly with the duration and severity of intestinal inflammation.[116] While multimodal therapy remains the cornerstone of CRC treatment, population-level analyses indicate that 5-year survival rates have plateaued at approximately 64–67%, highlighting a pressing need for novel and more effective therapeutic strategies.[117] Given these limitations, Tan IIA has emerged as a promising candidate due to its ability to suppress tumor proliferation, induce apoptosis, and reverse multidrug resistance, thereby potentially improving CRC prognosis.[13]

Current clinical management of CRC encompasses surgical resection, chemotherapy, radiotherapy, immunotherapy, and laser-based interventions.[118] Among these, chemotherapy is widely used but is frequently limited by the development of drug resistance and significant systemic toxicity.[119] Natural products, such as Tan IIA, represent a potential avenue to mitigate treatment-related adverse effects while enhancing therapeutic efficacy.

Research has demonstrated the multifaceted anticancer mechanisms of Tan IIA in CRC. It directly suppresses tumor cell proliferation, induces apoptosis, and inhibits migration and invasion. These effects are mediated through the downregulation of mTOR and VEGF signaling, as well as the induction of autophagy via the MEK/ERK/mTOR pathway, thereby restricting tumor growth and angiogenesis and reducing metastatic potential and recurrence.[11,12]

Furthermore, Tan IIA modulates multiple critical signaling pathways: it reverses epithelial–mesenchymal transition by targeting the β-arrestin1/β-catenin axis,[120] suppresses pro-survival signaling by inhibiting NF-κB-regulated targets (e.g., cyclooxygenase-2, c-Myc, Bcl-2, p-p65),[121] and exerts antiproliferative effects through ROS/JNK pathway-mediated induction of autophagy and apoptosis.[122] Network pharmacology and molecular docking analyses further identify the PI3K/AKT pathway as a key molecular target of Tan IIA, with its core targets showing significant associations with patient prognosis and tumor immune infiltration.[123,124]

A particularly compelling aspect of Tan IIA's profile is its potent activity in overcoming chemotherapy resistance, a major clinical hurdle. Tan IIA reverses 5-FU resistance by disrupting the S-phase kinase–associated protein 2/Akt/hexokinase 2 axis to inhibit aerobic glycolysis and by enhancing ubiquitin-mediated degradation of survivin via the Akt/WEE1 G2 checkpoint kinase/cyclin-dependent kinase 1 pathway.[94,125] Similarly, Tan IIA reverses oxaliplatin resistance by upregulating miR-30b-5p, thereby downregulating the anti-apoptotic protein apoptosis, and caspase activation inhibitor.[126] It also induces ferroptosis, a novel form of cell death, by downregulating SLC7A11 expression through inhibition of the PI3K/AKT/mTOR pathway.[127] These chemosensitizing effects are synergistic, as evidenced by the enhanced efficacy of Tan IIA in combination with an ubiquitin-specific protease 2 inhibitor in overcoming 5-FU resistance.[125]

Beyond direct cytotoxic and chemosensitizing effects, Tan IIA favorably modulates the TME. It exerts anti-angiogenic effects by downregulating HIF-1α, which suppresses the release of critical pro-angiogenic factors such as VEGF and impairs endothelial cell function.[13] Supporting evidence from related cancer models suggests that Tan IIA protects normal tissues (e.g., vasculature) from chemotherapeutic damage and reduces metastatic potential,[92] principles that may extend to CRC therapy. Preliminary translational evidence includes findings that drug serum containing Tan IIA induces time- and concentration-dependent antiproliferative and pro-apoptotic effects in chemoresistant Caco-2 cells,[128] and that the transcription factor Ikaros family zinc finger protein 1—within a pathway targeted by Tan IIA—inhibits tumor progression through the JAK/STAT pathway.[129]

In summary, preclinical studies demonstrate that Tan IIA inhibits CRC through a multitarget mechanism, encompassing direct tumor suppression, reversal of multidrug resistance, and modulation of the TME. Although clinical validation remains necessary, current evidence supports Tan IIA as a promising adjunctive therapeutic agent, particularly for overcoming treatment resistance in CRC.

To systematically summarize the available evidence, two summary tables are provided. Table 1 synthesizes key preclinical studies of Tan IIA in gastric, hepatic, and intestinal diseases, detailing experimental models, interventions, molecular mechanisms, and the strength of evidence. Table 2 summarizes clinical studies of *S. miltiorrhiza*-containing preparations in the corresponding diseases, highlighting study design, efficacy, and safety outcomes.

In addition, Figure 2 presents the pleiotropic mechanisms of Tan IIA across GI and hepatic diseases, summarizing its coordinated regulation of multiple signaling targets through a multitarget network.

5. Translation and challenges

Tanshinone IIA shows promise based on extensive investigation of its molecular mechanisms for treating GI and hepatic diseases. However, its translation from basic research to clinical application faces critical challenges in pharmacokinetics, safety, formulation optimization, clinical translation, and regulatory standards—all of which require systematic evaluation and methodological breakthroughs.

5.1. Adsorption, distribution, metabolism, and excretion and bioavailability

The inherent lipophilicity of Tan IIA results in poor aqueous solubility and a low dissolution rate, leading to extremely low oral bioavailability, which represents a primary bottleneck for its clinical application.[130,131]

Pharmacokinetic studies in rats demonstrate that Tan IIA is widely distributed after oral administration, with tissue concentrations ranking from highest to lowest: stomach > small intestine > lungs > liver > fat > muscle > kidneys > spleen > heart > plasma > brain > testes. However, plasma exposure remains low, further confirming its poor oral bioavailability.[132] Compared to pure Tan IIA, co-existing components in the liposoluble *S. miltiorrhiza* extract significantly increase Tan IIA's area under the concentration–time curve ($AUC_{0-\infty}$) in tissues such as the prostate, liver, and heart, suggesting that these components may promote its distribution and absorption by modulating metabolic processes.[133] Supporting this, components such as *Lignum Dalbergiae odoriferae* in *Xiangdan* injection suppress the metabolic breakdown and clearance of diterpene quinones, thereby enhancing Tan IIA bioavailability upon intravenous administration in rats.[134]

Similarly, combining *Panax notoginseng* saponin extract and borneol with *S. miltiorrhiza* enhances Tan IIA brain delivery and shortens its time to peak concentration (tmax) in plasma and brain.[135] However, disease-specific adsorption, distribution, metabolism, and excretion data for Tan IIA in the context of GI and hepatic pathologies (e.g., inflammation, fibrosis, cancer) remain limited. The specific impact of these states on Tan IIA's absorption, distribution, metabolism, and excretion therefore warrants targeted investigation.

5.2. Toxicity and safety

Current evidence suggests that Tan IIA-related preparations have relatively low toxicity and are considered safe in conventional TCM practice.[136] However, potential risks and important data gaps remain. Long-term or high-dose use of *S. miltiorrhiza* may be associated with organ-specific toxicity, including hepatotoxicity,[130] linked to dosage, formulation, and individual metabolic differences. A meta-analysis of eight *S. miltiorrhiza* injections across 148 randomized controlled trials (RCTs), encompassing 14,979 patients, reported mild and tolerable adverse events (e.g., nausea, headache, rash, dizziness) in only 24 trials.[137]

The water-soluble derivative sodium TAN IIA sulfonate (STS) also shows a favorable safety profile in clinical trials. For example, in patients with non-ST–elevation acute coronary syndrome, STS reduced 30-day major adverse cardiac events without increasing bleeding risk or other clinically significant adverse effects.[138] Nonetheless, human clinical evidence regarding Tan IIA toxicity remains limited, particularly for vulnerable populations (e.g., pregnant women, patients with hepatic or renal impairment). Clearly defined safety dose ranges and toxicity thresholds remain unavailable and require validation through rigorous, large-scale RCTs.

5.3. Formulation challenges and advances

To address poor solubility and bioavailability, various strategies have been developed, primarily focusing on nanocarriers, structural modifications, and compound compatibility. Nanocarrier systems include: pH-responsive calcium alginate nanoparticles (Tan IIA/CA);[131] galactose-modified pH-sensitive niosomes for liver targeting;[139] Tan IIA nanocrystal@liposome (TNC@Lipo) for hepatic fibrosis;[140] and specifically modified lipid nanocapsules.[72] These strategies enhance therapeutic outcomes by

Table 1. Preclinical studies of tanshinone IIA in gastric, hepatic, and intestinal diseases: Summary of models, interventions, mechanisms, and evidence

Disease	Model	Study type	Sample size	Intervention (dose)	Route of administration	Disease model
NAFLD	HepG2 cells	*In vitro* study	N/A	Tan IIA (10 μM)	Added to the culture medium	Palmitate-induced ER stress
NAFLD	RAW264.7 cells; $LDLR^{-/-}$ mice	*In vivo*+*in vitro* study	40	Tan IIA (7.5/15 mg/kg)	Added to medium+ intraperitoneal injection vs. oral gavage	HFD-induced mice; LPS-induced cell inflammation
NAFLD	HepG2 cells; Huh7 cells	*In vitro* study	N/A	Tan IIA (1–20 μM)	Added to the culture medium	Fatty acid-induced lipogenesis
NASH	C57BL/6J mice	*In vivo* study	50	Tan IIA (10/20 mg/kg/day)	Oral gavage	MCD diet-induced NASH
NAFLD	Preadipocytes; *Caenorhabditis elegans*; C57BL/6J mice	Gene editing+ i*n vivo*+i*n vitro* study	30	SMB extract (9/15 g/kg/day)	Added to medium+oral gavage	HFD-induced lipid deposition
Hypercholesterolemic hepatic steatosis	SD rats	*In vivo* study	64	Compound *Danshen* tablet (CDP) (0.095/0.189/0.378 g/kg)	Oral gavage	High-fat diet-induced model
NAFLD	C57BL/6J mice	*In vivo* study	40	*Xiao Zhi Fang* (2.835/5.67 g/kg/d)	Oral gavage	HFD-induced NAFLD
T2DM with NAFLD	Chinese Wuzhishan minipigs	*In vivo* study	9	FTZ (compound *Zhenzhu Tiaozhi* capsule) 1.2 g/kg/day	Oral	T2DM with NAFLD
Liver fibrosis	C57BL/6J mice	Network pharmacology analysis+i*n vivo* study	60	Tan IIA (10/20/40 mg/kg)	Oral gavage	CCl_4-induced liver fibrosis
Liver fibrosis	LX-2/HSC-T6 cells; C57BL/6 mice	*In vivo*+*in vitro* study	48	Tan IIA (10/20/40 mg/kg)	Added to medium+oral gavage	CCl_4-induced mice; TGF-β1–induced HSC activation
Liver fibrosis	LX-2 cells; Wistar rats	Network pharmacology prediction+*in vivo*+*in vitro* study	30	Tan IIA (10 mg/kg)	Added to medium+oral gavage	CCl_4-induced rats; HSC activation model
Liver fibrosis	HSCs; C57BL/6 mice	Network pharmacology prediction+*in vivo*+*in vitro* study	40	*Fuzheng Huayu* formula (2.8/5.6 g/kg/day)	Added to medium+oral gavage	CCl_4-induced; EGF-induced HSC activation
Liver fibrosis and portal hypertension	LX-2 cells; C57BL/6 mice	Network pharmacology prediction+*in vivo*+*in vitro* study	75	*Dan Tao* formula (2.7/6.4 g/kg)	Added to medium+oral gavage	CCl_4-induced; ET-1–induced HSC activation
Liver fibrosis	SD rats	Untargeted metabolomics+ network pharmacology analysis	50	Licorice–*Danshen* compound (0.1 g/mL)	Oral gavage	CCl_4-induced chronic liver fibrosis
UC	C57BL/6J mice	*In vivo* study	30	Tan IIA (20/40/60 mg/kg)	Intraperitoneal injection	DSS-induced UC model

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
Gastric cancer	MGC803 cells	*In vitro* study+proteomics analysis	N/A	Tan IIA (0–200 μmol/L)	Added to the culture medium	Normoxic/ hypoxic culture model
HCC	Hep3B cells; Huh-7 cells; THLE-2 cells; BALB/c nude mice	*In vivo+in vitro* study	N/A	Tan IIA (10 mg/kg/d)	Added to medium+ injection	HCC model; nude mouse xenograft model
HCC	97H/Huh7 cells; nude mice	*In vivo+in vitro* study	9	Tan IIA (5 mg/kg)	Added to medium+oral gavage	HCC cell migration and cytoskeleton morphology model; xenograft model
HCC	BALB/c nude mice	*In vivo* study+ computational simulation	20	Tan IIA (15 mg/ kg)+doxorubicin	Tail vein injection	HepG2 xenograft
HCC	SD rats; BALB/c nude mice	*In vivo* study	40	Shuang Dan Capsule (SDC) (33.4/50/2 mg/kg) ± Sorafenib	Oral gavage	Chemically-induced HCC (DEN); cell line xenograft (HepG2); growth factor-induced angiogenesis (VEGF–Matrigel)
CRC	HCT-116/LoVo cells; BALB/c nude mice	*In vivo+in vitro* study	40	Tan IIA (0.5/1/2 mg/kg)	Added to medium+tail vein injection	CRC lung metastasis model
CRC	SW480 cells; SCID mice	*In vivo+in vitro* study	30	Tan IIA (20 mg/kg)	Added to medium+oral gavage	Proliferation/ apoptosis model
CRC	HCT116/SW480 cells	Network pharmacology prediction+ database validation+ molecular docking+*i n vitro* study	N/A	Tan IIA (2.5–80 μM)	Added to the culture medium	Proliferation/ migration/ apoptosis model
CRC (5-FU resistant)	Resistant cells; nude mice	*In vivo+in vitro* study	29	Tan IIA (5 mg/kg)	Added to medium+ intraperitoneal injection	5-FU resistance model
CRC (oxaliplatin resistant)	Resistant cells	*In vitro* study	N/A	Tan IIA (concentration not specified)	Added to the culture medium	Oxaliplatin resistance model
CRC	OUMS23 cells	*In vitro* study	N/A	Tan IIA (0–20 μM)	Added to the culture medium	Proliferation/ apoptosis/ ferroptosis model
CRC (resistant)	Caco-2 cells; SD rats	*In vitro* study (using drug-containing serum)	N/A	*Qifang Weitong* granule-containing serum (2.5%, 5.0%, 10.0%, 20.0%)	Added to the culture medium	Cell proliferation/ apoptosis model

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
NAFLD	Alleviated hepatocyte damage, apoptosis, and lipid accumulation	Cell viability, apoptosis, caspase-3, TG, WB (ER stress proteins)	Pharmacological inhibition; readouts (WB)	Associative	[a]	Wang *et al.*[57]
NAFLD	Reduced atherosclerotic plaques and hepatic steatosis; anti-inflammatory effects associated with inhibition of the MAPKs/NF-κB pathway	Histopathology, serum biochemistry, inflammatory cytokines (ELISA), WB (phosphorylated proteins)	Pharmacological inhibition; rescue experiment; readouts (e.g., WB)	Mechanistic (gain-of-function)	[c]	Zhang *et al.*[61]
NAFLD	Inhibited expression of key lipogenic genes and reduced lipid accumulation in hepatocytes	RT-qPCR, Western blot, TG content, molecular docking	Pharmacological inhibition; readouts (RT-qPCR, WB, molecular docking)	Associative	[b]	Gao *et al.*[58]
NASH	Attenuated hepatic steatosis, inflammation, and fibrosis via the PPARα/FGF21 axis to alleviate ER stress	Histopathology, biochemistry, lipidomics, transcriptomics, WB	Pharmacological inhibition/activation; readouts (multi-omics data, WB)	Associative	[b]	Pi *et al.*[60]
NAFLD	Activated TFEB, reduced lipid deposition, improved NAFLD phenotype, and remodeled gut microbiota	TFEB nuclear translocation imaging, lipid staining, metabolic parameters, RNA sequencing, 16S rRNA sequencing	Gene knockout; pharmacological activation; rescue experiment; readouts (imaging, sequencing, etc.)	Mechanistic (loss-of-function and gain-of-function)	[c]	Zheng *et al.*[62]
Hypercholesterolemic hepatic steatosis	Improved blood lipids, liver function, reduced hepatic lipid droplet accumulation, and collagen fiber deposition	Serum biochemistry, liver/aorta histology, immunofluorescence, WB (Adipor1, PPARα, CYP27A1), metabolomics	Pharmacological inhibition/ activation; readouts (immunofluorescence, WB, metabolomics)	Associative	[b]	Li *et al.*[64]
NAFLD	Reduced obesity, adipocyte hypertrophy, hepatic lipid accumulation, and steatosis; improved glucose/ lipid metabolism and oxidative stress	Body/liver/fat weight, H and E and Oil Red O staining, serum biochemistry, insulin and glucose tolerance tests, oxidative stress markers, proteomics, RT-qPCR, WB	Pharmacological inhibition/activation; readouts (proteomics, RT-qPCR, WB)	Associative	[b]	You *et al.*[65]

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
T2DM with NAFLD	Decreased serum TG, TC, LDL-C, and FBG; increased HDL-C; improved insulin resistance; alleviated liver injury and steatosis	Serum biochemical parameters, liver histopathology, WB (PI3K/Akt phosphorylation, HIF-1α protein)	Pharmacological inhibition/activation; readouts (WB)	Associative	[b]	Wang *et al.*[66]
Liver fibrosis	Improved liver fibrosis, inhibited KRAS, PI3K/Akt and Nrf2/HO-1 signaling pathways, enhanced antioxidant capacity	Serum biochemistry, liver histopathology, WB, immunohistochemistry, antioxidant indices (SOD, GSH, MDA)	Pharmacological inhibition; readouts (WB, immunohistochemistry, biochemical indices)	Associative	[b]	Li *et al.*[69]
Liver fibrosis	Improved liver function, reduced collagen deposition; inhibited HSC viability and proliferation, arrested at G1 phase	Serum biochemistry, liver histopathology, CCK-8, colony formation, flow cytometry, WB, immunohistochemistry/ immunofluorescence	Pharmacological inhibition; readouts (WB, immunohistochemistry/ immunofluorescence, flow cytometry)	Associative	[b]	Liao *et al.*[71]
Liver fibrosis	Improved liver function, alleviated liver fibrosis, inhibited HSC activation and proliferation, and downregulated multiple targets, including c-Jun, c-Myc	Network pharmacology analysis, serum biochemistry, liver histopathology, WB (α-SMA, COL1A2, c-Jun, c-Myc, etc.)	Pharmacological inhibition; readouts (network pharmacology analysis, WB)	Associative	[b]	Shi *et al.*[74]
Liver fibrosis	Alleviated liver fibrosis, inhibited HSC activation, and downregulated phosphorylated-EGFR and the downstream ERK pathway	Network pharmacology analysis, serum proteomics, liver histopathology, WB (phosphorylated-EGFR, α-SMA, ERK pathway proteins)	Pharmacological inhibition; readouts (network pharmacology analysis, proteomics, WB)	Associative	[b]	Qi *et al.*[76]
Liver fibrosis and portal hypertension	Alleviated liver fibrosis and portal hypertension, inhibited ET-1/ EDNRA/ROCK axis, activated cAMP/PKA signaling	Portal pressure measurement, liver histology, hydroxyproline content, ELISA, WB, immunohistochemistry/ immunofluorescence	Pharmacological inhibition/activation; readouts (network pharmacology analysis, WB, immunohistochemistry/ immunofluorescence, ELISA)	Associative	[b]	Zeng *et al.*[77]

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
Liver fibrosis	Improved liver histomorphology, inhibited collagen hyperplasia and inflammation, and regulated metabolic pathways	Liver histopathology, UPLC-Q-TOF/MS, metabolic pathway analysis, network pharmacology, and molecular docking	Computational prediction and omics correlation; readouts (metabolite profiles, network diagrams, molecular docking)	Predictive/ associative	[a]	Hong *et al.*[78]
UC	Improved general condition, reduced disease activity index and pathological score, modulated inflammatory cytokines and metabolic pathways	Disease activity index, colon pathology score, serum inflammatory cytokines (ELISA), and metabolomics analysis	Pharmacological inhibition/modulation; readouts (disease activity score, pathology score, inflammatory cytokines, metabolite profiles)	Associative	[b]	Zhu *et al.*[85]
Gastric cancer	Enhanced anti-proliferative effect under hypoxia, inhibited the glycolytic pathway	Proteomics analysis, glycolytic function indices (glucose uptake, lactate production, ATP synthesis), gene and protein expression	Pharmacological inhibition; readouts (proteomics, glycolytic function indices, gene/ protein expression)	Associative	[b]	Liu *et al.*[102]
HCC	Inhibited cell viability, proliferation, invasion, stemness, and induced apoptosis; suppressed tumor growth in vivo	Flow cytometry, Transwell, EdU/ MTT/CCK-8, sphere formation assay, RT-qPCR/WB (METTL3, TRIB3), m6A quantification, MeRIP/RIP, mouse tumor volume/weight	Pharmacological inhibition; readouts (WB, RT-qPCR, flow cytometry, etc.)	Associative	[b]	Jiang *et al.*[108]
HCC	Inhibited cell migration, induced cytoskeleton remodeling	Cell morphology and migration phenotype, fluorescence staining, WB, protein synthesis rate	Pharmacological inhibition; rescue experiment; readouts (cell morphology, fluorescence staining, WB)	Associative	[b]	Liang *et al.*[110]
HCC	Synergistic antitumor effect, reduced ADM toxicity, improved quality of life	Mouse general condition, body weight, tumor volume and inhibition rate, serum AST, liver histopathology, cytochrome P450 content and activity, WB (CYP3A4), molecular docking	Pharmacological intervention; computational simulation; readouts (tumor growth, biochemical indices, protein expression, docking data)	Associative	[b]	Liu *et al.*[111]
HCC	Combination enhanced antitumor effect, alleviated sorafenib-induced hepatotoxicity	MRI, tumor volume, and weight, immunohistochemistry (VEGF, Ki67, CD31, caspase-3), WB (PI3K/ Akt/mTORC1 pathway), serum biochemistry	Pharmacological inhibition; readouts (imaging, tumor growth, immunohistochemistry, WB, serum biochemistry)	Associative	[b]	Ding *et al.*[113]

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
CRC	Inhibited CRC cell proliferation, migration, invasion, and EMT; suppressed lung metastasis *in vivo*	CCK-8 (cell viability); Transwell and scratch assay (migration); WB, immunofluorescence, immunohistochemistry (protein expression); *in vivo* imaging (metastatic foci); H and E staining (tissue morphology)	Pharmacological inhibition; readouts (WB, immunofluorescence, cell migration)	Associative	[b]	Song *et al.*[120]
CRC	Inhibited cell proliferation and tumor growth, activated the ROS/JNK pathway, induced autophagy, and apoptosis	Cell viability, colony number, protein expression, apoptosis rate, ROS level, and tumor growth data	Pharmacological activation; readouts (cell function data, protein expression, tumor growth)	Associative	[b]	Qian *et al.*[122]
CRC	Inhibited cell proliferation and migration, induced apoptosis, decreased PI3K/Akt pathway protein expression	Network pharmacology analysis, database validation, molecular docking, CCK-8/colony formation/scratch assay, flow cytometry (apoptosis), WB (PI3K/AKT pathway)	Pharmacological inhibition; rescue experiment; computational prediction; readouts (network diagrams, enrichment analysis, docking scores, cell function, WB)	Associative	[b]	Sun *et al.*[124]
CRC (5-FU resistant)	Overcame 5-FU resistance, inhibited aerobic glycolysis	Glycolytic function assay, co-immunoprecipitation, WB (e.g., Skp2, p-Akt, HK2), *in vivo* tumor growth experiment	Pharmacological inhibition; target regulation mechanism; combination therapy/rescue experiment; readouts (protein–protein interaction, protein stability, pathway protein expression, glycolytic function, *in vivo* efficacy)	Mechanistic (functional modulation and combination intervention)	[c]	Dong *et al.*[125]
CRC (oxaliplatin resistant)	Upregulated miR-30b-5p, enhanced sensitivity to oxaliplatin	RT-qPCR (miR-30b-5p, AVEN mRNA), MTT, flow cytometry (apoptosis), Transwell (migration), dual-luciferase reporter assay, WB (apoptosis-related proteins)	Gene overexpression/inhibition; pharmacological intervention; target validation; readouts (gene expression, cell function, reporter activity, protein expression)	Associative	[b]	Ge and Zhang[126]
CRC	Inhibited cell proliferation, induced apoptosis, and ferroptosis	EdU (proliferation), flow cytometry (apoptosis, lipid ROS), iron assay kit, RT-qPCR/WB (SLC7A11, PI3K/AKT/mTOR pathway proteins)	Pharmacological inhibition; rescue experiment; readouts (cell proliferation, apoptosis, ferroptosis indices, gene/protein expression)	Mechanistic (functional modulation)	[b]	Ge *et al.*[127]

(Cont'd...)

Table 1. ***(Continued)***

Disease	Main outcomes	Measurement methods	Mechanistic evidence	Nature of evidence	Strength of evidence	References
CRC (resistant)	Inhibited cell proliferation, induced apoptosis	MTT assay (cell proliferation inhibition rate), flow cytometry (apoptosis rate)	Pharmacological inhibition; readouts (MTT absorbance, flow cytometry)	Associative	[a]	Zhang *et al.*[128]

Notes: [a]Preliminary mechanistic evidence: This level includes basic pharmacological interventions and phenotype/molecular readouts, supported by a relatively singular line of evidence. [b]Intermediate-strength mechanistic evidence: Building upon preliminary evidence, this level involves more in-depth mechanistic exploration (e.g., predicted target binding, validation of upstream/downstream pathway components), but lacks confirmatory experiments. [c]Stronger mechanistic evidence: This level incorporates multi-tiered validation (*in vivo* and *in vitro*) and employs confirmatory experimental approaches such as rescue experiments or genetic manipulations, establishing a more robust causal relationship.
Abbreviations: 5-FU: 5-fluorouracil; α-SMA: α-smooth muscle actin; ADM: Adriamycin; Akt: Protein kinase B; AST: Aspartate aminotransferase; AVEN: Apoptosis and caspase inhibition regulator; cAMP: Cyclic adenosine monophosphate; CCK-8: Cell Counting Kit-8; CCl_4: Carbon tetrachloride; CDP: Compound *Danshen* tablet; CRC: Colorectal cancer; DEN: Diethylnitrosamine; DSS: Dextran sulfate sodium; EDNRA: Endothelin receptor type A; EdU: 5-ethynyl-2'-deoxyuridine; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; ELISA: Enzyme-linked immunosorbent assay; EMT: Epithelial–mesenchymal transition; ER: Endoplasmic reticulum; ERK: Extracellular signal-regulated kinase; ET-1: Endothelin-1; FBG: Fasting blood glucose; FGF21: Fibroblast growth factor 21; GC: Gastric cancer; HCC: Hepatocellular carcinoma; HDL-C: High-density lipoprotein cholesterol; H&E: Hematoxylin and eosin; HFD: High-fat diet; HIF-1α: Hypoxia-inducible factor 1α; HK2: Hexokinase 2; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; KRAS: Kirsten rat sarcoma viral oncogene homolog; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MCD: Methionine–choline-deficient diet; MDA: Malondialdehyde; MeRIP: Methylated RNA immunoprecipitation; m6A: N6-methyladenosine; METTL3: Methyltransferase-like 3; mTOR: Mechanistic target of rapamycin; mTORC1: Mechanistic target of rapamycin complex 1; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2: Nuclear factor erythroid 2-related factor 2; PI3K: Phosphoinositide 3-kinase; PPARα: Peroxisome proliferator-activated receptor α; ROCK: Rho-associated protein kinase; ROS: Reactive oxygen species; RT-qPCR: Reverse transcription quantitative polymerase chain reaction; SD: Sprague–Dawley; Skp2: S-phase kinase-associated protein 2; SOD: Superoxide dismutase; SMB: *Salvia miltiorrhiza* Bge; STAT: Signal transducer and activator of transcription; T2DM: Type 2 diabetes mellitus; Tan IIA: Tanshinone IIA; TC: Total cholesterol; TFEB: Transcription factor EB; TG: Triglyceride; TGF-β: Transforming growth factor β; TRIB3: Tribbles pseudokinase 3; UC: Ulcerative colitis; UPLC-Q-TOF/MS: Ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry; VEGF: Vascular endothelial growth factor; WB: Western blot.

improving solubility, enabling controlled release, achieving organ-specific targeting, and increasing bioavailability, thereby resulting in improved efficacy *in vitro* or in animal models. Orally administered colon-targeting systems (e.g., based on *Eucommia ulmoides* rubber/acetylated starch)[11] and cell-penetrating peptide-modified "nano-in-micro" hierarchical microcapsules for enhanced oral absorption also show promise.[141]

Regarding structural modifications and compound-based strategies, the derivative STS is successfully used clinically for cardiovascular diseases.[106,142] Previous studies confirm that including borneol in compound *Danshen* colon-specific osmotic pump capsules increased Tan IIA's relative bioavailability to 448.70% in beagle dogs, significantly outperforming the formulation without borneol (350.97%).[143] However, most nanocarrier-based formulations remain at the preclinical stage. Their targeted efficacy for GI and hepatic diseases remains unvalidated in humans, and challenges related to scale-up production, stability, and biocompatibility require further resolution.

5.4. Preclinical–clinical gap

Preclinical studies confirm Tan IIA's effects in anti-fibrotic, antitumor, and anti-inflammatory activities, but a significant gap remains for clinical application. Clinically, only STS has substantial clinical trial data (e.g., for cardioprotection[138]). Large-scale, multicenter trials for GI and hepatic diseases (e.g., CG, cirrhosis, IBD, GI cancers) are severely limited. Promising preclinical results on the enhanced bioavailability and efficacy of nanoformulations or compound preparations are difficult to translate due to the absence of established interspecies dose conversion standards.[130] Furthermore, the complexity of herbal extracts and variability in preparation processes significantly impact Tan IIA's dissolution, absorption, and efficacy,[133] further complicating clinical translation. The clinical effectiveness of Tan IIA for treating GI and hepatic diseases remains unproven, underscoring the need for targeted clinical trials.

5.5. Regulatory considerations

Regulatory evaluation of Tan IIA-related preparations must integrate TCM characteristics with modern drug assessment standards. Beyond the approved STS, new formulation development faces multiple challenges, including: inconsistent quality control standards for raw materials and preparations, which affect efficacy consistency; insufficient long-term safety and biocompatibility data for innovative delivery systems, such as nanocarriers, which

Table 2. Clinical studies of *Salvia miltiorrhiza*-containing preparations in gastric, hepatic, and intestinal diseases: Summary of study design, efficacy, and safety evidence

Disease	Study design	Patient population	Intervention versus control	Treatment duration	Primary efficacy outcomes	Safety outcomes	Nature of evidence	Level of evidence	References
Chronic atrophic gastritis	Meta-analysis of RCTs	1,140 (12 RCTs)	Western medicine+Chinese herbal medicine (containing *Salvia miltiorrhiza*) versus Western medicine alone	7–90 days	Higher overall clinical response rate (RR=4.87, 95% CI 3.24–7.30, $P<0.00001$)	Lower incidence of adverse events	Systematic review/ meta-analysis based on RCTs	High	Weng *et al.*[48]
Chronic atrophic gastritis	Meta-analysis+trial sequential analysis of RCTs	1,143 (7 RCTs)	Moluodan (monotherapy/ combination) versus folic acid/vitamins	3–6 months	Improved pathological response rate (RR=1.37–1.73, $P<0.00001$)	Insufficient safety data	Systematic review/ meta-analysis based on RCTs	Moderate	Yu *et al.*[51]
Ulcerative colitis	Systematic review and meta-analysis	2,426 (26 trials)	*Salvia miltiorrhiza* preparation+mesalazine versus mesalazine alone	7 days–2 months	Increased clinical response rate (RR=0.86, 95% CI 0.83–0.88); improved inflammatory markers	No significant adverse events reported	Systematic review based on RCTs	Moderate	Zhang *et al.*[86]
Ulcerative colitis	Network meta-analysis of RCTs	5,973 (70 RCTs)	*Salvia miltiorrhiza* injection+ 5-ASA vs. 5-ASA alone	7 weeks–3 months	Ranked first in reducing TNF-α levels; improved multiple inflammatory markers	Lower incidence of adverse events	Indirect comparison evidence based on RCTs	Moderate	Zhang *et al.*[87]
Postoperative gastric cancer	Retrospective Observational Study	62	FOLFOX6 chemotherapy+*Salvia miltiorrhiza* injection versus FOLFOX6 alone	3 chemotherapy cycles	More significant decrease in tumor markers; prolonged PFS (8.78 vs. 7.50 months)	Lower incidence of myelosuppression, liver dysfunction, etc.	Clinical retrospective observational data	Moderate to Low	Wu *et al.*[103]

Abbreviations: 5-ASA: 5-aminosalicylic acid (mesalazine); CI: Confidence interval; FOLFOX6: Folinic acid, fluorouracil, and oxaliplatin regimen (a specific chemotherapy protocol); PFS: Progression-free survival; RCT: Randomized controlled trial; RR: Risk Ratio; TNF- α: Tumor necrosis factor α.

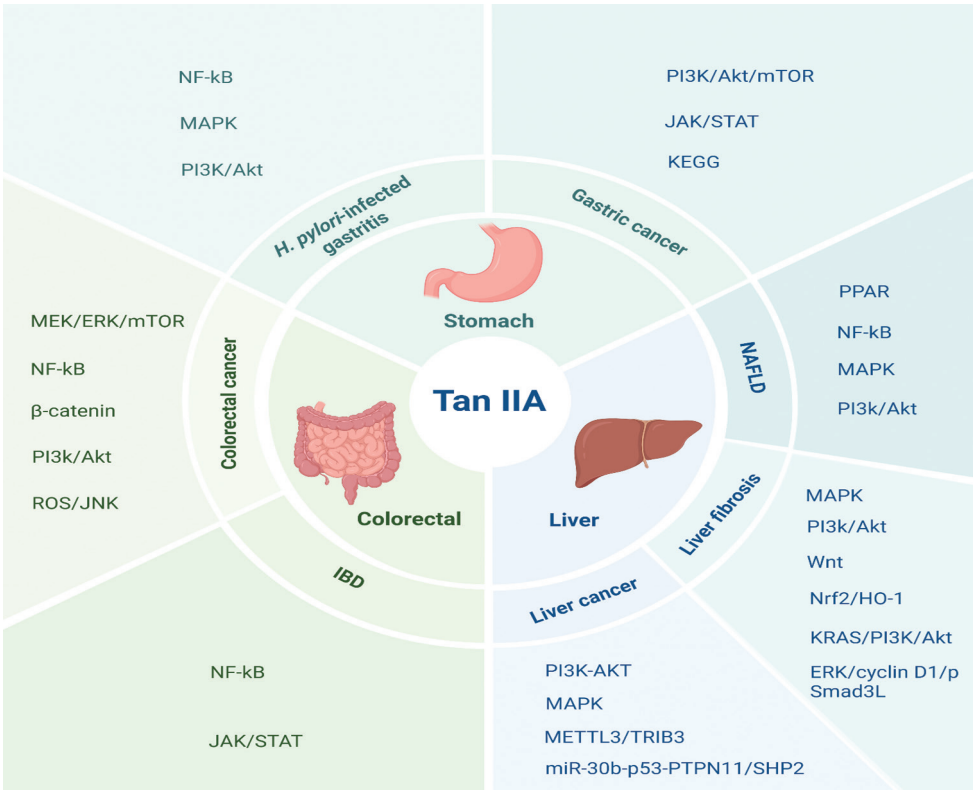


Figure 2. The core mechanisms of Tan IIA in gastrointestinal and hepatic diseases—a multitarget regulatory network. The figure was created using BioRender. (Source: yuke, X. (2026) https://BioRender.com/chkt3vq)
Abbreviations: IBD: Inflammatory bowel disease; NAFLD: Non-alcoholic fatty liver disease; Tan IIA: Tanshinone IIA.

Table 3. Translational roadmap for the clinical development of tanshinone IIA

Stage	Essential steps	Core objectives and content	Key deliverables
1. Candidate optimization and pharmaceutical development	Formulation optimization and locking	Finalize a stable targeted delivery system (e.g., nano-formulation) and characterize its physicochemical properties and *in vitro* efficacy	Stable candidate formulation with defined specifications; *in vitro* efficacy and mechanistic data
	GLP toxicology and safety assessment	Conduct systematic toxicology studies to determine NOAEL and a safe starting dose	GLP-compliant toxicology report; preliminary HED and safe starting dose
	GMP synthesis and manufacturing	Develop a GMP-compliant manufacturing process for API and drug product to ensure consistency	GMP-grade API and drug product; Complete QC/CMC documentation
2. IND-enabling studies	Preclinical PK	Assess the ADME profile and tissue distribution of the formulation in disease models	Comprehensive preclinical PK report to inform human dosing
	Efficacy biomarker exploration	Identify and validate mechanism-related biomarkers for tanshinone IIA	A validated panel of potential efficacy biomarkers for clinical use
	Patient stratification and protocol design	Define the target patient population and design a Phase I/II clinical trial protocol	Detailed clinical protocol with inclusion/exclusion criteria and endpoints
3. Regulatory submission and clinical initiation	IND preparation and submission	Compile and submit an IND application to regulatory authorities	Complete IND application package; regulatory feedback/approval.
	Phase I clinical trial	Evaluate safety, tolerability, and PK in humans to determine MTD and RP2D	Human safety, tolerability, and PK data; established RP2D
	Phase II clinical trial	Conduct preliminary efficacy and safety assessment in target patients to inform Phase III design	Preliminary efficacy and safety evidence; optimized Phase III trial design

Abbreviations: ADME: Absorption, distribution, metabolism, and excretion; API: Active pharmaceutical ingredient; CMC: Chemistry, manufacturing, and controls; GLP: Good laboratory practice; GMP: Good manufacturing practice; HED: Human equivalent dose; IND: Investigational New Drug (application); MTD: Maximum tolerated dose; NOAEL: No observed adverse effect level; PK: Pharmacokinetics; RP2D: Recommended phase II Dose; QC: Quality control.

hinder comprehensive risk assessment;[130] and the absence of clear regulatory guidelines for herb–drug interactions (e.g., *Danshen Yin* promoting clopidogrel activation via CYP2C11/CYP2C22 modulation[144]).

To advance translation, future efforts within an appropriate regulatory framework should prioritize standardized pharmacokinetic and toxicokinetic studies, facilitate the progression of promising formulations into early-phase clinical trials, and establish evidence-based post-marketing surveillance systems, thereby systematically overcoming these barriers and enabling the successful transformation of Tan IIA from a natural compound into a modern therapeutic agent.

To delineate the clinical translation pathway for Tan IIA, a translational roadmap is constructed and summarized in Table 3. This table systematically outlines the key stages from preclinical research to clinical trial application, detailing the essential steps, core objectives and content, and key deliverables for each phase, thereby providing a structured and actionable reference framework for subsequent translational research.

6. Conclusion

Tanshinone IIA, a key pharmacologically active constituent of *S. miltiorrhiza*, demonstrates broad and significant therapeutic potential in preclinical studies of digestive system diseases. This review highlights that Tan IIA exerts pleiotropic effects in gastric, hepatic, and intestinal disease models by modulating key signaling cascades, including NF-κB, MAPK, PI3K/Akt, Wnt/β-catenin, and nuclear factor erythroid 2-related factor/heme oxygenase-1.

In gastric disorders, Tan IIA acts by inhibiting inflammatory mediators, protecting the gastric mucosa, and inducing apoptosis in GC cells. In hepatic diseases, it improves conditions such as fatty liver disease and hepatic fibrosis, while suppressing HCC progression via mechanisms encompassing anti-inflammatory and antioxidant effects, suppression of hepatic stellate cell activation, and induction of ferroptosis and apoptosis in liver cancer cells. In intestinal diseases, it exerts antitumor effects against CRC by regulating the epithelial–mesenchymal transition process and inducing ferroptosis and apoptosis in tumor cells.

Compared to single-target synthetic drugs, the core advantage of Tan IIA lies in its natural origin and multitarget properties. It can simultaneously modulate both inflammatory and proliferative processes, shows a lower tendency for drug resistance, and exhibits a favorable safety profile in preclinical models, offering unique value for intervention in complex disease networks.

Currently, the clinical application of Tan IIA and its compound preparations is primarily concentrated in the cardiovascular field (e.g., hyperlipidemia, hypertension, myocardial injury, myocardial infarction, cardiac hypertrophy, fibrosis, and heart failure[3]). Within gastroenterology, they serve mainly as adjunctive therapies for CG and UC, reflecting the holistic "treating different diseases with the same principle" approach of TCM. However, its promising preclinical efficacy in indications such as NAFLD, GC, HCC, and CRC has yet to translate into establishment as a core clinical therapy.

It is important to acknowledge the limitations of this review. First, the numerous *in vitro* and animal studies included were not subjected to a systematic evaluation of quality or risk of bias. Consequently, the reliability of the reported mechanisms of action and efficacy outcomes from these foundational studies requires further validation through future large-sample, multi-center preclinical research. Second, while the meta-analyses referenced herein aimed for methodological rigor, the original RCTs incorporated may themselves exhibit methodological shortcomings, such as inadequate reporting on blinding and allocation concealment, which somewhat limits the overall strength of the synthesized evidence. Furthermore, this review primarily synthesizes evidence from studies reporting positive outcomes, without systematically exploring potential heterogeneity or negative data. For instance, variations across studies in dosage (e.g., 6–200 μM), model systems (e.g., different cell lines or animal modeling methods), and experimental conditions (e.g., oxygen concentration) may lead to differences in effect magnitude and mechanistic emphasis. Reported signaling pathways (e.g., liver X receptor α/sterol regulatory element-binding protein 1 vs. PPARα/FGF21) or cell death modalities (e.g., caspase-3–dependent apoptosis, ROS/JNK pathway, ferroptosis) have not been systematically integrated or differentiated across models and disease stages. Additionally, discrepancies exist between experimentally validated pathways and computationally predicted targets.

Therefore, future research has a clear translational trajectory. Building upon a full recognition of the existing evidence hierarchy and its limitations, there is a need for more standardized experimental designs and direct comparative studies to further clarify Tan IIA's optimal therapeutic context and boundary conditions. Ultimately, promoting well-designed clinical trials to validate their efficacy and safety in major digestive system diseases, such as GC, liver cancer, and CRC, could provide patients with a novel, naturally derived, multitarget treatment option, thereby expanding the current therapeutic landscape.

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Conflict of interest

The authors declare no conflicts of interest.

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