Wuweizisu B for cancer treatment from multitarget mechanisms to precision delivery strategies (Review)

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Abstract. Wuweizisu B (WSB), a bioactive lignan derived from *Schisandra chinensis*, has shown promise as a multi-target anticancer agent with unique therapeutic advantages over conventional therapies. The present review systematically examined the molecular mechanisms underlying the anticancer effects of WSB, including induction of cell cycle arrest, promotion of apoptosis through mitochondrial and death receptor pathways, inhibition of epithelial-mesenchymal transition and remodeling of the tumor immune microenvironment. WSB exhibits synergistic potential with chemotherapy and immunotherapy and can reverse multidrug resistance (MDR) by modulating key pathways such as STAT3, P-glycoprotein (P-gp), and survivin. To address pharmacokinetic limitations, particularly low oral bioavailability, the present review discussed innovative delivery strategies such as nanotechnology-based formulations to enhance tumor targeting. Thus, with its pleiotropic mechanisms, low toxicity profile, and broad-spectrum efficacy across multiple cancers, the WSB merits further investigation as a complementary oncology therapeutic. However, its clinical translation faces challenges, including potential hepatotoxicity and lack of clinical validation. The present review consolidated current knowledge of WSB's anticancer potential while providing a roadmap for clinical development, emphasizing the need for biomarker-driven trials and precision delivery systems to fully realize its therapeutic value in personalized medicine.

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Abbreviations: 5-FU, 5-Fluorouracil; AR, androgen receptor; BC, breast cancer; CAC, colitis-associated cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; DTX, docetaxel; DOX, doxorubicin; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; GA, gomisin A; GBC, gallbladder cancer; GC, gastric cancer; GD, gomisin D; GG, gomisin G; GJ, gomisin J; HCC, hepatocellular carcinoma; IARC, International Agency for Research on Cancer; LC, lung cancer; LEN, lenvatinib; MDR, multidrug resistance; MET, mesenchymal-epithelial transition; mesenchymal-epithelial transition factor; NAFLD, non-alcoholic fatty liver disease; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PC, prostate cancer; P-gp, P-glycoprotein; Rb, retinoblastoma protein; ROS, reactive oxygen species; SA, Schisandrol A; SAL, Schisanhenol; SC, Schisandrin C; Sch A, Schisandrin A; STA, Schisantherin A; TCM, Traditional Chinese Medicine; TME, tumor microenvironment; TNBC, triple-negative breast cancer; WSB, Wuweizisu B

Key words: Wuweizisu B, multi-target therapy, cancer microenvironment, Traditional Chinese Medicine, drug resistance reversal

Contents

1. Introduction

The global cancer burden has reached alarming proportions, with the International Agency for Research on Cancer (IARC) reporting >20 million new cases and 9.7 million fatalities in 2022, a figure projected to surge to 35 million by 2050, creating an urgent need for innovative therapies that balance efficacy with safety (1). This escalating crisis has renewed interest in Traditional Chinese Medicine (TCM) as a source of complementary agents to counter the limitations of conventional treatments, such as toxicity and resistance (2,3), with *Schisandra chinensis* (Wu Wei Zi) emerging as a pivotal candidate. Its berries, called 'five flavors' (sour, sweet, bitter, pungent, and salty), are classified in the Chinese Pharmacopoeia (2020) as warm and sour-sweet (5), targeting lung/heart/kidney meridians for chronic cough and liver disorders (4-6). Critically, modern research has validated its systemic bioactivities: organ protection via Nrf2/NF-κB modulation to alleviate oxidative stress and inflammation (7,8), neuro-hepatic shielding through antifibrotic repair (9-11), and immune reprogramming via macrophage/Th1-Th2 regulation (12,13) (Fig. 1).

Among its bioactive lignans, Wuweizisu B (Schisandrin B, WSB) stands out as the premier anticancer agent (6,14-17) (Fig. 2), boasting exceptional bioavailability and tissue distribution (14,18) to orchestrate pleiotropic effects from hepatoprotection to proliferation control (19-22). Its structural analogs (such as schisandrin A/C and gomisins) synergistically combat cancer through direct tumor suppression (apoptosis/cell cycle arrest), metastasis blockade, microenvironment remodeling (immune activation), and chemosensitization (MDR reversal via STAT3/P-gp/survivin modulation) (4,17,23-27). Notably, WSB's ability to reverse MDR, a major driver of chemotherapy failure, positions it as a key ally against refractory cancers (28-30).

The present review therefore deciphered WSB's anticancer potential through molecular mechanisms, organ-specific efficacy, and clinical translation strategies as a dual chemosensitizer-cytoprotective agent, bridging traditional wisdom with contemporary pharmacology to chart a roadmap for integrated oncology (Figs. 3-6).

2. Targeting digestive cancers with WSB: Molecular insights and therapeutic prospects

As a prototypical multitarget natural compound, WSB exhibits remarkable therapeutic potential across a spectrum of gastrointestinal malignancies through its unique ability to simultaneously modulate oncogenic signaling networks, metabolic reprogramming, and tumor microenvironment remodeling. This section systematically elucidates the organ-specific anticancer mechanisms of WSB along the digestive tract, supported by compelling preclinical evidence highlighting it as a promising candidate for integrative oncology approaches (Fig. 3).

WSB induces G_0/G_1 *arrest in gastric cancer (GC): Role of STAT3 inhibition and dose-dependent effects.* GC remains a significant global health burden, with the IARC reporting ~968,000 new cases and 660,000 deaths worldwide in 2022, ranking fifth in incidence and mortality among all cancers (1,31). Chemotherapy and immunotherapy, have spurred interest in TCM as a complementary approach for GC treatment (32). WSB exhibits potent antitumor effects in GC. WSB exerts its antitumor effects through a coordinated molecular cascade: by effectively inhibiting STAT3 phosphorylation, WSB inactivates this oncogenic transcription factor, thereby blocking downstream survival genes (Bcl-2 and Survivin) and metastatic drivers (33) (Fig. 3; Table I). Crucially, suppression of STAT3 expression directly represses Cyclin D1 transcription (34) (Fig. 3) , leading to significant downregulation of the expression of Cyclin D1 mRNA, the core regulator of the G_1/S transition, which induces cell cycle arrest at the G_0/G_1 phase in SGC-7901 cells. Notably, the optimal inhibitory effect was observed at a concentration of 50 mg/l after 48 h of treatment (35) (Fig. 3; Table I). However, this therapeutic cascade is concentration dependent: while 50 mg/l optimally balanced these effects, higher doses (100 mg/l) paradoxically activated protective autophagy via reactive oxygen species (ROS)/NF-κB feedback, potentially compromising treatment efficacy (36) (Fig. 3).

Despite these advances, the precise molecular mechanisms underlying the anti-GC effects of WSB remain unclear. Furthermore, studies indicate that the effective *in vitro* concentration of WSB (50 mg/l) far exceeds the achievable peak plasma concentration in humans (2.1 μM) (37). Existing research is based solely on cell and mouse experiments and lacks tumor microenvironment simulation, which may lead to overestimation of clinical efficacy. Future studies should focus on elucidating these pathways to facilitate the clinical translation of WSB-based therapies.

Targeting TGF-β signaling and epithelial-mesenchymal transition (EMT): WSB's core mechanism against colorectal cancer (CRC). CRC ranks as the third most prevalent malignancy globally, with GLOBOCAN 2022 reporting 1.9 million new cases and 930,000 mortalities annually (38). Projections indicate that this burden will increase to 3.2 million cases by 2040, underscoring the urgent need for safer therapies. While current regimens combining 5-Fluorouracil (5-FU)-based chemotherapy with surgery/radiotherapy remain standard, ≥50% of patients experience grade 3-4 toxicity, including myelosuppression, gastrointestinal injury, and neurotoxicity (39,40). These limitations highlight the imperative for novel agents such as WSB that synergize with conventional therapies while mitigating adverse effects.

WSB exerts potent antiproliferative effects in CRC by inducing G_0/G_1 phase arrest in CRC cells through cyclin D1/cyclin-dependent kinase 4/6 (CDK4/6) suppression. Concurrently, it activates the CHOP-mediated unfolded protein response, triggering caspase-dependent apoptosis (41) (Fig. 3; Table I). WSB disrupts CRC progression by downregulating the expression of SIRT1, an NAD+-dependent deacetylase that is overexpressed in 60-70% of CRC cases (42) (Table I). This inhibition increases the level of SMAD ubiquitination regulatory factor 2 (SMURF2), which targets TGF-β receptors (TβRI/TβRII) for ubiquitin-mediated degradation, thereby suppressing TGF-β signaling at the receptor level (43,44) (Fig. 3). Consequently, WSB blocks TGF-β-induced EMT through two core mechanisms: i) inhibition of the SMAD-dependent pathway, in which SMURF2

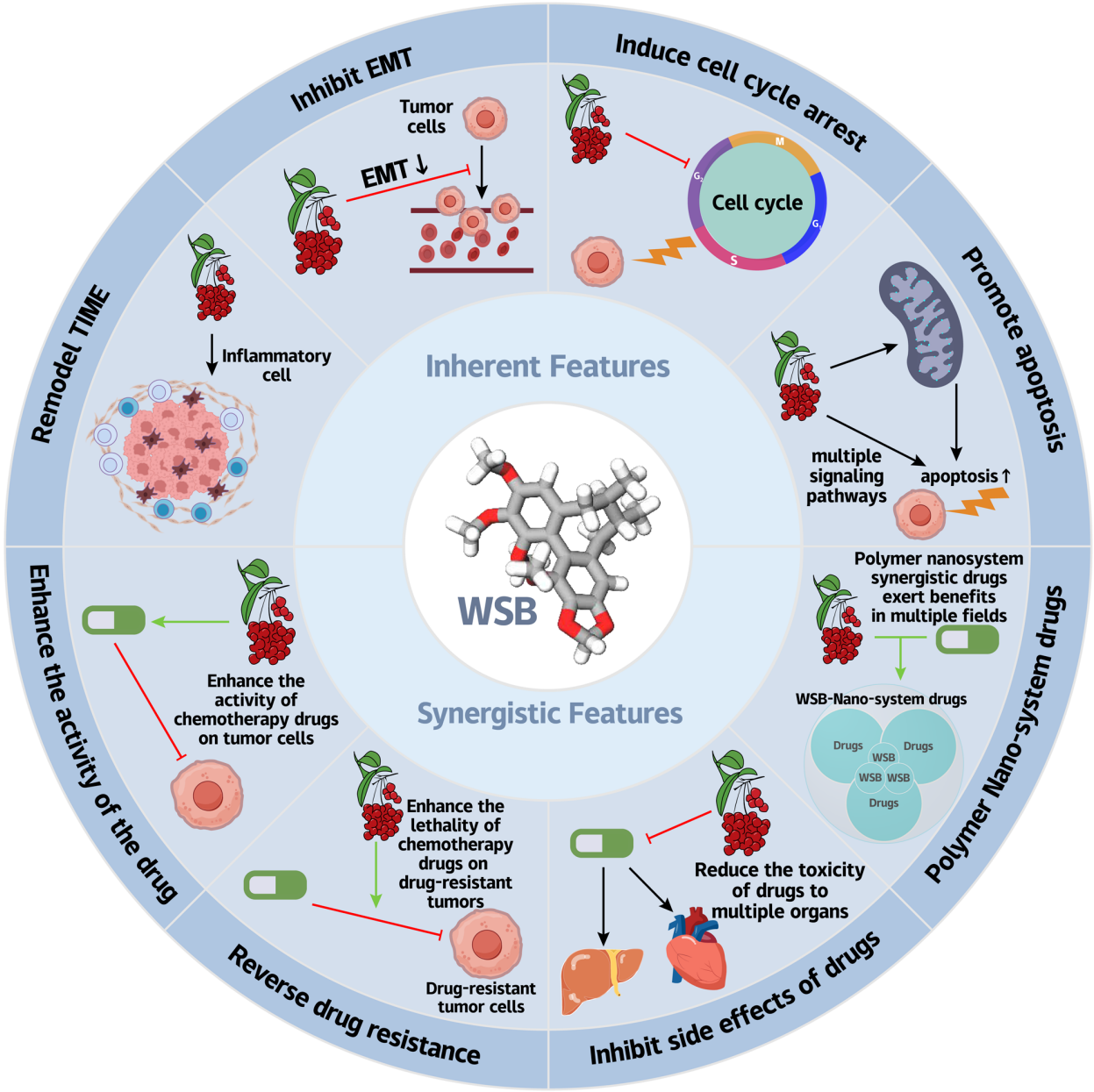

Figure 1. Evolution of WSB research: From anti-cancer targets to multi-disease modulator. WSB, Wuweizisu B; EMT, epithelial-mesenchymal transition; TIME, tumor immune microenvironment.

blocks the SMAD2/3 phosphorylation and nuclear translocation, downregulates the expression of the EMT transcription factors (SNAIL, ZEB, and TWIST) and restores the expression of the epithelial marker E-cadherin (45,46) (Fig. 3); ii) blocking the non-SMAD pathway, in which it inhibits the activation of PI3K/AKT/mTOR mediated by TGF-β and hinders the phosphorylation and cytoskeleton recombination of TWIST1 (42,47) (Fig. 3).

Critically, TGF-β drives metastatic plasticity by dynamically regulating both EMT and its reverse process, mesenchymal-epithelial transition (MET). TGF-β induces EMT through the activation of the suppressor of mothers against decapentaplegic (SMAD) and non-SMAD pathways, leading to the suppression of epithelial genes (such as CDH1) and the upregulation of mesenchymal markers (such as VIM and FN1), thereby enabling cancer cell migration and invasion (45,48) (Fig. 3). Conversely, at metastatic sites, reduced TGF-β signaling promotes MET through SMAD7-mediated suppression of the EMT transcription factors SNAIL/ZEB and reactivation of the miR-200 family, which collectively restore epithelial phenotypes to facilitate metastatic colonization (49,50) (Fig. 3). This bidirectional regulation of cellular plasticity highlights the central role of TGF-β in coordinating both the dissemination and secondary outgrowth of metastatic cancer cells.

Similar to its mechanism in colorectal cancer, WSB also exhibits inhibitory effects on TGF-β-induced EMT in lung cancer (LC) and breast cancer (BC). In LC, the WSB downregulates the expression of proteins such as TGF-β1 and Bcl-2 while upregulating p53 and p21 expression (51) (Fig. 3; Table I). These regulatory effects reduce the suppression of epithelial genes and the upregulation of mesenchymal markers. In BC,

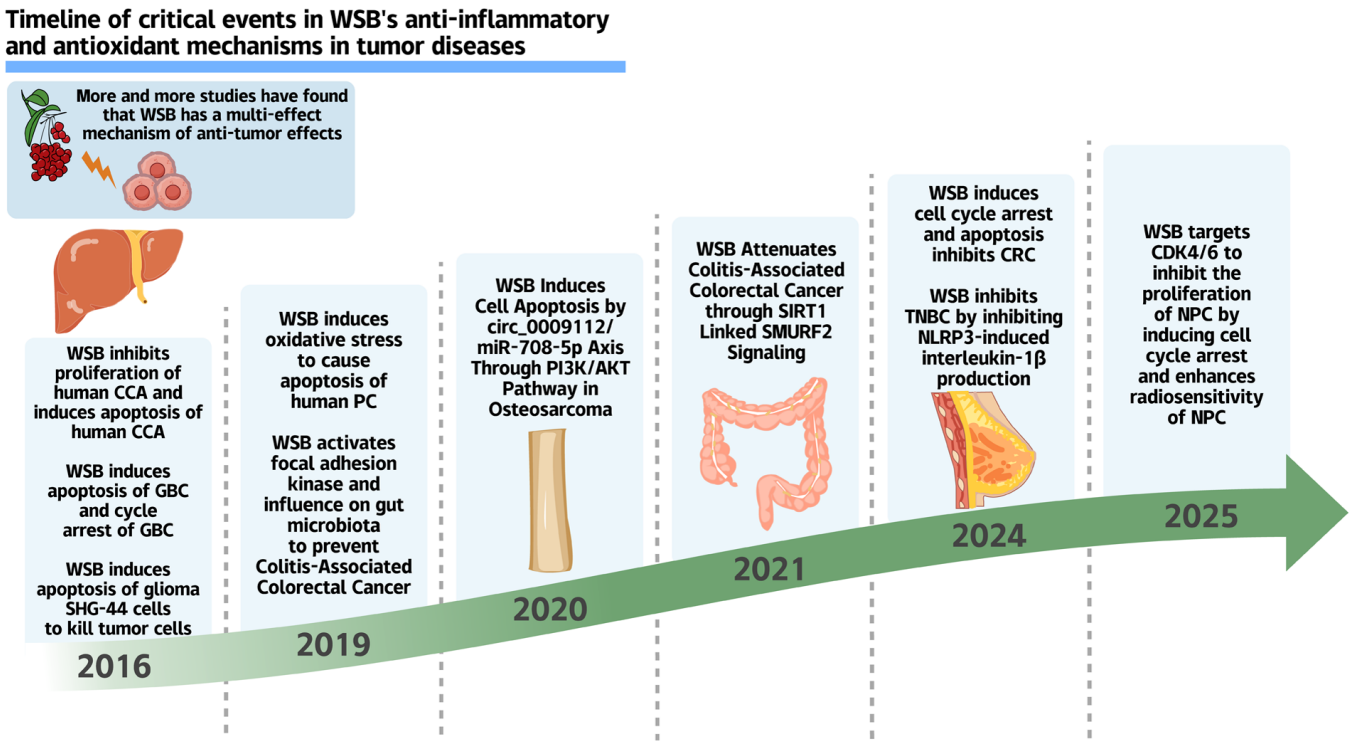

Figure 2. Multifaceted Roles of WSB in tumor and non-tumor pathologies. WSB, Wuweizisu B; CRC, colorectal cancer; TNBC, triple negative breast cancer; CCA, cholangiocarcinoma; GBC, gallbladder cancer; PC, prostate cancer; NPC, nasopharyngeal carcinoma.

WSB blocks TGF-β-promoted ROS production and increases cell motility by inhibiting NADPH oxidase 4, thereby reducing the metastasis of BC cells (52) (Fig. 3). Collectively, these findings underscore WSB's conserved capacity to target the TGF-β-mediated EMT across diverse malignancies, with context-dependent molecular nuances tailored to tissue-specific pathways. Such cross-organ inhibitory activity reinforces the WSB as a promising candidate for developing broad-spectrum antimetastatic therapeutics, in cancers characterized by dysregulated TGF-β-EMT signaling axes.

In colitis-associated cancer models, WSB demonstrates dual chemopreventive effects: FAK-dependent tight junction stabilization (increased ZO-1 expression) and microbiota remodeling (increased *Lactobacillus* abundance with reduced *Escherichia coli* colonization), reducing tumor multiplicity by 75% (53) (Fig. 3; Table I). Additionally, compared with that in the general population, the incidence of colitis-associated cancer (CAC) induced by ulcerative colitis (UC) is markedly greater (54,55). Moreover, the pathogenesis of UC is closely associated with environmental factors, genetic predisposition, the gut microbiota, and immune dysregulation (56,57). WSB markedly inhibits the differentiation of the proinflammatory Th17 cells and IL-17 secretion while promoting the generation of immunosuppressive Treg cells, thereby preventing CAC development and maintaining intestinal immune homeostasis (21) (Fig. 3).

Building upon the multitarget mechanism of WSB in coordinately regulating the microbiota-barrier-immunity axis, through the FAK-dependent tight junction restoration and the microbiota remodeling to suppress the carcinogenic microenvironment coupled with immune reprogramming to block the inflammation-cancer transition from UC to CRC, its integrated preventive and therapeutic potential offers novel strategies for high-risk UC patients. Although preclinical data are promising, clinical translation of WSB still faces challenges in terms of pharmacokinetic optimization and validation of target biomarkers such as SIRT1/SMURF2. Current exploratory trials are focusing on combination therapies of WSB with immune checkpoint inhibitors (TCM + immunotherapy), which may overcome chemoresistance through synergistic effects and unlock new therapeutic dimensions for high-risk CAC patients. Furthermore, integration with targeted delivery systems could enhance its translational value, enabling the transition from the multi-mechanism intervention to precision medicine (58).

Combating liver disease progression with WSB: From metabolic regulation to fibrosis and hepatocellular carcinoma (HCC) inhibition. Nonalcoholic fatty liver disease (NAFLD) has emerged as a significant global health challenge, affecting 25-30% of adults worldwide; the progressive of NAFLD, nonalcoholic steatohepatitis, occurs in 10-20% of cases and often progresses to cirrhosis and HCC (59-61). In the absence of FDA-approved therapies for NAFLD/nonalcoholic steatohepatitis, WSB, a bioactive lignan derived from *Schisandra chinensis*, has shown promise as a multi-target therapeutic agent capable of modulating metabolic homeostasis, inflammatory responses, and fibrotic processes. Mechanistically, WSB ameliorates hepatic steatosis by activating the AMPK/mechanistic target of mTOR pathway, which enhances autophagic flux, promotes fatty acid oxidation, and suppresses de novo lipogenesis (62-64) (Fig. 4).

Notably, hepatic steatosis is often the initial step in NAFLD progression, and unresolved steatosis can drive the

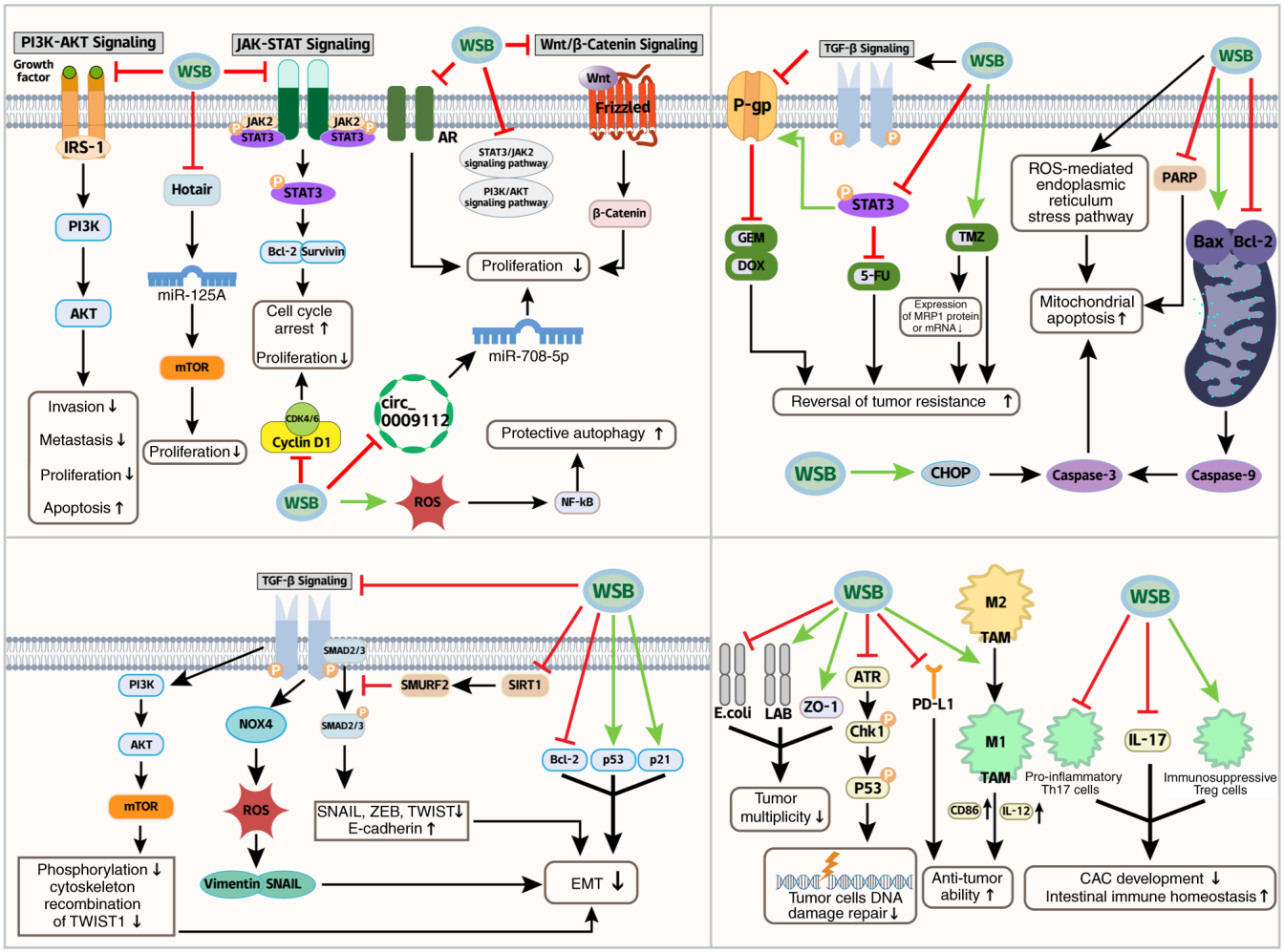

Figure 3. WSB in non-oncological diseases: Organ-protective mechanisms and signaling pathways. WSB, Wuweizisu B; AR, androgen receptor; P-gp, P-glycoprotein; ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; TAM, tumor-associated macrophage; p-, phosphorylated; PI3K, Phosphatidylinositide 3-kinases; AKT, Protein kinase B; IRS-1, insulin receptor substrate 1; HOTAIR, HOX transcript antisense RNA; mTOR, mammalian target of rapamycin; JAK, Janus kinase; JAK2, Janus kinase 2; STAT, signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription 3; Bax, BCL2 Associated X Protein; Bcl-2, B-cell lymphoma-2; CDK4, cyclin dependent kinase 4; CDK6, cyclin dependent kinase 6; NF-κB, nuclear factor kappa-B; Wnt, Wingless-Type MMTV Integration Site Family; GEM, Gemcitabine; DOX, Doxorubicin; TGF-β, transforming growth factor-β; 5-FU, 5-Fluorouracil; TMZ, Temozolomide; CHOP, C/EBP-homologous protein; PARP, Poly ADP-ribose polymerase; MRP1, Multidrug Resistance Protein 1; Caspase-3, Cysteine-dependent aspartate-specific protease-3; Caspase-9, Cysteine-dependent aspartate-specific protease-9; TWIST1, Twist Family BHLH Transcription Factor 1; NOX4, NADPH oxidase 4; ZEB, Zinc finger E-box binding homeobox; SIRT1, Silent information regulator 1; p53, Tumor protein 53; p21, Tumor protein 21; E.coil, Escherichia coli; LAB, Lactic acid bacteria; ZO-1, Zonula occludens-1; ATR, ATR serine/threonine kinase; CHK1, Checkpoint kinase 1; M1, Macrophage 1; M2, Macrophage 2; CD86, Cluster of Differentiation 86; IL-12, Interleukin-12; IL-17, Interleukin-17; Th17 cells, T helper 17 cells; Treg cells, Regulatory T cells; CAC, colitis-associated cancer.

development of liver fibrosis, a critical pathological feature that accelerates disease severity. Liver fibrosis is primarily driven by the activation of hepatic stellate cells (HSCs), and WSB targets these activated HSCs through multiple coordinated pathways to exert anti-fibrotic effects. It induces mitochondrial-dependent apoptosis in HSCs by modulating the Bax/Bcl-2 ratio and activating caspase-3, while simultaneously inhibiting TGF-β1-induced HSC activation (65) (Fig. 4). WSB promotes ferroptosis in HSCs via NCOA4-mediated ferritinophagy, suggesting a novel approach for fibrosis treatment (66) (Fig. 4). Cannabinoid receptor 2 has been identified as a key target in liver fibrosis, and WSB alleviates CCl_4-induced fibrosis by inhibiting the NF-κB and p38 mitogen-activated protein kinase (MAPK) signaling pathways in Kupffer cells, thereby reducing inflammatory cytokine release (67-69) (Fig. 4). Further studies revealed that WSB directly targets miR-101-5p, downregulating the activity of the TGF-β signaling pathway to inhibit fibrosis (70-72) (Fig. 4).

As well as targeting HSCs and Kupffer cells, WSB modulates macrophage polarization to further alleviate liver inflammation and fibrosis, although this regulation is context- and dose-dependent, reflecting its adaptability to diverse microenvironments. WSB inhibits peroxisome proliferator-activated receptor γ (PPARγ)-mediated NF-κB activation to suppress M1 macrophage markers (CD86/TNF-α) in liver fibrosis models (73) (Fig. 4), under oxidative stress, it promotes M2 polarization via the Nrf2 pathway (74) (Fig. 4), while in tumor microenvironments, high-dose WSB may increase immunosuppression through STAT3 (75) (Fig. 4). These seemingly contradictory results probably reflect the WSB's multitarget regulatory effects on macrophage plasticity rather than genuine mechanistic conflicts.

Table I. Antitumoral and molecular target of WSB in several cancer cell lines.

Type of cancer	Targets	Pathway	Cell Lines	Anti-Tumor Mechanism	48 h IC_{50}	Chemotherapeutic agent	(Refs.)
Breast cancer	IL-1β, STAT3, TGF-β	/	4T1	Apoptosis, Metastasis, G_0/G_1 Phase Arrest, Inhibit EMT, ROS generation	9.3 μM (4T1)	DOX, Epirubicin	(51,122,124)
Lung cancer	cyclin D1, CDK4/6, p21, ATR, p53, Chk1	ATM/ ATR axis	A549	Disrupts G_2/Mcheckpoint function, Enhancing UV-induced tumor cell killing, Post-DNA damage	/	Cisplatin	(96,102,250)
Colorectal cancer r	CDK4/6, CHOP, SIRT1, FAK, Gut Microbiota	SIRT1-SMURF2	HCT116	Apoptosis, Metastasis, e G_0/G_1 PhasArrest, Enhances intestinal barrier function	89.6 μM (HCT116)	Panitumumab, Fluorouracil, Capecitabine	(41,42,53, 152,251)
Glioma	caspase-3, Bax, HOTAIR/ miRNA-125a/mTOR, mTOR	HOTAIR/ miRNA-125a/ mTOR Axis, Combination with mTOR Inhibitor	SHG-44, U87MG	Apoptosis, Metastasis, Sub G_1 Phase Arrest, G_0/G_1 Phase Arrest	70 μM (U87), 60 μM (U251)	Temozolomide	(114,116, 118,252)
Cholangiocarcinoma	Bax, caspase-3/9, PARP, Cyclin D1, CDK4/6	/	HCCC-9810, RBE	Apoptosis, G_0/G_1 Phase Arrest	40±1.6 μM (HCCC-9810), 70±2.6 μM (RBE)	Gemcitabine, Cisplatin	(84,253)
Gastric cancer	CyclinD1	/	SCG-7901	G_0/G_1 Phase Arrest	/	5-FU, Vinorebine	(33,35,254)
Hepatocellular Carcinoma	/	RhoA/ROCK1, Perforin-Granzyme B-Caspase 3-GSDME	Huh-7, HepG2	Autophagy Induction, Apoptosis, Pyroptosis	/	PTX	(24,79,255)
Prostate cancer	Androgen Receptor (AR)	PI3K/AKT, STAT3/JAK2, Oxidative Stress Induction	DU145, LNCaP	Apoptosis, S-Phase Arrest, Androgen Receptor Suppression,	25 μM (LNCaP), 48 μM (du145), 84 μM (sw480), 93 μM (sgc-7901)	MDV 3100, Abiraterone	(15,108,256)
Osteosarcoma	circ_0009112/DOX,	circ_0009112/ miR-708-5p Axis, PI3K/Akt	143B, MG63, Saos2, U2OS	Apoptosis, G_1 Phase Arrest	70.32 μM (143B), 58.68 μM (MG63), 65.33 μM (Saos2), 72.38 μM (U2OS)	Cisplatin miR-708-5p	(129,257)
Nasopharyngeal carcinoma	CDK4/6, γ-H2AX	ATR/ATM	HONE-1, CNE-1	Rb phosphorylation is blocked, G_1 Phase Arrest, Enhance the sensitivity of radiotherapy	/	Cisplatin	(95,101,102)

Table I. Continued.

Type of cancer	Targets	Pathway	Cell Lines	Anti-Tumor Mechanism	48 h IC_{50}	Chemotherapeutic agent	(Refs.)
Gallbladder cancer	Bax, Bcl-2, Cytochrome *c*, Caspase-9/3, PARP, Cyclin D1, CDK4/6, p21, Rb	/	/	Apoptosis, G_0/G_1 Phase Arrest, Disrupts mitochondrial membrane potential	/	Cisplatin	(84,86-88)

IL-1β, Interleukin-1 beta; STAT3, Signal Transducer and Activator of Transcription 3; TGF-β, Transforming Growth Factor beta; EMT, Epithelial-Mesenchymal Transition; ROS, Reactive Oxygen Species; DOX, Doxorubicin; CDK4/6, Cyclin-Dependent Kinase 4 and 6; ATR, Ataxia Telangiectasia and Rad3-related protein; p53, Tumor Protein p53; Chk1, Checkpoint Kinase 1; ATM, Ataxia Telangiectasia Mutated; UV, Ultraviolet; CHOP, C/EBP Homologous Protein; SIRT1, Sirtuin 1; FAK, Focal Adhesion Kinase; HOTAIR, HOX Transcript Antisense RNA; mTOR, Mammalian Target of Rapamycin; PARP, Poly (ADP-ribose) Polymerase; 5-FU, 5-Fluorouracil; RhoA, Ras Homolog Family Member A; ROCK1, Rho-associated Coiled-coil containing Protein Kinase 1; GSDME, Gasdermin E; PTX, Paclitaxel; AR, Androgen Receptor; PI3K, Phosphoinositide 3-Kinase; AKT, AKT Serine/Threonine Kinase; JAK2, Janus Kinase 2; circ_0009112, circular RNA_0009112; miR-708-5p, microRNA-708-5p; γ-H2AX, phosphorylated Histone H2AX; Rb, Retinoblastoma protein; Bcl-2, B-cell Lymphoma 2; Bax, BCL2-Associated X protein.

Moreover, the therapeutic potential of WSB in liver disease extends to regenerative strategies: It enhances the differentiation of human umbilical cord mesenchymal stem cells into functional hepatocyte-like cells by activating the JAK2/STAT3 pathway, which could complement its antifibrotic effects by promoting liver repair (76) (Fig. 4). However, compared with those of other differentiation methods, the efficiency and functional maturity of WSB-induced HLCs require thorough assessment. More importantly, the direct application of WSB *in vivo* to modulate the fate of the endogenous or the transplanted MSCs requires a careful evaluation of pharmacokinetics, targeted delivery, potential off-target effects on other cell types, and long-term safety.

As NAFLD progresses to advanced stages, cirrhosis can predispose patients to HCC, a leading cause of cancer-related mortality globally, with limited therapeutic options for advanced-stage patients (77). WSB demonstrates significant anti-HCC activity through mechanisms that align with its earlier roles in metabolic regulation and inflammation while also targeting tumor-specific pathways. It synergizes with NK cells to induce pyroptosis in HepG2 cells via perforin-granzyme B-caspase 3-GSDME, highlighting its role in immune microenvironment modulation (24) (Fig. 4; Table I). The Ras homolog family member α/ϱ-associated protein kinase 1 (RhoA/ROCK1) pathway, which is involved in HCC cell proliferation and metastasis, is effectively suppressed by WSB, leading to inhibited migration and invasion of Huh-7 cells both *in vitro* and *in vivo* (78-80) (Fig. 4; Table I). These findings underscore the potential of WSB as a multifaceted therapeutic agent for treating HCC that targets both tumor cells and the immune system. However, the narrow therapeutic window (IC_{50} ~266.4 μM in HepG2 cells vs. significant toxicity in normal cells at >200 μM) poses a major translational challenge (81). In addition, achieving effective antitumor concentrations *in vivo* without unacceptable toxicity may require advanced delivery strategies or synergistic combinations with standard therapies.

In summary, while WSB shows preclinical promise for NAFLD, fibrosis, and HCC via multiple target mechanisms, its translational challenges are significant. The narrow therapeutic window and context-dependent immune modulation complicate clinical application. Key gaps include defining the *in vivo* therapeutic window, developing toxicity mitigation strategies (such as targeted delivery), and obtaining human pharmacokinetic/safety data, necessitating rigorous clinical trials.

Inducing apoptosis and cell cycle arrest: WSB's dual mechanism against cholangiocarcinoma (CCA). CCA, a highly aggressive malignancy originating from the biliary epithelium with frequent extension to the ampulla of Vater (82), represents the second most common primary liver cancer and remains notoriously resistant to conventional chemotherapy, contributing to its dismal 5-year survival rate, which is <20% for advanced cases (83). Preclinical studies have demonstrated that WSB exerts multimodal anti-CCA activity through i) potent induction of mitochondrial apoptosis, as evidenced by an increased Bax/Bcl-2 ratio and significant activation of caspase-3/9 and PARP cleavage and ii) effective G_0/G_1 cell cycle arrest via downregulation of Cyclin D1 and CDK4/6 inhibition at clinically achievable concentrations (84) (Fig. 3;

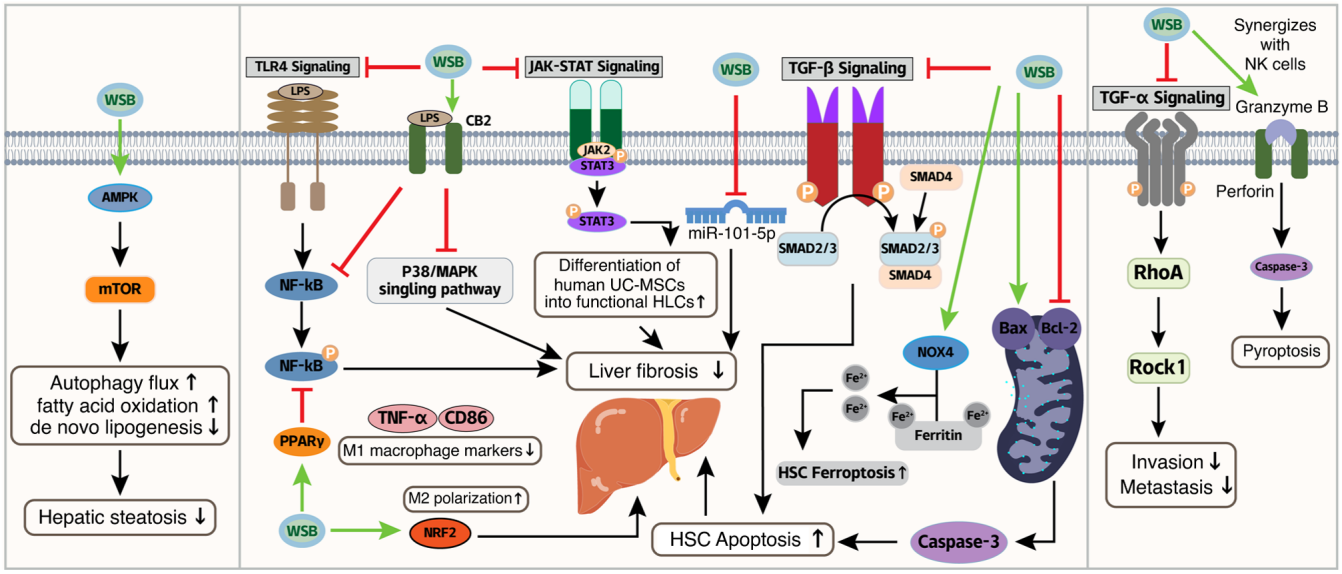

Figure 4. Anti-tumor effects of WSB: From apoptosis induction to immune modulation. WSB, Wuweizisu B; p-, phosphorylated; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; TLR4, Toll-like receptor 4; LPS, Lipopolysaccharide; NF-κB, nuclear factor kappa-B; PPARγ, peroxisome proliferators-activated receptor Gamma; CB2, Cannabinoid Receptor 2; p38, Tumor protein 38; TNF-α, Tumor necrosis factor-alpha; CD86, Cluster of Differentiation 86; M1, Macrophage 1; M2, Macrophage 2; NRF2, Nuclear Factor erythroid 2-Related Factor 2; JAK, Janus kinase; JAK2, Janus kinase 2; STAT, signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription 3; UC-MSCs, Umbilical cord mesenchymal stem cells; HLCs, hepatocyte-like cells; HSC, Hepatic Stellate Cells; TGF-β, transforming growth factor-β; NOX4, NADPH oxidase 4; Bax, BCL2 Associated X Protein; Bcl-2, B-cell lymphoma-2; Caspase-3, Cysteine-dependent aspartate-specific protease-3; RhoA, Ras Homolog Family Member A; Rock, Rho-associated coiled-coil kinase 1.

Table I). These findings demonstrate the potential of WSB as a promising therapeutic candidate, particularly given its dual-targeting ability against both proliferative signaling and apoptotic resistance pathways, two hallmark features of CCA pathogenesis that contribute to clinical chemoresistance.

Mechanisms of WSB against gallbladder cancer (GBC): Apoptosis induction and CDK4/6 inhibition. GBC, one of the most aggressive malignancies of the biliary system, is associated with a dismal clinical prognosis. Studies by Pehlivanoglu *et al* (85) have indicated that only 5% of invasive GBC patients are diagnosed at the early T1b stage, with a 5-year survival rate of up to 92%; however, most patients are diagnosed at the locally advanced or metastatic stage, resulting in an overall 5-year survival rate of <10%. Furthermore, Brindley *et al* (86) reported that the objective response rate to current chemotherapy regimens (such as gemcitabine plus cisplatin) for biliary tract cancers, including GBC, is only ~20%, highlighting the urgency to explore novel therapeutic agents (86) (Table I). As an active component derived from the traditional Chinese herb, WSB has recently demonstrated multitargeted antitumor potential in GBC treatment, with its mechanisms of action supported by multiple studies (84,87,88). In terms of apoptosis induction, Yang *et al* (84) reported that WSB can upregulate the proapoptotic protein Bax and downregulate the antiapoptotic protein Bcl-2, disrupt mitochondrial membrane potential, promote the release of cytochrome *c*, activate the caspase-9/3 cascade, and cleave PARP, thereby inducing apoptosis in cholangiocarcinoma cells (Fig. 3; Table I). Similarly, studies on BC have confirmed that WSB can enhance mitochondrial apoptotic signaling through a ROS-mediated endoplasmic reticulum stress pathway (such as upregulating CHOP and GPR78), suggesting a common mechanism of apoptotic regulation across different tumor types (52) (Fig. 3). With respect to cell cycle regulation, Hui *et al* (87) reported that the overexpression of Cyclin D1 in GBC is closely associated with poor prognosis. WSB can markedly inhibit the activity of the Cyclin D1/CDK4/6 complex while upregulating the expression of the CDK inhibitor p21, thereby blocking the phosphorylation of the retinoblastoma protein (Rb) and causing cell arrest in the G_0/G_1 phase (Fig. 3; Table I). This mechanism is highly consistent with the action pathway of CDK4/6 inhibitors observed in BC, further validating its rationality (88) (Table I).

Notably, the antitumor potential of WSB is not limited to GBC. Studies on its mechanisms in various other tumors, such as BC, have shown commonalities in regulating apoptosis, the cell cycle, and metastasis, providing a basis for its potential as a broad-spectrum antitumor candidate. In terms of clinical translation, combined with the current application of targeted drugs such as FGFR and IDH1 inhibitors in biliary tract cancers (89), WSB is expected to be used in combination with existing targeted immunotherapies, further enhancing the therapeutic efficacy of GBC through synergistic effects on multiple pathways (90,91).

CDK4/6 and DNA repair: WSB's dual mechanism for radiosensitizing nasopharyngeal carcinoma (NPC). NPC represents a distinct epithelial malignancy with a unique geographical distribution and strong etiological association with EBV infection (92). While radiotherapy demonstrates excellent efficacy in early-stage disease (achieving 90% cure rates), the majority of patients present with locally advanced or metastatic disease at diagnosis because of the tumor's insidious growth pattern

and early metastatic propensity (93). This clinical reality highlights the urgent need for novel therapeutic strategies that can overcome the limitations of current treatments, which are often associated with significant toxicity and suboptimal outcomes in advanced cases (94).

The mechanism of action of WSB in NPC is reflected mainly in two aspects: First, WSB inhibits cell proliferation by targeting CDK4/6. It can directly bind to CDK4/6 and downregulate the expression of CDK4/6 in NPC cells (such as HONE-1 and CNE-1 cells) and although it upregulates Cyclin D1, it inhibits the formation of complexes between Cyclin D1 and CDK4/6, thereby hindering Rb phosphorylation and inducing cell cycle arrest at the G_1 phase. Notably, it has no significant effect on normal nasopharyngeal epithelial cells. Second, it enhances radiosensitivity by promoting radiotherapy-induced DNA double-strand breaks [at 4 h after radiotherapy, the number of phosphorylated histone H2A variant X (γ-H2AX) foci in the combination group was markedly greater than that in the radiotherapy alone group: for example, 21.4 vs. 13.2 foci/nucleus in HONE-1 cells] and delaying damage repair (at 12 h after radiotherapy, the number of γ-H2AX foci was still greater: For example, 7.6 vs. 3.9 foci/nucleus in HONE-1 cells) (95) (Fig. 3; Table I). In addition, WSB can induce NPC cells to arrest at the G_1 phase, which is more sensitive to radiotherapy, and prevent them from entering the S phase (radiation-resistant phase), thereby enhancing the killing effect of radiotherapy on tumor cells.

Notably, this mechanism of action of WSB is highly consistent with its performance in other malignant tumors. For instance, in LC studies, WSB also blocks the cell cycle at the G_0/G_1 phase by downregulating the expression of CDK4/6 and Cyclin D1 (96) (Fig. 3; Table I) . Similarly, in gallbladder cancer (GBC), a correlation between CDK4 downregulation and G_1 phase arrest has been observed, suggesting that its conservation of cell cycle regulation may make it a potential therapeutic agent across tumor types (97). More importantly, compared with clinically used CDK4/6 inhibitors such as palbociclib, WSB is safer. Although palbociclib can enhance the radiosensitivity of NPC by inhibiting DNA damage repair, it is often accompanied by adverse reactions such as neutropenia and peripheral neuropathy (98). By contrast, WSB at a concentration of 40 μM exerts no significant effect on the proliferation or cell cycle of normal nasopharyngeal epithelial cells (NP69) and has even been confirmed to exert protective effects on tissues such as the liver and myocardium in animal models, which supports its low toxicity advantage in clinical applications (65,99,100).

From the perspective of the molecular mechanisms of radioresistance, the radioresistance of NPC cells is often associated with efficient DNA double-strand break repair capacity (101) (Table I). The repair-inhibiting effect of WSB, as reflected by the delay in γ-H2AX foci, may be related to the regulation of the ATM and ATR kinases pathway (102) (Table I). Existing studies have shown that WSB can inhibit ATR protein kinase activity to interfere with the DNA damage response, and this mechanism may further explain its radiosensitizing effect in NPC. In addition, the synergistic effect of WSB and radiotherapy in 3D organoid models (markedly reduced activity of HONE-1 organoids) is more consistent with the *in vivo* tumor microenvironment, verifying its effectiveness under complex physiological conditions and providing key evidence for translation from basic research to clinical practice. These characteristics make WSB not only promising for improving the radiotherapy effect of locally advanced NPC, but also potentially applicable in combination with existing targeted drugs (such as EBV-related signaling inhibitors) to construct multitarget therapeutic regimens, thereby offering new ideas for overcoming the therapeutic bottlenecks of NPC.

3. Dual targeting of DNA repair and metastasis: WSB inhibits ATR and ZEB1/E-cadherin signaling in LC

LC is the most commonly diagnosed malignancy globally, with recent epidemiological data revealing ~2.5 million new cases each year, 12.4% of all cancer diagnoses worldwide and 1.8 million annual fatalities, accounting for 18.7% of total cancer mortality (1). While the advent of molecularly targeted therapies and immunotherapies has revolutionized treatment paradigms, the prognosis for advanced non-small cell lung cancer (NSCLC) patients remains poor, with 5-year survival rates persistently <20% (103). This therapeutic impasse stems primarily from two key challenges: The development of drug resistance mechanisms and dose-limiting treatment toxicity.

At the molecular level, the WSB strongly inhibits the ATR protein kinase activity, effectively compromising the G_2/M checkpoint integrity following DNA damage through the suppression of critical phosphorylation events in p53 and checkpoint kinase 1 (CHK1) (102) (Fig. 3; Table I). This distinctive mechanism of action potentiates the efficacy of conventional DNA-damaging anticancer therapies, presenting a novel strategic approach for targeting ATR-dependent DNA repair mechanisms in LC treatment.

In the A549 non-small cell LC cell line, WSB demonstrates dual cell cycle regulatory effects, inducing G_0/G_1 phase arrest while simultaneously promoting caspase-dependent apoptotic cell death. Notably, it suppresses TGF-β1-induced EMT in A549 cells through epigenetic silencing of ZEB1 and restoration of E-cadherin expression (104), a key mechanism given that EMT drives LC metastasis by disrupting epithelial adhesion via downregulated the E-cadherin and upregulated mesenchymal markers (Fig. 3), enabling invasive potential, thereby equipping WSB with the capacity to inhibit metastatic progression through suppression of the EMT pathway.

These findings collectively position WSB as a multifaceted therapeutic candidate capable of targeting both primary tumor growth and metastatic dissemination. The anti-cancer mechanisms of WSB require further elucidation, particularly regarding its dose-response relationship/optimal therapeutic window. Systematic pharmacokinetic/pharmacodynamic studies are needed to establish clinically effective and safe dosing regimens.

4. Overcoming therapy resistance in prostate cancer (PC): WSB's effects on the androgen receptor (AR), PI3K/AKT, and STAT3 pathways

WSB demonstrates significant antitumor activity in PC through a multipronged mechanism that addresses both disease progression and therapeutic resistance (15,105,106). In the context of standard androgen deprivation therapies, which aim to block

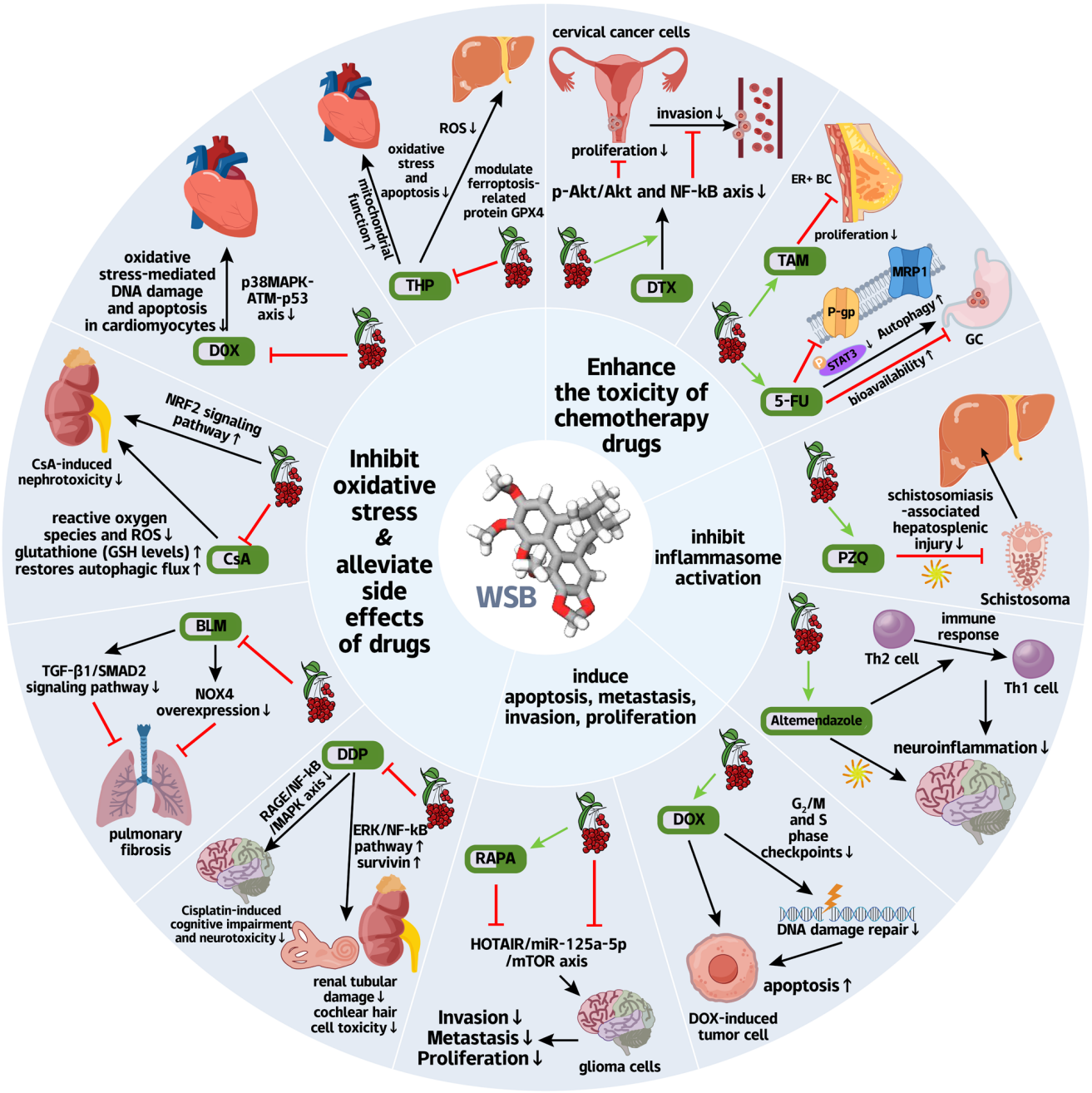

Figure 5. WSB as a pleiotropic chemo-adjuvant. WSB, Wuweizisu B; P-gp, P-glycoprotein; p-, phosphorylated; MRP1, Multidrug Resistance Protein 1; STAT3, signal transducer and activator of transcription 3; TAM, Tamoxifen; 5-FU, 5-Fluorouracil; GC, gastric cancer; ER, Estrogen receptor; BC, breast cancer; PZQ, Praziquantel; Th1 cell, T helper 1 cell; Th2 cell, T helper 2 cell; DOX, Doxorubicin; RAPA, Rapamycin; HOTAIR, HOX transcript antisense RNA; mTOR, mammalian target of rapamycin; DDP, Cisplatin; RAGE, Receptor for Advanced Glycation End Products; NF-κB, nuclear factor kappa-B; MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular regulated protein kinases; TGF-β, transforming growth factor-β; NOX4, NADPH oxidase 4; CsA, Cyclosporin A; NRF2, Nuclear Factor erythroid 2-Related Factor 2; ROS, reactive oxygen species; GSH, Glutathione; p38, Tumor protein 38; p53, Tumor protein 53; ATM, Ataxia-telangiectasia mutated proteins; THP, Pirarubicin; GPX4, Glutathione Peroxidase 4; AKT, Protein kinase B; NF-κB, nuclear factor kappa-B; DTX, Docetaxel.

AR signaling, which is crucial for PC cell growth (107), WSB effectively suppresses AR signaling (108) (Fig. 3; Table I). This not only complements the action of existing therapies but also enhances sensitivity to them, potentially overcoming the resistance that often develops over time. For instance, drugs such as gonadotropin-releasing hormone agonists/antagonists and anti-androgen drugs target AR signaling, and the modulation of this pathway by WSB could enhance the efficacy of these drugs.

WSB also induces oxidative stress in PC cell lines (15) (Table I). Like some chemotherapeutic agents, such as those that disrupt the cell cycle machinery, WSB triggers S-phase cell cycle arrest and caspase-dependent apoptosis (109) (Fig. 3). In chemotherapy, drugs interfere with processes such as DNA synthesis or mitosis (110); the induction of oxidative stress by WSB may disrupt normal cellular functions, leading to cell cycle arrest and apoptosis (111). Mechanistic studies have revealed that the antiproliferative effects of WSB are

mediated through the inhibition of key oncogenic pathways, particularly the PI3K/AKT and STAT3/JAK2 cascades, which are frequently hyperactivated in advanced and treatment-resistant PC (15) (Fig. 3). These pathways are also targeted by some emerging targeted therapies for PC, and the effects of WSB suggest potential synergy.

Of particular clinical relevance, WSB maintains its efficacy against chemotherapy-resistant phenotypes. In radiotherapy, which aims to kill cancer cells by damaging their DNA, the ability of WSB to modulate cellular processes may enhance the radiosensitivity of cancer cells (95) (Table I). Overall, these findings underscore the promise of WSB as a multitarget therapeutic agent for PC management, with potential applications in combination with existing endocrine, chemotherapy, and radiotherapy approaches.

5. WSB anti-glioblastoma via apoptosis induction and synergy with temozolomide/rapamycin

Gliomas, which originate from brain glial cells, represent the most prevalent primary intracranial tumors in adults (40-60% of central nervous system tumors) (112). WSB exerts potent antitumor effects on glioblastoma through the induction of mitochondrial apoptosis (via Bax/Bcl-2 modulation and caspase-3 cleavage) and G_0/G_1 cell cycle arrest (through CDK4/6-Cyclin D1 suppression) in SHG-44 and U87MG cells (113,114) (Fig. 3; Table I). RNA sequencing analyses reveals that WSB inhibits the HOTAIR/miR-125a/mTOR pathway, reducing glioma cell migration by 55-70% (115) (Fig. 3).

Synergy with standard therapies enhances efficacy: Temozolomide combination therapy overcomes resistance by suppressing O6-methylguanine-DNA methyltransferase activity and blocking the repair of O6-methylguanine lesions. This leads to unrepaired DNA damage, persistent double-strand breaks, and enhanced apoptotic signaling through DNA damage response pathway activation (116,117) (Fig. 3; Table I). Similarly, rapamycin synergizes with WSB through dual epigenetic and mTOR-targeted inhibition, WSB indirectly suppresses mTOR expression via downregulation of HOTAIR expression and upregulation of miR-125a-5p expression, whereas rapamycin directly inhibits mTOR activity. Preclinically, WSB monotherapy achieves 68% tumor growth inhibition, which increases to 85% when WSB is combined with rapamycin (115,118) (Figs. 3 and 5; Table I).

These findings position WSB as a multifaceted therapeutic agent against glioblastoma, leveraging intrinsic pro-apoptotic and cell cycle regulatory properties while synergizing with conventional and targeted (rapamycin) therapies to overcome key resistance mechanisms. Future clinical translation should prioritize optimizing delivery strategies to penetrate the blood-brain barrier and validating predictive biomarkers (such as HOTAIR/MGMT expression) for patient stratification in combination regimens.

6. WSB reverses BC chemoresistance via STAT3/P-gp suppression and immune remodeling

In BC, WSB overcomes chemoresistance through multimodal targeting: i) Chemosensitization: STAT3 is often overactivated, which contributes to the upregulation of P-gp, a major efflux pump responsible for pumping chemotherapeutic drugs out of cancer cells, leading to drug resistance (119,120). WSB acts by inhibiting STAT3 signaling. As reported in studies on other cancer types, such as neuroblastoma, the activation of STAT3 can protect cells from apoptosis and is associated with drug resistance (121) (Fig. 3). By blocking the STAT3 phosphorylation and nuclear translocation, WSB effectively downregulates the expression of P-gp in MCF-7/ADR cells. This downregulation reverses the efflux of doxorubicin (DOX), thereby increasing the intracellular concentration of DOX. As a result, the IC_{50} of DOX in MCF-7/ADR cells is markedly reduced from 12.3 to 2.8 μM, enhancing the sensitivity of cancer cells to chemotherapeutic agents (122) (Fig. 3; Table I); ii) by blocking the TGF-β/NOX4/ROS signaling, WSB inhibits vimentin and Snail expression, reducing metastatic potential in 4T1-Luc models (lung nodules ↓65%) (52,104,123) (Fig. 3); and iii) WSB polarizes tumor-associated macrophages (TAMs) toward the antitumor M1 phenotype, increasing the expression of the M1 marker CD86 and upregulating M1-characteristic IL-12. In triple-negative breast cancer (TNBC) cells, WSB suppresses programmed cell death ligand 1 (PD-L1) and high levels of PD-L1 bind to T-cell PD-1, inhibiting T-cell activation and cytotoxicity. By reducing PD-L1 expression, WSB enhances T-cell recognition and the killing of cancer cells, strengthening antitumor immune responses in the BC microenvironment (23,124) (Fig. 3; Table I). Preclinical studies have demonstrated that WSB monotherapy achieves 58% tumor growth inhibition in estrogen receptor (ER) + BC xenografts, synergizing with tamoxifen to achieve 82% suppression (Fig. 5).

Building on its dual anti-inflammatory and chemosensitizing actions, WSB warrants clinical prioritization in endometritis and TNBC, conditions with unmet therapeutic needs. Synergistic strategies (such as PD-1 inhibition) could amplify STAT3/PD-L1 blockade, while nanotechnology may overcome bioavailability barriers. The mechanistic exploration of AR-mitochondrial crosstalk in orchitis could redefine the management of male infertility. Cross-disciplinary innovation will catalyze WSB's transition to transformative therapies.

7. Targeting the PI3K/Wnt pathways: WSB's antimetastatic effect on osteosarcoma

Osteosarcoma, the most prevalent malignant bone tumor in adolescents, has a poor prognosis, especially in metastatic cases (125-127) (Fig. 3). WSB inhibits osteosarcoma progression by targeting circ_0009112/miR-708-5p and by suppressing migration and invasion via the PI3K/AKT pathway while inducing apoptosis (128,129) (Fig. 3; Table I). It also blocks Wnt/β-catenin and PI3K/AKT signaling, arresting the cell cycle at the G_1 phase, inhibiting proliferation, and reducing lung metastasis in preclinical models without significant toxicity (63). These findings highlight WSB's potential as a therapeutic candidate for osteosarcoma.

8. Synergistic potential of WSB with conventional therapeutics

As a pleiotropic bioactive compound, WSB enhances chemotherapy efficacy while mitigating adverse effects through multitarget modulation of oxidative stress, inflammation,

and cell death pathways. Its integration with advanced drug delivery systems further improves pharmacokinetics, offering a paradigm for low-toxicity precision oncology (Fig. 5).

Chemoprotective effects against treatment-related toxicity. Notably, the capacity of WSB to modulate MDR, enhance chemosensitivity, particularly well-characterized in BC, extends to a coordinated protective role against chemotherapy-induced organ damage, creating a synergistic therapeutic profile. In BC, WSB reverses DOX resistance by downregulating the P-gp via STAT3 inhibition (122) (Fig. 5; Table II), while simultaneously counteracting DOX-induced cardiotoxicity through p38MAPK-ATM-p53 axis regulation (130,131) (Fig. 5; Table II), thus amplifying anti-tumor efficacy while mitigating cardiac injury. This dual action aligns with its ability to sensitize ER+ BC to tamoxifen (achieving 82% tumor suppression in combination) (132) (Fig. 5), demonstrating that WSB's MDR-reversing effects are paired with tissue-specific toxicity attenuation.

Furthermore, in cisplatin-based regimens, where drug resistance and systemic toxicity often limit efficacy, WSB not only enhances chemosensitivity by overcoming efflux mechanisms but also protects normal tissues: it upregulates survivin via ERK/NF-κB to shield renal tubules and cochlear hair cells (133,134) (Table II) and inhibits the RAGE/NF-κB/MAPK pathways to prevent neurotoxicity (135) (Fig. 5; Table II). Similarly, for thiotepa, the pro-oxidant activity of WSB in tumor cells (driving apoptosis) is balanced by its suppression of excessive ROS in normal tissues, preserving hepatic and cardiac function via GPX4-mediated ferroptosis inhibition (136-138) (Fig. 5; Table II).

Beyond specific chemotherapeutics, WSB synergizes with supportive agents to mitigate broader complications: In combination with glycyrrhizic acid, it suppresses TGF-β1/SMAD2 signaling and NOX4 overexpression in bleomycin-induced pulmonary fibrosis (139) (Fig. 5), a common side effect of alkylating agents; in cyclosporine A-induced nephrotoxicity, it activates Nrf2 to reduce ROS, elevate glutathione, and restore autophagy (140) (Fig. 5), thus protecting renal function during immunosuppressive chemotherapy regimens; and in schistosomiasis, it enhances praziquantel efficacy while alleviating hepatosplenic injury (141,142) (Fig. 5), a model for reducing parasitic coinfection complications during chemotherapy.

Collectively, these findings underscore the unique therapeutic duality of WSB in cancer chemotherapy: It not only enhances antitumor efficacy by reversing MDR and sensitizing malignancies (as exemplified in BC) but also safeguards normal tissues through targeted mechanisms, mitigating the systemic toxicity that often limits treatment tolerance. This multifaceted profile positions WSB as a promising adjuvant in chemotherapeutic regimens, addressing the longstanding challenge of balancing efficacy and safety across diverse cancer types and treatment modalities.

Enhancement of antitumor efficacy in combination regimens. WSB potentiates chemotherapy through synergistic pathway inhibition: When combined with docetaxel (DTX), WSB downregulates phosphorylated (p-)AKT/AKT and NF-κB expression, ultimately inhibiting cervical cancer proliferation and invasion (143) (Fig. 5; Table II). In GC, WSB and apatinib induce G_0/G_1 arrest and suppress MMP-9-mediated metastasis (144,145) (Fig. 5; Table II). With the DOX, WSB disrupts DNA repair by abrogating G_2/M checkpoints and amplifying apoptosis (146,147) (Table II). Moreover, Additional studies have demonstrated that WSB can also increase the sensitivity of glioblastoma cells (GBM U87 and A172) to the antitumor drug temozolomide by downregulating the expression of MRP1 protein or mRNA (116,148) (Fig. 3; Table II).

However, when WSB is co-administered with P-gp substrate chemotherapeutic agents such as paclitaxel and doxorubicin, it promotes the drug efflux, thereby reducing intracellular drug accumulation in tumor cells (81,149) (Figs. 3 and 5; Table II). Additionally, WSB downregulates organic anion transporting polypeptide 1B1 (OATP1B1) expression, which may impair the hepatic uptake and subsequent activation metabolism of OATP-dependent drugs such as irinotecan (150). Furthermore, WSB exhibits complex pharmacokinetic interactions with FK506; by competing for CYP3A-mediated metabolism, WSB accelerates its own clearance while simultaneously inhibiting FK506 metabolism (149) (Table II). These findings necessitate the preclinical-to-clinical translation via the pharmacogenomic screening: tumors with low P-gp/MRP1 and high OATP1B1 could prioritize WSB combinations (such as DTX/WSB in cervical cancer) while avoiding coadministration with P-gp substrates in ABCB1-overexpressing tumors.

In summary, WSB acts as a double-edged sword in combination chemotherapy: On one hand, it enhances the antitumor efficacy of drugs such as docetaxel and apatinib by inhibiting key signaling pathways (p-AKT/NF-κB) and disrupting DNA repair mechanisms. On the other hand, the WSB-induced upregulation of P-gp/MRP efflux pumps and suppression of OATP1B1 may antagonize the therapeutic effects of paclitaxel, doxorubicin, and irinotecan. Additionally, it engages in complex pharmacokinetic competition with CYP3A substrate drugs (such as tacrolimus). Therefore, clinical combination strategies must be precisely designed on the basis of drug transport and metabolic profiles to mitigate interaction risks and maximize synergistic benefits.

9. Overcoming chemoresistance via apoptotic sensitization

MDR, driven by drug efflux, cancer stem cells and the tumor microenvironment (TME), remains a critical clinical hurdle (151).

Preclinical studies have demonstrated that WSB effectively overcomes RAS-mediated resistance to EGFR inhibitors in colorectal cancer (152) (Fig. 6; Tables I and II). Resistance to EGFR-targeted therapy in colorectal cancer primarily arises from tumor-intrinsic and microenvironment-driven adaptive mechanisms: RAS/RAF mutations (such as KRAS in 40% and BRAF V600E in 8-10% of cases) lead to constitutive activation of downstream signaling, while bypass pathways such as the ERBB2/MET/IGF-1R amplification or overexpression maintain survival signals through feedback loops (153-156). Additionally, metabolic reprogramming (enhanced glycolysis and dysregulated lipid synthesis) and tumor microenvironment factors (such as HGF/TGF-β secretion by cancer-associated fibroblasts) further contribute to drug resistance (157-159). To counteract these resistance mechanisms, WSB synergizes with panitumumab by activating caspase-3-dependent apoptosis

Table II. Synergy of WSB and drugs.

Function	Agent/System	Cancer type	Target/Pathway	Effect and mechanism	(Refs.)
Chemoresistance reversal	5-FU	CRC	STAT3, P-gp, MRP1	Downregulates efflux transporters, reverses MDR, and induces autophagic death via STAT3 inhibition.	(14,33)
	Panitumumab	CRC (RAS mutant)	Caspase-3, Bcl-2	Activates caspase-3-dependent apoptosis and suppresses Bcl-2, reversing resistance to EGFR inhibitors.	(152)
	DOX	BC	P-gp	Reverses DOX resistance by downregulating P-gp via STAT3 inhibition.	(122)
Chemosensitization	DTX	Cervical cancer	p-AKT/AKT, NF-κB	Downregulates key signaling pathways, inhibiting proliferation and invasion.	(143)
	Apatinib	GC	MMP-9	Induces G_0/G_1 arrest and suppresses MMP-9-mediated metastasis.	(144,145)
	DOX	BC	DNA repair mechanism	Abrogates G_2/M checkpoints, disrupts DNA repair, and amplifies apoptosis.	(146,147)
	Temozolomide	Glioblastoma	MRP1	Downregulates MRP1 expression, enhancing sensitivity to temozolomide.	(116,148)
Organ protection and detoxification	DOX	BC	p38MAPK-ATM-p53 axis	Alleviates DOX-induced cardiotoxicity.	(130,131)
	Cisplatin	Multiple cancers	ERK/NF-κB, RAGE/NF-κB/MAPK	Protects renal tubules and cochlear hair cells; prevents neurotoxicity.	(133-135)
	Thiotepa	/	GPX4	Suppresses excessive ROS and ferroptosis in normal tissues via GPX4, preserving hepatic and cardiac function.	(136-138)
Advanced delivery systems	PH-sensitive micelle (methotrexate-SOR/WSB Micelles)	HCC	/	Dissociates in the acidic tumor microenvironment, simultaneously inhibiting HCC progression and reducing systemic toxicity.	(173)
	PSA Systems	/	NF-κB, M1 macrophage	Achieves targeted delivery to M1 macrophages, effectively suppressing NF-κB-mediated inflammation and improving survival by 50%.	(174)
	Polymeric nanosystems	BC	Mitochondria	Leverages pH-dependent release kinetics to enhance mitochondrial targeting in BC stem cells, overcoming chemoresistance while protecting cardiac function.	(175,176)
	PFV-modified liposomes	/	Integrinαvβ3, VM channel	Exploits tumor-specific integrin αvβ3 overexpression to disrupt metastatic vasculogenic mimicry networks.	(177)
	R8-modified liposomes	GC	/	Achieves deep tumor penetration while inhibiting EMT and preventing myelosuppression.	(180,181)
PK interactions	Tacrolimus	/	CYP3A	Competes for CYP3A-mediated metabolism, accelerating its own clearance while inhibiting FK506 metabolism.	(149)
	Tacrolimus	/	OATP1B1	Downregulates OATP1B1 expression, potentially impairing its hepatic uptake and activation metabolism.	(150)

Table II. Continued.

Function	Agent/System	Cancer type	Target/Pathway	Effect and mechanism	(Refs.)
	Paclitaxel/Dox	/	P-gp	As a P-gp substrate, co-administration may promote drug efflux, reducing intracellular accumulation in tumor cells.	(81,149)

5-FU, 5-Fluorouracil; CRC, Colorectal Cancer; STAT3, Signal Transducer and Activator of Transcription 3; P-gp, P-glycoprotein; MRP1, Multidrug Resistance-Associated Protein 1; MDR, Multidrug Resistance; DOX, Doxorubicin; BC, Breast Cancer; EGFR, Epidermal Growth Factor Receptor; DTX, Docetaxel; AKT, AKT Serine/Threonine Kinase; NF-κB, Nuclear Factor Kappa B; GC, Gastric Cancer; MMP-9, Matrix Metallopeptidase 9; MAPK, Mitogen-Activated Protein Kinase; ATM, Ataxia Telangiectasia Mutated; p53, Tumor Protein p53; ERK, Extracellular Signal-Regulated Kinase; RAGE, Receptor for Advanced Glycation End-products; GPX4, Glutathione Peroxidase 4; ROS, Reactive Oxygen Species; PH, pH-sensitive; SOR, Sorafenib; WSB, Wuweizisu B; HCC, Hepatocellular Carcinoma; PSA, Phosphatidylserine-specific; M1, Macrophage Phenotype 1; PFV, Peptide PFV (a specific targeting peptide); VM, Vasculogenic Mimicry; R8, Arginine Octapeptide; EMT, Epithelial-Mesenchymal Transition; PK, Pharmacokinetic; CYP3A, Cytochrome P450 3A; OATP1B1, Organic Anion Transporting Polypeptide 1B1.

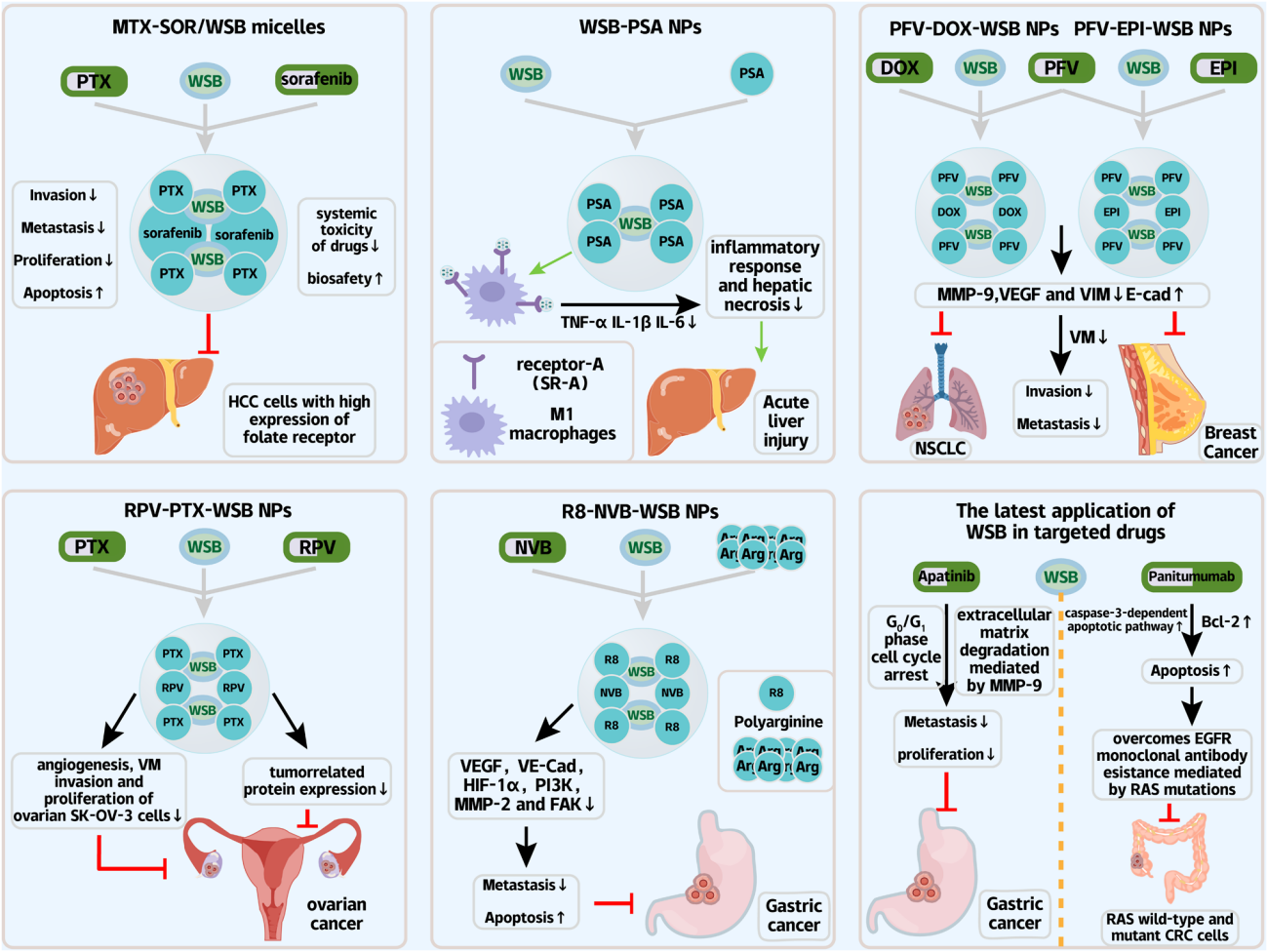

Figure 6. Bridging multidrug synergy and organ protection *via* lipid-based nanocarriers of WSB. WSB, Wuweizisu B; DOX, doxorubicin; HCC, hepatocellular carcinoma; PTX, Paclitaxel; SOR, sorafenib; NPs, Nanoparticles; PSA, Palmitic acid-modified serum albumin; TNF-α, Tumor necrosis factor-alpha; IL-1β, Interleukin-1β2; IL-6, Interleukin-6; M1, Macrophage 1; PFV, Penetratin-derived peptide, FV variant; EPI, Epirubicin; MMP-9, Matrix metallopeptidase 9; VEGF, Vascular endothelial growth factor; VIM, Vimentin; E-cad, E-cadherin; VM, Vasculogenic mimicry; NSCLC, Non-small cell lung cancer; RPV, Cell-penetrating peptide(Consists of arginine, proline and valine); Arg, Arginine; R8, cell-penetrating peptide(consists of eight consecutive arginine amino acids); NVB, VE-Cad, VE-cadherin; HIF-1α, hypoxia inducible factor 1 subunit alpha; PI3K, Phosphatidylinositide 3-kinases; MMP-2, Matrix metallopeptidase 2; FAK, Focal Adhesion Kinase; Bcl-2, B-cell lymphoma-2; Caspase-3, Cysteine-dependent aspartate-specific protease-3; EGFR, Epidermal growth factor receptor; CRC, colorectal cancer.

and suppressing Bcl-2 expression, thereby reversing drug resistance. This mechanism could translate to clinical trials testing WSB + panitumumab in RAS-mutant CRC, with Bcl-2 as a predictive biomarker (Fig. 6).

In combination with 5-FU, WSB downregulates P-gp and MRP1, reverses MDR, and triggers autophagic death via STAT3 inhibition (33,160) (Figs. 3 and 5; Table II). This mechanism is supported by extensive evidence that ABC transporters (such as P-gp/ABCB1 and MRP1/ABCC1) mediate drug efflux in CRC (161-164), and TCM compounds (such as evodiamine and neferine) restore chemosensitivity by suppressing these transporters (165,166). Such data support the potential of WSB as a chemosensitizer in neoadjuvant settings, where reducing the ABC transporter activity could increase 5-FU response rates.

These findings confirm the potential of WSB as an ideal chemosensitizer and provide a new strategy for the comprehensive treatment of colorectal cancer.

10. Advanced delivery strategies for WSB in precision oncology

WSB has been established as a promising and clinically feasible anticancer agent (167). The core advantages of these systems include the following: i) Passive tumor targeting leveraging the enhanced permeability and retention effect (168); ii) enhanced active targeting via ligand modification (169); and iii) precise drug release enabled by the design of pH/enzyme-sensitive carriers (170). Clinically, this is evidenced by successful nanoscale antitumor formulations, such as the polymeric micelle Genexol®-PM (loaded with paclitaxel), approved in South Korea for the treatment of metastatic BC and NSCLC. Compared with conventional paclitaxel, Genexol®-PM markedly improved the objective response rate (ORR: 56 vs. 27%) and reduced the incidence of neutropenia (171) (Fig. 6). Similarly, the liposomal formulation Lipusu® (paclitaxel for injection) is approved in China for the treatment of ovarian cancer and BC. Its combination regimen with cisplatin effectively treats inoperable NSCLC patients (172) (Fig. 6).

Stimulus-responsive nanotechnology have yielded the pH-sensitive formulations in which methotrexate-modified sorafenib/WSB micelles (methotrexate-SOR/WSB) demonstrate remarkable tumor specificity, dissociating in the acidic tumor microenvironment to simultaneously inhibit HCC progression and reduce systemic toxicity (173) (Fig. 6; Table II). With the respect to inflammatory modulation, albumin-based nanocarriers engineered with palmitic acid modifications (PSA systems) achieve targeted WSB delivery to M1 macrophages, effectively suppressing NF-κB-mediated inflammation in liver injury models while improving survival by 50% (75 vs. 25% in controls) (174) (Fig. 6; Table II).

Combinatorial approaches use polymeric nanosystems that coencapsulate the WSB with doxorubicin. These factors leverage the pH-dependent release kinetics to enhance mitochondrial targeting in BC stem cells, demonstrating the dual benefits of overcoming chemoresistance while preserving cardiac function (175,176) (Fig. 6; Table II). The field has further advanced through peptide-directed delivery platforms, including the PFV-modified liposomes that exploit tumor-specific integrin αvβ3 overexpression to disrupt metastatic vasculogenic mimicry networks (177) (Fig. 6; Table II), and RPV-conjugated systems that the achieve tumor penetration while suppressing the angiogenesis through VE-cadherin/MMP-9 regulation (178,179) (Fig. 6). Particularly innovative are charge-mediated R8-modified vinorelbine/WSB liposomes that concurrently inhibit EMT and prevent the treatment-limiting myelosuppression (180,181) (Fig. 6; Table II).

Despite these compelling preclinical results, clinical translation faces the significant hurdles associated with Good Manufacturing Practice manufacturing. For PFV-liposomes, extrusion-based preparation results in shear sensitivity during scale-up, risking lipid bilayer destabilization and drug leakage (177). The PSA platform requires strict control of palmitic acid conjugation stoichiometry to maintain targeting efficacy, a critical quality attribute that is challenging to standardize in large batches (182,183). Organic solvent residues necessitate complex purification (174), increasing production costs. Analytical complexity is heightened in codelivery systems, where simultaneous quantification of hydrophilic/hydrophobic drugs requires specialized methods (177).

To bridge this translational gap, integrated solutions are essential. These include the adoption of continuous manufacturing approaches such as microfluidic mixing to replace batchwise liposome extrusion (184,185), coupled with the greener synthesis methods such as supercritical CO_2-based nanoparticle production to eliminate toxic chlorinated solvents (186,187). The implementation of QbD principles is essential for optimizing critical conjugation parameters (such as reaction time and pH control) in PSA nanoparticle fabrication, whereas advanced process analytical technology (PAT) systems should be employed for real-time monitoring of critical quality attributes throughout production (188). These synergistic advancements, spanning manufacturing innovation, sustainable chemistry, systematic process optimization and enhanced quality control, collectively address the key technical and regulatory hurdles impeding clinical translation (Fig. 7).

While WSB nanocarriers exemplify the TCM-modern oncology integration, industrial viability hinges on resolving the material, process, and regulatory gaps, a challenge demanding cross-disciplinary collaboration.

11. Structural diversity and anticancer potential of Schisandra lignans

The TCM herb *Schisandra chinensis* produces a unique class of dibenzocyclooctadiene lignans that demonstrate significant anticancer potential through diverse molecular mechanisms (27). These compounds, including WSB and its structurally related analogs (SA, Sch A, SC, STA and SAL and gomisin compounds GA, GD, GG and GJ), share a conserved dibenzocyclooctadiene skeleton with variations in the substituents and stereochemistry, this structural homology underpins their overlapping yet distinct anticancer mechanisms, supporting the translational value of lignan-based drug development (4,189). While WSB has been extensively studied, emerging evidence reveals that these analogs exhibit complementary activities, amplifying the therapeutic potential of the lignan class (Figs. 8 and 9).

SA: A multifaceted lignan with potent anticancer and MDR-reversal properties. SA, a bioactive lignan derived

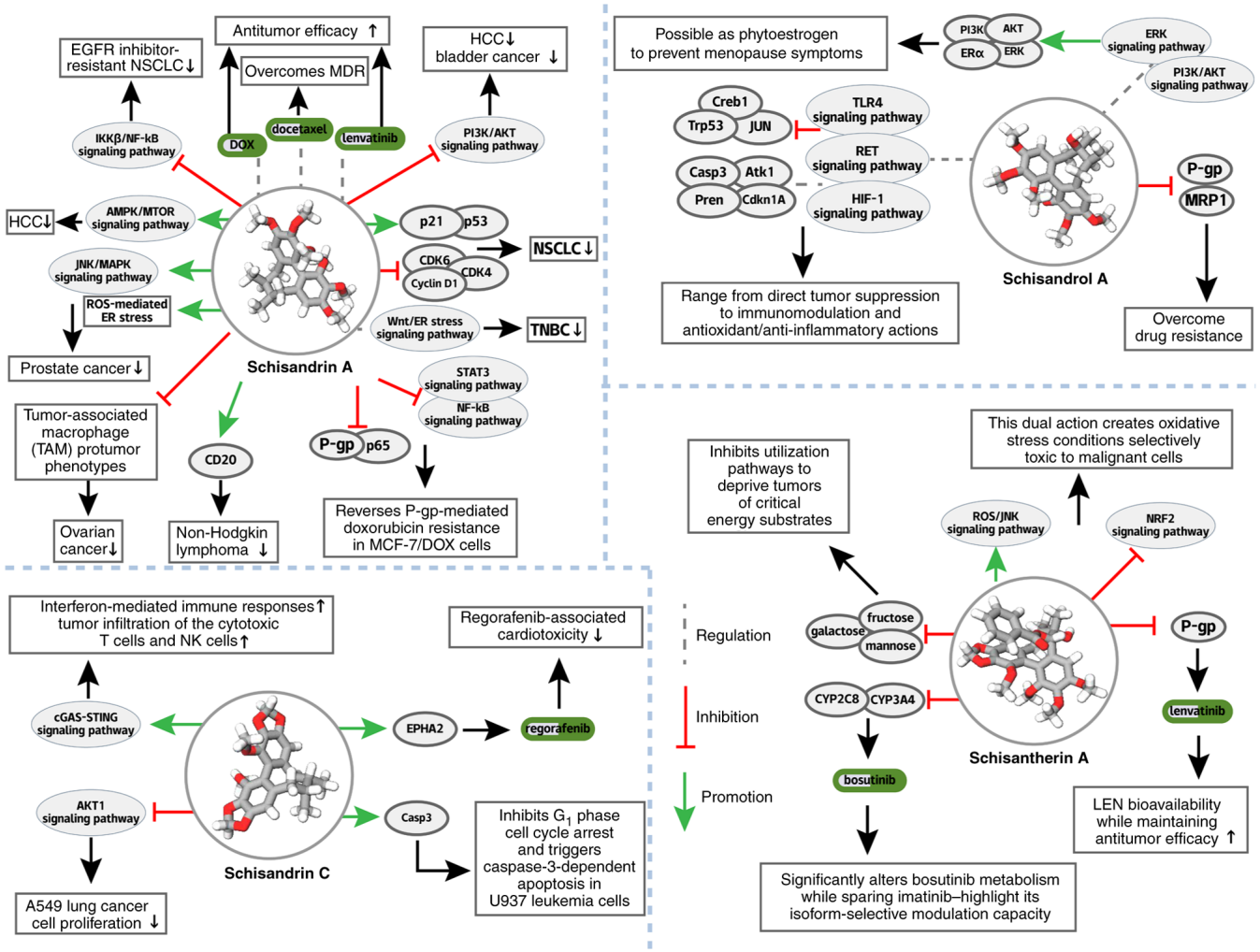

Figure 7. WSB analogues in synergistic tumor suppression (SA, Sch A, SC, and STA). WSB, Wuweizisu B; HCC, hepatocellular carcinoma; SA, Schisandrol A; SC, Schisandrin C; Sch A, Schisandrin A; STA, Schisantherin A; TAM, tumor-associated macrophage; NSCLC, non-small cell lung cancer.

from *Schisandra chinensis*, shares WSB's abilities to reverse MDR and target oncogenic pathways (190-193). Like WSB, which downregulates the P-gp via STAT3 inhibition (194) (Table III), SA disrupts P-gp-substrate complex formation (a novel mechanism distinct from WSB but complementary in overcoming efflux-mediated resistance) (195) (Fig. 8). It also inhibits MRP1, mirroring WSB's suppression of ABC transporters, while modulating the PI3K/AKT and ERK pathways, similar to the WSB's targeting of these cascades in various cancers (196) (Fig. 8). The favorable safety profile of SA enhances its potential as a combination partner, addressing unmet needs in the context of resistant malignancies (197).

Sch A: A multifaceted lignan with broad anticancer potential. Sch A, a dibenzocyclooctadiene lignan from *Schisandra chinensis*, shares a conserved core structure with WSB, driving overlapping yet complementary anticancer mechanisms (198-203).

In TNBC, Sch A induces G_0/G_1 cell cycle arrest and promotes apoptosis by modulating Wnt/ER stress signaling pathways (204) (Fig. 8; Table III). In NSCLC, Sch A regulates p53 and p21 expression; downregulates Cyclin D1, CDK4 and CDK6 and triggers mitochondria-dependent apoptosis, leading to G_1/S and G_2/M phase arrest (205) (Fig. 8; Table III). In ovarian cancer, Sch A suppresses TAM protumor phenotypes and induces G_0/G_1 phase arrest, highlighting its immunomodulatory potential (13) (Fig. 8; Table III).

Further studies have demonstrated the efficacy of Sch A in bladder cancer through inhibition of the ALOX5-mediated activity of the PI3K/AKT signaling pathway (206) (Fig. 8; Table III). In HCC, Sch A acts via AMPK/mTOR-dependent mitochondrial ferroptosis (207) (Fig. 8; Table III) and in PC, it activates ROS-mediated ER stress and the JNK/MAPK signaling pathway (208) (Fig. 8; Table III). Emerging evidence also suggests its activity against non-Hodgkin lymphoma through CD20 inhibition (209) (Fig. 8; Table III).

In addition, Sch A reverses P-gp-mediated doxorubicin resistance via the P-gp/NF-κB/STAT3 inhibition (210) (Fig. 8), complementing the WSB's STAT3-dependent P-gp downregulation by disrupting transporter-substrate interactions. It restores gefitinib sensitivity in EGFR-resistant NSCLC (211) (Fig. 8), synergizing with Lenvatinib (LEN) (212) (Fig. 8), expanding WSB's chemosensitization scope to the EGFR-TKI resistance.

Innovative drug delivery platforms have augmented the therapeutic potential of Sch A. Ultrasound-targeted

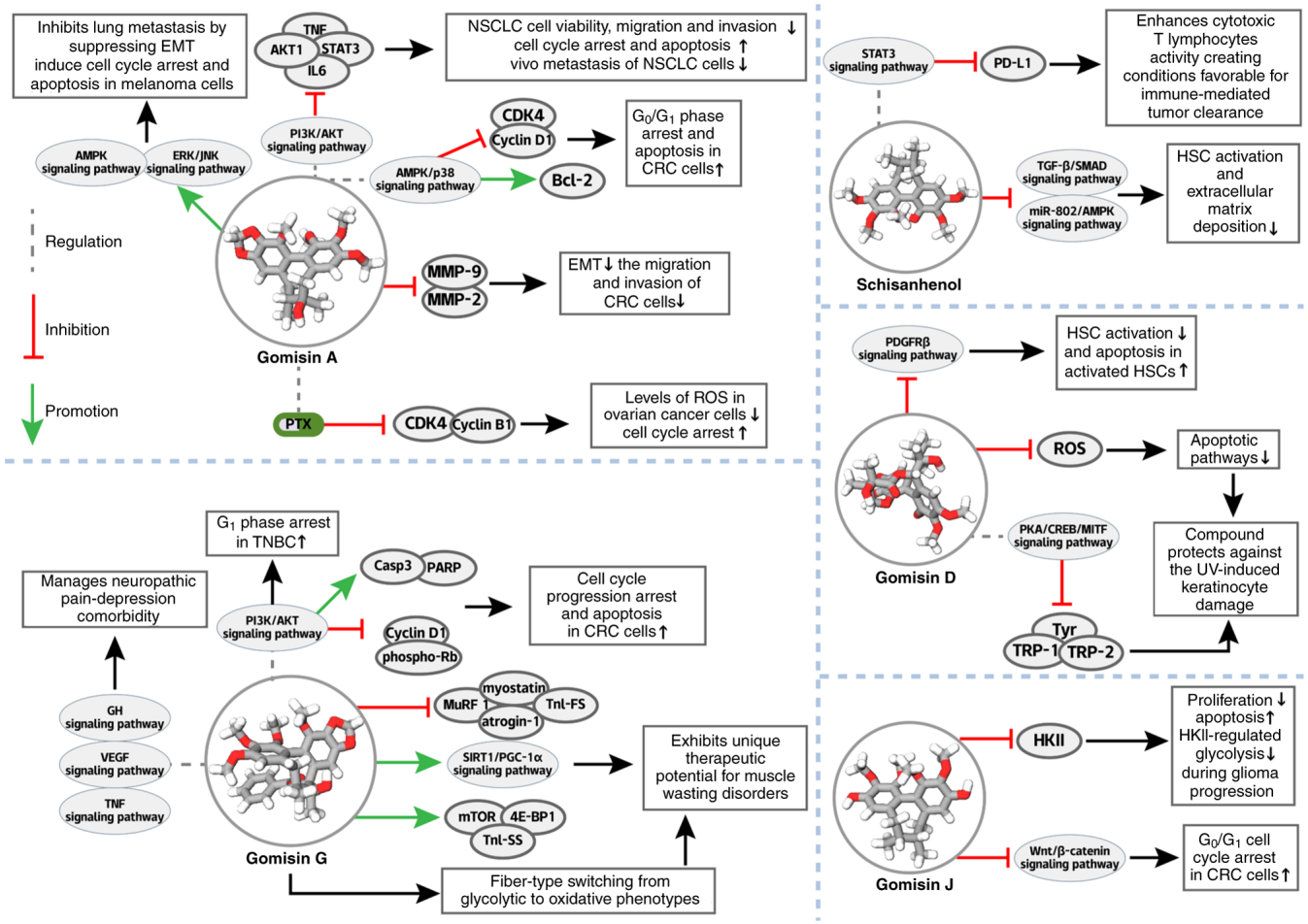

Figure 8. WSB analogues in synergistic tumor suppression (SA, Sch A, SC, and STA). WSB, Wuweizisu B; HCC, hepatocellular carcinoma; SA, Schisandrol A; SC, Schisandrin C; Sch A, Schisandrin A; STA, Schisantherin A; TAM, tumor-associated macrophage; NSCLC, non-small cell lung cancer; EGFR, Epidermal growth factor receptor; IKKβ, inhibitor of kappa B kinase; NF-κB, nuclear factor kappa-B; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-Activated Protein Kinase; HCC, hepatocellular carcinoma; ROS, reactive oxygen species; ER, Estrogen receptor; CD20, Cluster of Differentiation 20; P-gp, P-glycoprotein; p53, Tumor protein 53; p21, Tumor protein 21; p65, Tumor protein 65; DOX, doxorubicin; STAT3, signal transducer and activator of transcription 3; TNBC, Triple negative breast cancer; CDK4, cyclin dependent kinase 4; CDK6, cyclin dependent kinase 6; PI3K, Phosphatidylinositide 3-kinases; AKT, Protein kinase B; MDR, multi-drug resistant; TLR4, Toll-like receptor 4; RET, Rearranged during transfection proto-oncogene; HIF-1, hypoxia inducible factor 1; Creb1, Cyclic AMP-responsive element-binding protein 1; Trp53, Tumor protein 53; Casp3, Cysteine-dependent aspartate-specific protease-3; Atk1, protein kinase B; Cdkn1A, Cyclin-dependent kinase inhibitor 1A; ERK, Extracellular regulated protein kinases; ERα, Estrogen Receptor alpha; MRP1, Multidrug Resistance Protein 1; cGAS, Cyclic GMP-AMP synthase; STING, Stimulator of interferon genes; EPHA2, Erythropoietin-producing hepatocellular A2; NRF2, Nuclear Factor erythroid 2-Related Factor 2.

microbubble destruction with Span-PEG carriers enhances Sch A uptake in Walker-256 hepatoma cells, inhibiting the PI3K/AKT/mTOR pathway (213) (Fig. 8). A microemulsion system loaded with docetaxel and Sch A overcomes esophageal cancer MDR (211) (Fig. 8), whereas long-circulating liposomes loaded with Sch A/doxorubicin (SchA-DOX-Lip) enhance apoptosis induction and tumor targeting in HCC (214) (Fig. 8). These advancement strategies are directly applicable to WSB, leveraging structural similarity for formulation optimization. Together, their complementary mechanisms and shared delivery solutions support lignan-based combination therapies, maximizing clinical utility.

SC: A dual-function agent in toxicity mitigation and cancer therapy. SC, a dibenzocyclooctadiene lignan from *Schisandra chinensis*, shares structural homology with WSB, suggesting its dual role in mitigating chemical toxicity and antitumor activity (215,216).

In toxicity mitigation, SC counteracts regorafenib-induced hepatotoxicity and cardiotoxicity via EphA2 Ser897 phosphorylation and EPHA2 restoration (217,218), complementing WSB's DOX cardioprotection (p38MAPK-ATM-p53 axis) (130,131) (Fig. 8), with structural similarity enabling tissue-specific cytoprotection (liver/heart vs. WSB's cardiac focus).

Antitumorally, SC induces G_1 arrest and caspase-3-dependent apoptosis in leukemia (219) (Table III) and suppresses A549 proliferation via inhibition of the AKT1 activity (220) (Fig. 8; Table III), which aligns with the ability of WSB to target the AKT pathway in solid tumors. Its unique activation of cGAS-STING to enhance cytotoxic T/NK cell infiltration promotes WSB's TAM polarization in BC, broadening lignan-mediated immune modulation (221-223) (Fig. 8; Table III).

SC's dual capacity supports combination strategies: Coadministration with regorafenib to reduce toxicity while enhancing efficacy. Formulation advances (such as targeted

Table III. Anti-tumor effects of the isomer of WSB.

Authors, year	Isomers	Type of cancer	Targets/ Pathways	IC_{50} (24 h or 48 h)	Effect	(Refs.)
Fong *et al*, 2007	SA	HCC	P-gp	/	Reversal of P-gp MDR	(194)
Xu *et al*, 2019	SchA	TNBC	Wnt/ER	26.90±2.13 μM (MDA-MB-231), 80.30±2.52 μM (BT-549), 61.94±9.14 μM (MCF-7)	Apoptosis, induces G_0/G_1 phase arrest	(204)
Zhu *et al*, 2021		NSCLC	p53, p21, cyclin D1, CDK4, CDK6	61.09 μM (A549), 101.5 μM (H1299), 39.99 μM (H1975), 49.45 μM (BEAS-2B)	Apoptosis, induces G_1/S and G_2/M phase arrest	(205)
Lee *et al*, 2018		Ovarian cancer	Tumor-associated macrophage	27.81 μM (27.81), 70.34 μM (OVCAR3), 67.99 μM (SKOV3)	Induces G_0/G_1 phase arrest	(13)
Chi *et al*, 2022		Bladder cancer	ALOX5-mediated the PI3K/Akt	/	Apoptosis	(206)
He *et al*, 2024		HCC	AMPK/mTOR	/	Mitochondrial ferroptosis	(207)
Peng *et al*, 2025		PC	ROS-mediated ER stress, JNK/MAPK	/	Apoptosis	(208)
Ding *et al*, 2024		Non-Hodgkin lymphoma	CD20	/	Targeted immunity	(209)
Park *et al*, 2009	SC	U937 leukemia cells	caspase-3	/	Apoptosis, G_1 phase arrest	(219)
Wang *et al*, 2024		LC	AKT1	/	Suppress the proliferation and viability	(220)
Wu *et al*, 2024		BC, CRC	cGAS-STING	/	Promoting tumor infiltration of the cytotoxic T cells and NK cells	(223)
Wang *et al*, 2020	STA	GC	ROS/JNK, Nrf2	/	Apoptosis, G_2/M phase arrest	(225)
Feng *et al*, 2022		HCC	/	/	Regulate glucose metabolism in HCC cells to inhibit cell proliferation and migration	(226)
Zhang *et al*, 2025	SAL	HCC	STAT3, PD-L1	/	Enhance immune regulation	(235)
Liu *et al*, 2024	Gomisin A	NSCLC	PI3K/Akt	/	Suppression metastasis	(237)
Kee *et al*, 2018		CRC	MMP-2, MMP-9	/	Suppresses EMT	(239)
Han *et al*, 2020		Melanoma	AMPK, ERK, JNK	/	Suppression Metastasis	(240)
Maharjan *et al*, 2019	Gomisin G	CRC	PI3K-Akt, PARP, caspase-3, cyclin D1, phospho-Rb	/	Apoptosis, suppressing cell cycle progression	(243)
Maharjan *et al*, 2018		TNBC	PI3K/Akt	/	G_1 phase arrest	(258)
Kang *et al*, 2012	Gomisin J	CRC	Wnt/β-catenin	/	G_0/G_1 phase arrest	(248)

Table III. Continued.

Authors, year	Isomers	Type of cancer	Targets/ Pathways	IC_{50} (24 h or 48 h)	Effect	(Refs.)
Li *et al*, 2020		Glioma	HKII	15.19±1.38 μM (24 h U87), 21.90±1.75 μM (24 h U251)	Mitochondrial apoptosis, disrupting tumor metabolism	(249)

WSB, Wuweizisu B; SA, Schisandrol A; Sch A, Schisandrin A; SC, Schisandrin C; STA, Schisantherin A; SAL, Schisanhenol; SA, Schisandrin A; HCC, Hepatocellular Carcinoma; P-gp, P-glycoprotein; MDR, Multidrug Resistance; TNBC, Triple-Negative Breast Cancer; Wnt/ER, Wnt/Estrogen Receptor pathway; NSCLC, Non-Small Cell Lung Cancer; p53, Tumor Protein p53; p21, Cyclin-Dependent Kinase Inhibitor 1A; CDK4, Cyclin-Dependent Kinase 4; CDK6, Cyclin-Dependent Kinase 6; ALOX5, Arachidonate 5-Lipoxygenase; PI3K, Phosphoinositide 3-Kinase; Akt, AKT Serine/Threonine Kinase; AMPK, AMP-Activated Protein Kinase; mTOR, Mammalian Target of Rapamycin; PC, Prostate Cancer; ROS, Reactive Oxygen Species; ER, Endoplasmic Reticulum; JNK, c-Jun N-terminal Kinase; MAPK, Mitogen-Activated Protein Kinase; LC, Lung Cancer; AKT1, AKT Serine/Threonine Kinase 1; BC, Breast Cancer; CRC, Colorectal Cancer; cGAS-STING, cyclic GMP-AMP Synthase-Stimulator of Interferon Genes pathway; NK cells, Natural Killer cells; GC, Gastric Cancer; Nrf2, Nuclear Factor Erythroid 2–Related Factor 2; STAT3, Signal Transducer and Activator of Transcription 3; PD-L1, Programmed Death-Ligand 1; MMP-2, Matrix Metallopeptidase 2; MMP-9, Matrix Metallopeptidase 9; EMT, Epithelial-Mesenchymal Transition; ERK, Extracellular Signal-Regulated Kinase; PARP, Poly (ADP-ribose) Polymerase; phospho-Rb, Phosphorylated Retinoblastoma protein; Wnt/β-catenin, Wnt/Beta-Catenin pathway; HKII, Hexokinase II.

delivery), adaptable from WSB's nanotechnology research, could optimize tissue-specific distribution, maximizing its integrative potential.

STA: An agent with direct antitumor and pharmacokinetic modulation properties. STA, a dibenzocyclooctadiene lignan from *Schisandra chinensis* sharing structural homology with WSB, exhibits dual functions, direct antitumor activity and pharmacokinetic modulation, that complement the mechanisms of WSB, expanding the therapeutic scope of the lignan class (224). In GC, STA triggers ROS/JNK-mediated apoptosis while suppressing Nrf2, creating selective oxidative stress in malignant cells (225) (Fig. 8; Table III), complementing WSB's ROS regulation in tumor cells (such as BC) but with distinct Nrf2 targeting, thus broadening redox-based anticancer strategies. In HCC, it uniquely inhibits galactose/fructose/mannose utilization to starve tumors (226) (Fig. 8; Table III), extending WSB's metabolic regulation (such as AMPK/mTOR in NAFLD (62-64)) by focusing on sugar metabolism, a pathway underutilized by WSB (Fig. 8).

Pharmacokinetically, the STA modulates drug metabolism to enhance efficacy: it increases the cyclophosphamide exposure (227), selectively inhibits CYP3A4/CYP2C8 (altering bosutinib but not imatinib metabolism) (228) (Fig. 8) and, most notably, increases LEN bioavailability in patients with HCC via intestinal P-gp suppression (229,230) (Fig. 8).

This isoform-specific control complements WSB's broader CYP3A interactions (149), reducing off-target risks while enhancing chemotherapeutic efficacy, a critical advantage over WSB's occasional drug-drug antagonism (such as with P-gp substrates). Clinically, the synergy of STA with LEN supports its use as a 'pharmacokinetic enhancer' in HCC, paired with WSB pathway inhibition (such as TGF-β/EMT) for combined efficacy. Formulation advances, adaptable from WSB delivery research, could optimize metabolic targeting and reduce CYP-mediated interactions, with therapeutic drug monitoring (as with WSB) critical to balance synergy and toxicity. This dual activity positions STA as a valuable complement to WSB, leveraging structural similarity for coordinated, mechanism-driven combination therapies.

SAL: A multitargeted therapeutic agent for liver diseases and HCC. SAL, a dibenzocyclooctadiene lignan that shares structural homology with WSB, exhibits multitargeted activity across liver diseases, from NAFLD to HCC, complementing the hepatic effects of WSB through overlapping yet distinct mechanisms (231,232).

In NAFLD, SAL reprograms metabolism via the miR-802/AMPK axis (233) (Fig. 9), paralleling the AMPK/mTOR activation of WSB in hepatic steatosis, with structural similarity enabling shared regulation of energy homeostasis but via unique miRNA-mediated fine-tuning. Its antifibrotic activity, driven by dual inhibition of TGF-β/SMAD and MAPK (234) (Fig. 9), aligns with WSB's suppression of TGF-β signaling in liver fibrosis, reinforcing the ability of the lignan class to target fibrotic pathways through conserved structural features.

In HCC, SAL targets STAT3 to inhibit proliferation and downregulate PD-L1, enhancing CTL activity (235) (Fig. 9) and complementing anti-HCC mechanisms of WSB [such as RhoA/ROCK1 inhibition (78-80) (Fig. 9)] by increasing the degree of immunomodulation and WSB minimally affects liver cancer. This convergence of metabolic, fibrotic, and immunologic regulation positions SAL as a bridge between WSB's hepatic protection and novel immunotherapeutic strategies in HCC.

Clinically, the ability of SAL to span NAFLD-fibrosis-HCC progression, paired with the broader anticancer spectrum of WSB, supports the use of combination strategies. Formulation advances, which are adaptable to WSB research, could optimize the pharmacokinetics of both compounds, maximizing their synergistic potential in liver disease management.

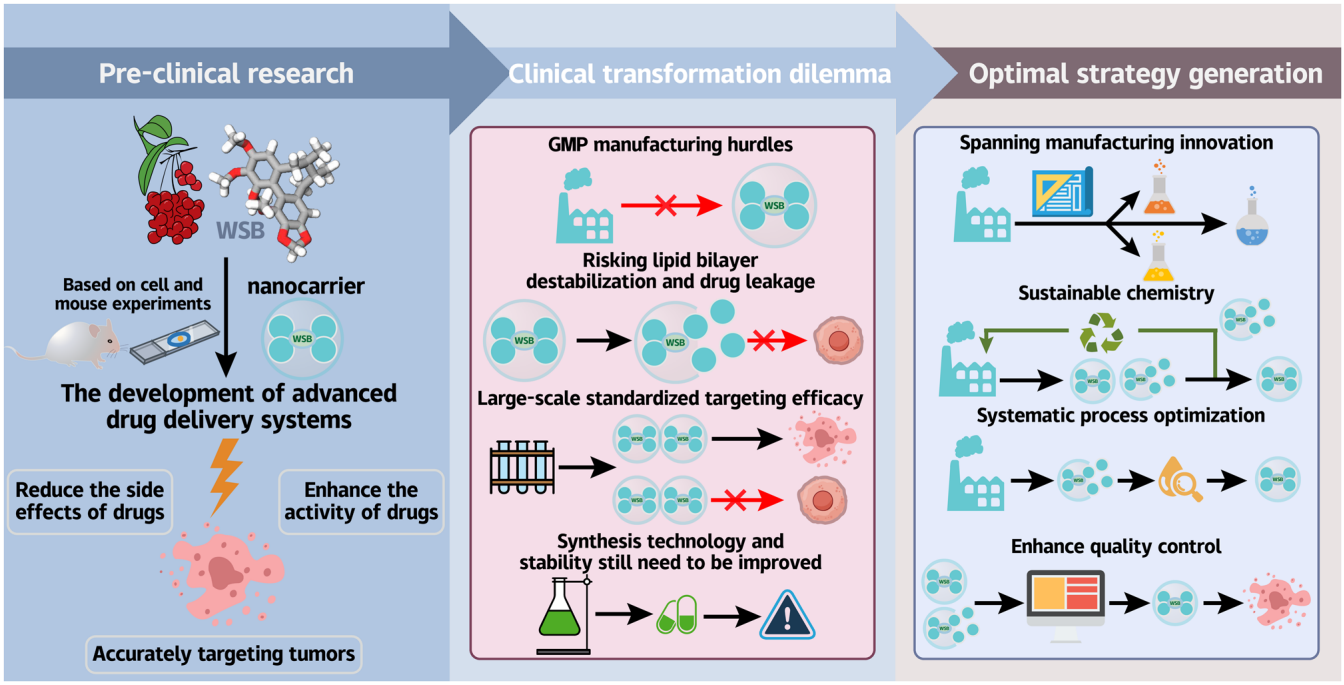

Figure 9. Schematic diagram of WSB conversion. WSB, Wuweizisu B; GMP, Good Manufacturing Practice.

GA: A lignan with broad-spectrum anticancer activity. GA, a dibenzocyclooctadiene lignan from *Schisandra chinensis* that shares structural homology with the WSB, exhibits the broad-spectrum anticancer activity through the multitargeted pathway modulation, complementing WSB's mechanisms across diverse malignancies (236). In NSCLC, GA targets TNF, AKT1, STAT3, IL6 and PI3K/AKT (237) (Fig. 9; Table III), paralleling WSB's inhibition of PI3K/AKT and STAT3 in LC, with structural similarity enabling overlapping pathway engagement while expanding to the TNF/IL6, which WSB minimally affects. In osteosarcoma, GA enhances paclitaxel efficacy via ROS modulation and CDK4/Cyclin B1 regulation (238) (Fig. 9), mirroring WSB's chemosensitization of taxanes but with distinct cell cycle control nodes, reinforcing the synergy of lignans with taxane-based regimens. In CRC, GA induces G_0/G_1 arrest, promotes apoptosis, and suppresses EMT via MMP-2/9 inhibition (239) (Fig. 9; Table III), aligning with WSB's EMT suppression through the blockade of TGF-β activity, with GA extending coverage to MMP-mediated metastasis, a key complementary mechanism. In melanoma, it activates AMPK, ERK, and JNK (240) (Fig. 9; Table III), pathways also targeted by WSB in other cancers, highlighting conserved lignan-mediated stress signaling.

Translational efforts should focus on optimizing bioavailability (exploiting WSB's formulation advances), identifying biomarkers and developing combinations, capitalizing on the structural overlap of GA with WSB to design coordinated regimens that maximize pathway coverage across NSCLC, osteosarcoma, CRC and melanoma.

GD: A dual-target therapeutic agent for hepatic and dermatological pathologies. GD, a dibenzocyclooctadiene lignan from *Schisandra chinensis* sharing structural homology with WSB, acts as a dual-target agent, modulating hepatic fibrogenesis and dermatological pathologies through mechanisms that complement WSB activity.

In hepatic fibrosis, GD selectively disrupts the PDGF-BB/PDGFRβ cascade to suppress HSC activation and induce apoptosis in activated HSCs (241) (Fig. 9), complementing the anti-fibrotic effects of WSB (such as TGF-β/SMAD inhibition) by targeting PDGFRβ, a pathway that WSB does not directly engage in, thereby broadening lignan-mediated control of fibrosis in CCl_4-induced models. Beyond the liver, GD protects against UV-induced keratinocyte damage via the ROS scavenging and the apoptotic pathway inhibition while suppressing melanogenesis through the PKA/CREB/MITF axis inhibition (242) (Fig. 9), extending the ROS-modulating properties (shared with WSB) of the lignan class to dermatological contexts, with structural similarity enabling both to regulate oxidative stress, but in tissue-specific ways (hepatic vs. cutaneous).

Translational efforts should focus on optimizing targeted delivery systems (adaptable from formulation research on WSB), exploring synergies with existing antifibrotics/dermatological agents and investigating preventive potential in high-risk populations, leveraging the structural overlap of GD with WSB to design combination strategies that maximize dual efficacy in hepatic and dermatological pathologies.

GG: A multimodal therapeutic agent with diverse clinical applications. GG, a dibenzocyclooctadiene lignan from *Schisandra chinensis* sharing structural homology with WSB, exhibits multimodal activity, spanning oncology, musculoskeletal and neuropsychiatric disorders, with mechanisms that complement the profile of WSB.

In oncology, GG inhibits PI3K-AKT signaling to induce apoptosis (via PARP/caspase-3 cleavage) and suppresses the cell cycle (Cyclin D1/phospho-Rb downregulation) in

colorectal cancer and triggers G_1 arrest in TNBC through inhibition of the AKT activity (243,244) (Fig. 9; Table III) , mirroring the ability of WSB to target PI3K/AKT in various types of cancer but with enhanced specificity for inhibition of the activity of PI3K, creating a complementary strategy with respect to the broader inhibition of WSB. As well as tumors, GG counteracts muscle wasting via myostatin modulation and the SIRT1/PGC-1α-mediated mitochondrial biogenesis (245) (Fig. 9) and alleviates neuropathic pain-depression comorbidity through TNF/VEGF/GH regulation (246) (Fig. 9), extending the multitarget potential (shared with WSB) of the lignan class to nononcologic contexts, leveraging structural similarity to drive pleiotropic effects.

Translational efforts should focus on WSB progress: Optimizing structure-activity relationships (to increase target specificity), improving pharmacokinetics via advances in formulation (adaptable from WSB delivery research) and identifying biomarkers for stratification. The ability of GG to complement WSB in oncology while expanding into other therapeutic areas underscores the versatility of the lignan class, rooted in their conserved dibenzocyclooctadiene scaffold.

12. GJ: A multi-mechanistic anticancer agent with broad therapeutic potential

GJ demonstrates significant potential as an anticancer agent, exhibiting efficacy across multiple cancer types through simultaneous targeting of diverse oncogenic pathways. In BC models, GJ uniquely induces both classical apoptosis and necroptosis, showing particular efficacy against apoptosis-resistant populations that drive treatment failure and recurrence (247). This dual cell death mechanism addresses a critical clinical challenge in managing aggressive BC subtypes.

The anticancer activity of GJ extends to CRC, where it suppresses the Wnt/β-catenin pathway (a key driver of colorectal carcinogenesis) and induces G_0/G_1 cell cycle arrest (248) (Fig. 9; Table III). These coordinated actions on oncogenic signaling and cell cycle regulation underlie its potent antitumor effects in CRC. In glioma models, GJ adopts a multifaceted approach: triggering mitochondrial apoptosis while disrupting tumor metabolism via the HKII-mediated glycolysis inhibition (249) (Fig. 9; Table III), simultaneously targeting cell survival and energy production pathways essential for tumor growth.

The multi-target activity of GJ its and capacity to overcome treatment resistance position it as a promising therapeutic candidate, necessitating further development of optimized formulations, predictive biomarkers, and rational combination strategies for clinical translation.

13. Conclusion and future perspectives

WSB, a bioactive lignan derived from *Schisandra chinensis*, demonstrates significant potential as a multi-target anticancer agent through its ability to modulate key oncogenic pathways, induce apoptosis and remodel the TME. However, while extensive preclinical studies support its efficacy across various types of cancer and demonstrate synergy with conventional therapies, clinical translation requires addressing critical challenges. The absence of large-scale clinical validation poses a major limitation, necessitating rigorous phase I-II trials to evaluate safety, pharmacokinetics and efficacy in humans. Further research is needed to precisely delineate the molecular targets of WSB, particularly its immunomodulatory and metabolic effects within the TME. Addressing inherent pharmacokinetic limitations requires developing advanced drug delivery systems, such as nanoparticle formulations or structural analogs, to enhance bioavailability and tumor specificity. Future research should also explore integrating WSB into personalized treatment regimens, leveraging its dual role as a chemosensitizer and cytoprotective agent to optimize therapeutic outcomes.

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Availability of data and materials

Not applicable.

Authors' contributions

LZ, YL, CL, and YT conceived and supervised this work. LZ, YL, ZC, JM, ZH, and XS organized the literature, wrote the manuscript and created charts. LZ and YL provided funding. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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