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Review Article

Pharmacological Insights into *Scleromitrion diffusum* (Willd.) Against Gastric Cancer: Active Components and Mechanistic Pathways

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Abstract

Gastric cancer remains a significant global health burden, with limited therapeutic options and poor clinical outcomes. Although conventional treatments such as surgery and chemotherapy are widely used, their effectiveness is often hindered by adverse effects and high recurrence rates, highlighting the urgent need for safer and more effective alternatives. *Scleromitrion diffusum* (Willd.) (*S. diffusum*), a well-established anticancer herb in traditional Chinese medicine, has demonstrated promising clinical potential against gastric cancer. This review systematically examines the bioactive components of *S. diffusum* and their multi-target mechanisms of action against gastric cancer. Key active compounds, including flavonoids, anthraquinones, and terpenoids, have been identified as exerting synergistic anti-gastric cancer effects. These compounds collectively target critical pathways in gastric cancer pathogenesis, including apoptosis induction, suppression of proliferation and angiogenesis, and immune modulation. The mechanistic elucidation presented in this review not only validates the traditional use of *S. diffusum* in cancer management but also provides a molecular basis for its potential application in precision medicine strategies for gastric cancer. Beyond summarizing existing evidence, this work highlights critical gaps in current knowledge and proposes essential directions for future research, providing important references for integrating traditional medicine with modern oncology approaches.

Introduction

Gastric cancer is a malignant disorder of the digestive tract, predominantly affecting middle-aged and elderly populations. Globally, it ranks fifth in incidence and fourth in mortality.[1] Its pathogenesis involves multiple factors, including genetics, environment, and dietary habits. As a high-incidence region for gastric cancer, China faces challenges with low long-term survival rates among advanced-stage patients. The disease ranks third in cancer-related mortality,[2] with a five-year survival rate of merely 35.9%, significantly lower than that of South Korea (68.9%) and Japan (60.3%).[3] Although surgery remains the curative approach for early-stage gastric cancer, approximately 70% of patients are diagnosed at an advanced stage due to insidious and nonspecific symptoms.[4] Despite advances in systemic therapy, achieving curative treatment remains biologically unattainable. This current landscape urgently necessitates the development of novel anticancer agents by medical researchers to overcome the limitations of existing therapies.

In the landscape of anticancer drug discovery, traditional Chinese medicine (TCM) has emerged as a valuable resource offering unique therapeutic perspectives. Among pharmacologically validated TCM herbs, *Scleromitrion diffusum* (Willd.) (*S. diffusum*; nomenclature verified via The Plant List, http://www.theplantlist.org, accessed February 24, 2025) holds particular significance. This herb, first documented in the *Flora of Guangxi*, has been clinically employed for millennia in oncology practice, especially for gastrointestinal malignancies. *S. diffusum* is pharmacologically characterized by its bitter taste and cold nature, with particular affinity for the stomach and large intestine meridians. Its traditional applications center on heat-clearing, toxin-resolving, blood-invigorating, and stasis-dissipating properties—therapeutic actions that align precisely with TCM's understanding of gastric

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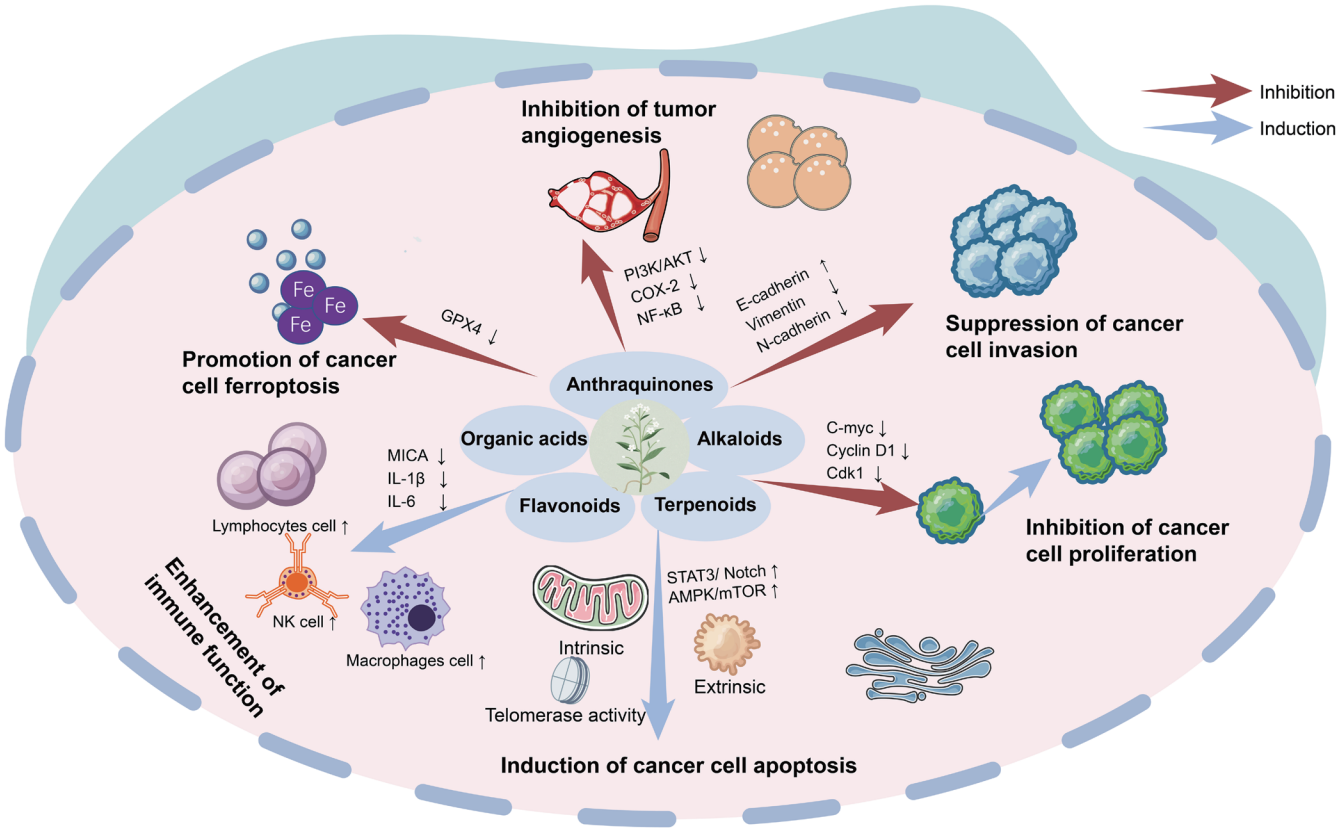

Fig. 1. A comprehensive overview of *Scleromitrion diffusum*'s multi-component, multi-target anticancer mechanisms through a systems biology approach. The figure demonstrates how its major bioactive compound classes work synergistically to target multiple oncogenic processes simultaneously. AKT, protein kinase B; AMPK, AMP-activated protein kinase; COX-2, cyclooxygenase-2; GPX4, glutathione peroxidase 4; IL, interleukin; MICA, major histocompatibility complex class I-related chain A; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NK, natural killer; PI3K, phosphatidyqinositol-3 kinase; STAT3, signal transducer and activator of transcription 3.

cancer pathogenesis. According to TCM theory, gastric cancer develops through a progression from external pathogen exposure to qi stagnation, blood stasis, and ultimately the formation of "toxin-stasis interbinding". This pathophysiological state represents the accumulation of heat-toxin in the middle energizer, combined with persistent qi stagnation and blood stasis. Therefore, the anti-gastric cancer mechanism of *S. diffusum* precisely targets these TCM pathological characteristics. Prior studies demonstrate that the combined use of *S. diffusum* and *Scutellaria barbata* at standard doses of 15–30 g significantly enhances anticancer efficacy without observable toxicity within therapeutic ranges.[5] In a clinical study of advanced cachexia patients (including gastric cancer cases), treatment with the Detoxification and Anti-Cancer Decoction containing *S. diffusum* (standard dose: 30 g) resulted in significantly higher hemoglobin and albumin levels compared to controls. Concurrently, clinical symptoms including fatigue, abdominal distension, and anorexia showed marked improvement, leading to significantly enhanced quality of life.[6]

Modern pharmacological studies have substantiated *S. diffusum*'s traditional applications, revealing significant progress in understanding its bioactive constituents and their multi-target mechanisms against gastric cancer. These compounds collectively exert anticancer effects by disrupting stasis through angiogenesis inhibition and metastasis suppression, and by directly inducing apoptosis and immune modulation. This review systematically examines *S. diffusum*'s anti-gastric cancer potential by analyzing its active components, elucidating molecular mechanisms aligned with TCM theory, and identifying key research gaps (Fig. 1). By integrating millennia of clinical experience with modern pharmacological insights, we discuss *S. diffusum*'s translational potential as a well-tolerated therapeutic agent, providing a paradigm for bridging traditional medicine and contemporary oncology research.

Active anticancer compounds of *S. diffusum*

The significant advantage of *S. diffusum* as an anticancer herb primarily stems from the well-documented anticancer activity of its major chemical constituents.[7] Utilizing modern spectroscopic techniques and advanced analytical instruments, multiple active substances in *S. diffusum*, such as flavonoids, anthraquinones, sterols, terpenoids, and polysaccharides, can now be systematically identified and characterized. Figure 2 illustrates the structural features of these anticancer components. The total flavonoids in *S. diffusum* inhibit liver cancer, gastric cancer, and colorectal cancer by suppressing proliferation, invasion, and metastasis, and by promoting apoptosis of cancer cells. Total flavonoid content varies geographically: *S. diffusum* from Guangdong, China, contains approximately 1.3%, slightly exceeding that from Guangxi (1.16%) and Jiangxi (1.038%). Over a dozen flavonoids have been isolated from *S. diffusum*, with kaempferol, quercetin, and

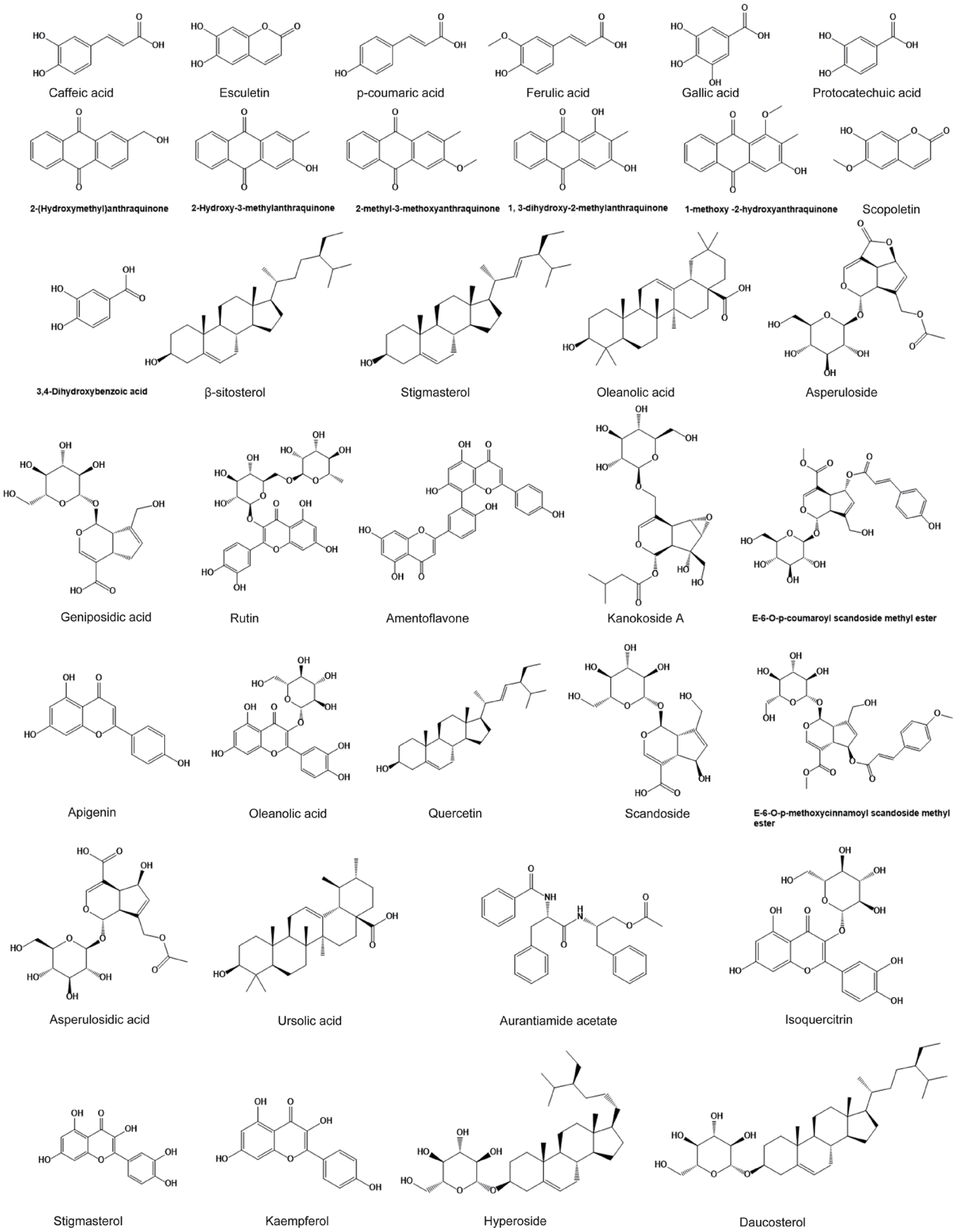

Fig. 2. Structural formula of the active anticancer compound in *Scleromitrion diffusum*. This figure presents the chemical structure of the primary bioactive compound responsible for *Scleromitrion diffusum*'s anticancer activity.

their glycosides serving as the primary anticancer agents.[8] Terpenoids comprise mainly triterpenes (e.g., oleanolic acid, ursolic acid, dicoumaric acid) and iridoids (typically glycosidic). These components suppress gastric cancer by targeting key tumor proteins, blocking oncogenic signaling pathways, and modulating the tumor microenvironment. Anthraquinones (e.g., 1,3-dihydroxy-2-methylanthraquinone, 2-hydroxy-3-methylanthraquinone) are predominantly alizarin-type, with minor emodin-type derivatives, inhibiting cancer via mitochondrial apoptosis. Furthermore, *S. diffusum* polysaccharides exhibit dual regulation: selectively inhibiting cancer cell growth without significant impact on normal cells, while enhancing immune function through elevated superoxide dismutase activity, scavenging of oxygen free radicals, and resistance to lipid peroxidation, thereby amplifying anticancer efficacy.[9]

Molecular pathways of *S. diffusum* in gastric cancer intervention

S. diffusum is a crucial anticancer drug in TCM and contains many anticancer active compounds. These compounds exhibit remarkable activity both *in vivo* and *in vitro* and exert anticancer effects through different pathways (Table 1).[10–44] Its bioactive compounds ultimately achieve anticancer effects by interfering with multiple cell signaling pathways (Fig. 3).

Induction of cancer cell apoptosis

Apoptosis is a genetically controlled, autonomous, and orderly process of cell death, whose traditional pathways include the extrinsic pathway (receptor-mediated apoptosis pathway) and the intrinsic pathway (mitochondria-mediated apoptosis pathway).[45] In addition, telomerase is a reverse transcriptase complex that synthesizes telomeric DNA using RNA as a template to extend cell lifespan.[46] It is inhibited in normal tissues and activated in cancer cells. In this pathway, apoptosis mainly occurs through the inhibition of the expression of the human telomerase reverse transcriptase (hTERT) gene. Therefore, it can serve as a cancer-specific marker and a therapeutic target.[47]

S. diffusum can promote apoptosis in cancer cells by activating specific signaling pathways.[48,49] Phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase, and many other signaling pathways play important roles in cell proliferation and apoptosis.[50] In inducing exogenous apoptosis, *S. diffusum* significantly promotes apoptosis in gastric cancer cells. Kaempferol can inhibit the expression of the hTERT gene and the PI3K/AKT pathway, thereby reducing telomerase activity, inducing apoptosis, and suppressing the proliferation of gastric cancer cells.[51] When combined with the chemotherapeutic drug cisplatin, *S. diffusum* enhances cisplatin's inhibitory effect on gastric cancer cell proliferation while reducing glycolysis, promoting apoptosis, and lowering chemoresistance, demonstrating synergistic anticancer effects. These actions may be associated with the suppression of the signal transducer and activator of transcription 3/Notch signaling axis, downregulation of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2), and upregulation of P53 expression.[52] Furthermore, the 5-Fluorouracil/protocatechuic acid synergy exerts anti-proliferative/pro-apoptotic effects and suppresses colony formation in AGS cells via P53 activation and Bcl-2 inhibition, demonstrating dual clinical advantages: reduced 5-Fluorouracil dosing requirements and enhanced apoptosis pathway targeting.[53] Regarding the intrinsic apoptotic pathway, the total flavonoids in *S. diffusum* induce the accumulation of reactive oxygen species in gastric cancer cells, causing mitochondrial membrane damage and abnormal changes in membrane potential, which subsequently lead to alterations in cell morphology and reduced cell numbers. This process further promotes the release of cytochrome C and apoptosis-inducing factor into the cytosol, triggering the caspase cascade and ultimately mediating gastric cancer cell apoptosis.[54,55] Notably, quercetin, a key component of *S. diffusum*, acts synergistically through multiple pathways: it not only enhances caspase-3/9 activity in human gastric cancer MKN45 cells to promote apoptosis,[8] but also dose-dependently reduces mammalian target of rapamycin (mTOR) expression by increasing the light chain 3-II/ I autophagic flux ratio and elevating P53 and AMP-activated protein kinase (AMPK) protein levels.[56] Simultaneously, it suppresses gastric cancer cell proliferation via the AMPK/mTOR signaling pathway, concurrently inducing autophagy and promoting apoptosis.[57]

Promotion of cancer cell ferroptosis

Ferroptosis, a novel form of programmed cell death, is morphologically, genetically, and biochemically distinct from other cell death pathways. It is characterized by iron-dependent accumulation of lipid peroxides and resultant oxidative damage. Current evidence establishes ferroptosis as a crucial regulator in fundamental biological processes, particularly iron, lipid, and amino acid metabolism. Recent studies highlight its therapeutic potential as an emerging anticancer pathway.[58] Notably, quercetin induces ferroptosis in gastric cancer cells by elevating lipid peroxidation levels. Mechanistically, it targets SLC1A5 to suppress the NRF2/xCT antioxidant axis while activating the phosphorylated CaMKII/DRP1 pathway, thereby accelerating iron deposition. These cumulative effects promote ferroptotic cell death and inhibit gastric cancer progression.[10]

Inhibition of cancer cell proliferation

Cell proliferation is an increase in the number of cells caused by cell division and is a process that requires strict regulation. Abnormal proliferation of cells leads to the formation of cancers, which are populations of cells that are constantly dividing during the cell cycle. Dysregulation of the cell cycle can lead to the indefinite proliferation of cancer cells. Therefore, regulating the cell cycle and inhibiting cell proliferation are essential for inhibiting cancer growth. The quercetin contained in *S. diffusum* can upregulate the expression of the P16 gene by reducing the expression of the Myelocytomatosis viral oncogene homolog gene, thereby blocking gastric cancer cells in the G0/G1 phase and inhibiting cell proliferation. Additionally, quercetin can also decrease the expression of the proliferating cell nuclear antigen protein, which is upregulated by angiotensin II, and can induce cell cycle arrest both *in vitro* and *in vivo* by inhibiting the expression of cyclin D1 and cyclin-dependent kinase (CDK-4).[59] In addition to quercetin, kaempferol inhibits gastric cancer cell proliferation by inducing G2/M phase arrest and autophagic cell death. This process is mediated through the upregulation of pro-apoptotic factors and the Immunoglobulin-Regulated Enhancer 1 - C/EBP-homologous protein / c-Jun N-terminal kinase pathway, achieved by suppressing Bcl-2 survival signaling, extracellular regulated protein kinases/AKT phosphorylation, CDK1/cyclin B1 complexes, and cyclooxygenase-2 (COX-2).[60] Furthermore, oleanolic acid suppresses gastric cancer cell proliferation by concurrently targeting multiple signaling pathways: it inhibits PI3K/AKT/mTOR signaling cascades, blocks macrophage M2 polarization, reduces proliferation linked to aerobic glycolysis along with glycolytic enzyme expression, and promotes nitric oxide release. Critically, this compound downregulates Bcl-2, cyclin D1, and CDK4 while upregu-

Table 1. Mechanisms of action of bioactive anticancer compounds derived from *Scleromitrion diffusum* (Willd.)

Compound	Compound type	Cancer type	In vitro activity	In vivo activity	Regulatory pathway	Reference
1. Induction of cancer cell apoptosis						
2-hydroxy-3-methyl anthraquinone	Anthraquinones	Hepatocellular carcinoma	Inhibit HepG2 cell viability (the IC50 values at 24, 48, and 72 h were 126.3, 98.6, and 80.55 μM, respectively)	N/A	Promotes P53 expression by inhibiting SIRT1 and activates the Bcl-2/Bax/Caspase 9/3 apoptotic signal	14
1,3-dihydroxy-2-methyl anthraquinone	Anthraquinones	Hepatocellular carcinoma	Promote cancer cell apoptosis through the mitochondrial apoptosis and death receptor pathway	N/A	Increase the Bax/Bcl-2 ratio (mitochondrial apoptotic pathway) by promoting the upregulation of P53, and promote the activation of Fas-L and Fas (death receptor pathway)	15
Amentoflavone	Flavonoids	Bladder cancer	Inhibit cell viability (the IC50 is 200 μM after treating TSGH 8301 for 48 h)	N/A	Increase the expression of apoptotic proteins FAS, FAS-L, and BAX, and decrease the expression of XIAP, Mantle cell lymphoma -1, and C-FLIP	16
Quercetin	Flavonoids	Breast cancer; colon cancer	Inhibit the activity of cells (CT-26 and MCF-7) in a dose (10, 20, 40, 80, and 120 μM) - and time (24, 48, and 72 h) - dependent manner	50, 100, and 200 mg/kg of quercetin can all reduce the cancer volume in mouse models with subcutaneous injection of CT-26 and MCF-7 cells and improve the survival rate of the animals	Increase the expression of BAX while reducing the expression of anti-apoptotic proteins	17
Hyperoside	Flavonol glycosides	Breast cancer	Inhibit the viability of MCF-7 and 4T1 cells in a time (6, 12, or 24 h) and concentration (12.5, 25, 50, 75, or 100 μM)-dependent manner	Inhibit the cancer growth in a syngeneic transplantation mouse model with subcutaneous injection of 4T1 cells	Inactivate the NF-κB pathway and reduce the intracellular ROS level, thereby reducing the accumulation of XIAP, Bcl-2, and Bax	18,19
Rutin	Flavonoids	Cervical cancer	Inhibit the viability of Caski cervical carcinoma cells and alter cell morphology in a dose (0 - 180 μM)-dependent manner	N/A	Downregulate the mRNA expression of Notch-1 and HES-1 genes in Notch signaling transduction	20
Apigenin	Flavonoids	Gastric cancer	Inhibit the proliferation of (HGC-27 and SGC-7901) Gastric cancer cells	N/A	Increase the expression levels of caspase-3 and Bax and down-regulate Bcl-2 expression in a dose-dependent manner	21
Isoquercitrin	Flavonol glycosides	Gastric cancer	Inhibit the viability and proliferation of AGS and HGC-27 cells in a time (0, 24, 48, and 72 h) and dose (0, 10, 20, 40, and 80 μM) - dependent manner	N/A	Induce endoplasmic reticulum stress and immunogenic cell death	22

(continued)

Table 1. *(continued)*

Compound	Compound type	Cancer type	In vitro activity	In vivo activity	Regulatory pathway	Reference
Ferulic acid	Phenolic acids	Colon cancer	Inhibit the viability of CT-26 cells (the IC50 values at 24 h and 48 h are both 800 μM)	40 mg/kg and 80 mg/kg of ferulic acid significantly reduced the size and weight of cancers in the CT26 cell xenograft model	Induce the phosphorylation of proteins related to the MAPK pathway and simultaneously increase the expression of Bax	23
Protocatechuic acid	Phenolic acids	Colon cancer	Treatment with 100 - 500 μM protocatechuic acid for 72 h significantly reduces the viability of CaCo-2 cells	N/A	Downregulate HO-1 and upregulate P21, thereby promoting oxidative stress	24
Asperuloside	Iridoids	Cervical cancer	Inhibit the activity of ASP cells (the IC50 after 24 h of treatment is 639.8 μg/mL)	N/A	Increase the intracellular ROS level, decrease the mitochondrial membrane potential, significantly reduce the expression level of Bcl-2 protein, and increase the expression of Bax, Cyt-c, GRP78, and cleaved-caspase-4	25
Oleanolic acid	Triterpenes	Liver cancer	Inhibit the viability of HepG2 cells (the IC50 values at 24 h and 48 h are 32.58 μM and 27.56 μM, respectively)	Oral administration of 75 mg/kg of Oleanolic Acid can inhibit DMBA-induced liver carcinogenesis	Downregulate the levels of TNF-α, NF-κB, COX-2, and VEGF	26
Ursolic acid	Triterpenes	Oral cancer	Inhibit the viability of Ca922 and SCC2095 cells in a concentration- and time-dependent manner (the IC50 values of Ca922 and SCC2095 cells are 11.5 and 13.8 μM, respectively, at 48 h) and induce cell autophagy	N/A	Downregulate AKT/mTOR/NF-κB signal transduction and p38 expression	27
Stigmasterol	Sterols	Gastric cancer	Inhibit the cell viability of SGC-7901 and MGC-803 cells in a time (24, 48, and 72 h) - and dose (0, 2.5, 5, 10, 15, 20, 25, 30 μM) - dependent manner	Inhibit the cancer size in the SGC-7901 cell xenograft model	Inhibit the AKT/mTOR pathway	28
Kaempferol	Flavonoids	Cervical cancer	Inhibit the viability of SiHa cells (the IC50 values at 24, 48, and 72 h are 61.37 ± 4.6, 48.6 ± 4.56, and 27.06 ± 5 μg/mL, respectively)	N/A	Downregulate the PI3K/AKT pathway and inhibit the expression of hTERT	29
2. Promotion of cancer cell ferroptosis						
Quercetin	Flavonoids	Gastric cancer	Inhibit cell viability (the IC50 for AGS cells is 38.78 μM)	Reduced the expression of Ki67 in the xenograft tumor model of nude mice	Reducing the expression of xCT and GPX4 and inhibiting SLC1A5/NRF2 leads to the inhibition of GPX4 expression	10

(continued)

Table 1. *(continued)*

Compound	Compound type	Cancer type	In vitro activity	In vivo activity	Regulatory pathway	Reference
3. Inhibition of cancer cell proliferation						
Quercetin	Flavonoids	Ovarian cancer	Inhibit the survival and proliferation of the human metastatic ovarian cancer PA-1 cell line (concentrations set at 50 μM and 75 μM)	N/A	Downregulate the PI3K/AKT/mTOR and Ras/Raf pathways	30,31
Quercetin	Flavonoids	Melanoma	Reduce the viability of B16 melanoma (treated with 50 μg/mL for 6, 24, and 48 h)	N/A	Increase the cells in the sub-G1 gate	32
Gallic acid	Phenolic acids	Lung carcinoma	Inhibit cell viability (the IC50 values at 24 h and 48 h are 22.03 and 21.34 μg/mL, respectively) and suppress cell proliferation	Gallic acid at a dose of 40 mg/kg significantly reduced the cancer size in nude mice with H1299 cell xenograft models	Upregulate the expression of pro-apoptotic proteins c - c-caspase8 and c-caspase-9 and the ratio of γ-H2AX/H2A	33
Asperulosidic acid	Iridoids	Hepatocellular carcinoma	Enhanced the sensitivity of cells to chemotherapy drugs	25–50 mg/kg of Asperulosidic acid reduced the tumor size in the subcutaneous model injected with Huh7 cells	Inhibit the MEKK1/NF-κB pathway	34
Esculetin	Coumarins	Laryngeal cancer	Inhibit the viability of Hep-2 cells (the IC50 after 72 h of intervention is 1.958 μM)	Esculetin at doses of 50 mg/kg and 100 mg/kg can inhibit the tumor volume in the xenograft model of male BALB/c nude mice	Inhibit the JAK/STAT signaling pathway	35
Esculetin	Coumarins	Gastric cancer	Inhibit the viability of MGC-803, BGC-823, and HGC-27 cells in a dose (0, 140, 280, 560, 850, or 1,700 μM) - and time (24, 48, or 72 h) - dependent manner	Subcutaneous injection of Esculetin at 50 and 100 mg/kg inhibited the cancer growth and size in the nude mouse model of MGC-803 cell xenograft	Downregulate the IGF-1/PI3K/AKT pathway	36
Hyperoside	Flavonol glycosides	Bladder cancer	Inhibit cell viability (the IC50 values for T24 cells at 12, 24, 48, and 72 h are approximately 629, 330, 252, and 159 μM, respectively; the IC50 values for 5,637 cells at 12, 24, and 48 h are approximately 667, 431, and 250 μM, respectively) and induce apoptosis in a small number of cells	Inhibit the cancer xenograft model by subcutaneous injection of T24 cells	Activate the EGFR-Ras and Fas signaling pathways	37
Rutin	Flavonoids	Cervical cancer	Stimulate cell cycle arrest in the G0/G1 phase	N/A	Downregulate the expression of cyclin D1 and CDK4 mRNA in cells	20

(continued)

Table 1. *(continued)*

Compound	Compound type	Cancer type	In vitro activity	In vivo activity	Regulatory pathway	Reference
4. Suppression of cancer cell invasion						
2-hydroxy-3-methyl anthraquinone	Anthraquinones	Lung carcinoma	Significantly inhibit the growth of lung cancer cells in a dose (0, 20, 40, 80 μM) - and time (24, 48 h) - dependent manner	N/A	Inhibit the IL-6-induced JAK2/STAT3 signaling pathway	38
2-hydroxy-3-methyl anthraquinone	Anthraquinones	Hepatocellular carcinoma	Inhibit HepG2 cell viability (the IC50 values at 24, 48, and 72 h were 126.3, 98.6, and 80.55 μM, respectively)	N/A	Inhibit invasion by suppressing SIRT1	14
Amentoflavone	Flavonoids	Colorectal cancer	Inhibit the migration ability of rectal cancer cells and the invasion of EMT	Inhibited the growth of tumors in the PDX model, increased miR-16-5p in PDX, and inhibited HMGA2 and β-catenin proteins in PDXs	Increase the expression of miR-16-5p and then inhibit the activation of the HMGA2/Wnt/β-catenin pathway	39
Quercetin	Flavonoids	Ovarian cancer	Inhibit the migration and adhesion of the human metastatic ovarian cancer PA-1 cell line (concentrations set at 50 μM and 75 μM)	N/A	Downregulate uPA, N-cadherin, and MMP-2/-9 and upregulate occludin to inhibit the EMT process	30
Quercetin	Flavonoids	Prostate cancer	Reverse docetaxel resistance and inhibit invasion by reversing the phenotypes of mesenchymal and stem cell-like cells	N/A	Reduce the expression of Twist2 and EpCAM and increase the expression of E-cadherin	40
Oleanolic acid	Triterpenes	Osteosarcoma	Inhibit the viability and invasion of U2OS and KHOS cells	N/A	Reduce the activity of the SOX9/Wnt1 signaling pathway	41
5. Inhibition of tumor angiogenesis						
Quercetin	Flavonoids	Esophageal cancer	Inhibited the colony formation, migration, and invasion of Eca109 cells	N/A	Reduce the expression levels of VEGF-A, MMP9, and MMP2	42
Quercetin	Flavonoids	Abdominal aortic aneurysm	Reduced the activity of MMP in VSMC	Quercetin at a dose of 60 mg/kg significantly reduced the incidence of aortic aneurysms	Reduce the expression of VEGF-A, ICAM-1, VCAM-1, and VE-cadherin	11
β-Sitosterol	Sterols	Gastric cancer	Inhibit the viability of MKN-45 cells (IC50 value is 51.85 μM)	N/A	Downregulating the expression of angiogenic factors attenuated the promoting effect of PTGS1 overexpression on the progression of gastric cancer cells	43

(continued)

Table 1. *(continued)*

Compound	Compound type	Cancer type	In vitro activity	In vivo activity	Regulatory pathway	Reference
Kaempferol	Flavonoids	Ovarian cancer	20 μM kaempferol inhibits the proliferation and VEGF secretion of ovarian cancer cells in a time (0.5, 6, 12, 24, 30, and 48 h)-dependent manner	N/A	Inhibit the expression of VEGF and NFκB by regulating the C-MYC gene and the ERK signaling pathway, respectively	12
6. Enhancement of immune function						
Ursolic acid	Triterpenes	Gastric cancer	50 μmol/L Ursolic acid strongly inhibits the viability of BGC-823 cells when acting for 12 - 72 h	10 mg/kg ursolic acid inhibited LPS-induced tumor proliferation in a mouse gastric tumor model with subcutaneous injection of BGC-823 cells	Inhibited the activation of the NLRP3 inflammasome and reduced the expression of IL-1β, TNF-α, IL-6, and CCL-2	13
7. Other approaches						
Ursolic acid	Triterpenes	Gastric cancer	After treating different gastric cancer cells (AGS, SC-M1, and MKN45) with increasing concentrations (0, 20, 40, 60, 80, and 100 μM) of UA for 48 h, concentrations of 40 μM and above could inhibit the viability of gastric cancer cells	Ursolic acid at a dose of 20 mg/kg can inhibit tumor growth in the MKN45 xenograft mouse model	Silence the transcription of the CYP19A1 gene	44

AKT, protein kinase B; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; CCL-2, C-C motif ligand 2; CDK4, cyclin-dependent kinase-4; C-FLIP, Cellular Fas-associated death domain-like interleukin-1 β-converting enzyme inhibitory protein; C-MYC, myelocytomatosis viral oncogene; Cyt-c, cytochrome complex; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; Fas-L, factor-related apoptosis ligand; GRP, glucose-regulated protein; HO-1, heme oxygenase-1; hTERT, human telomerase reverse transcriptase; ICAM-1, intercellular cell adhesion molecule-1; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; JAK, Janus kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MEKK1, mitogen-activated protein kinase/ERK kinase kinase-1; MMP, matrix metallopeptidase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; PI3K, phosphatidylinositol-3 kinase; PTGS1, prostaglandin-endoperoxide synthase 1; RAS, Renin-angiotensin system; ROS, reactive oxygen species; SIRT1, silent information regulator 1; SOX9, SRY-box transcription factor 9; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; uPA, urokinase-type plasminogen activator; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein.

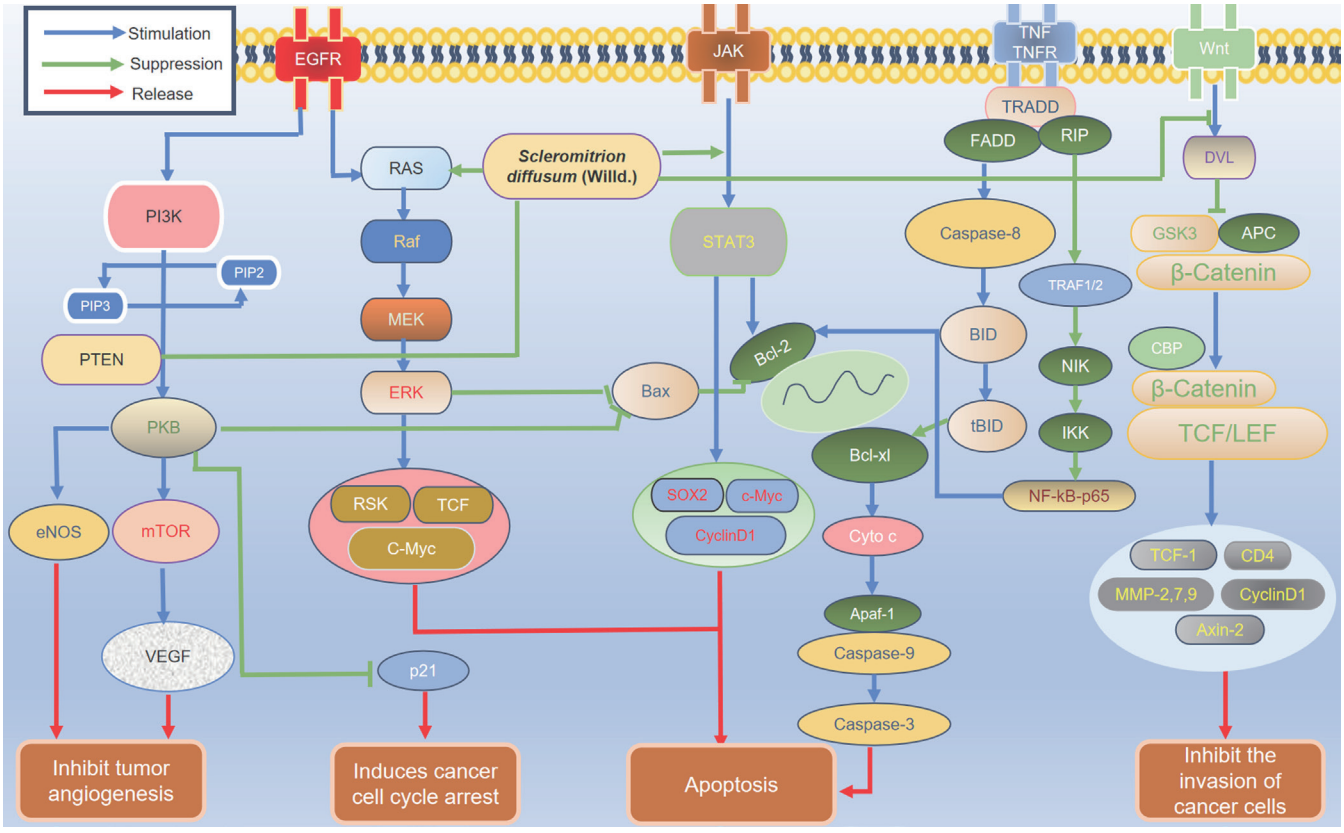

Fig. 3. Anticancer mechanism of action of *Scleromitrion diffusum*. This schematic diagram illustrates the multi-targeted anticancer mechanisms of *Scleromitrion diffusum* through modulation of key oncogenic signaling pathways. APC, antigen-presenting cell; Bcl-2, B-cell lymphoma-2; BcL-xl, B-cell lymphoma-extra large; BID, BH3-interacting domain death agonist; CBP, CREB binding protein; CD, cluster of differentiation; C-MYC, myelocytomatosis viral oncogene; DVL, dishevelled; eNOS, endothelial nitric oxide synthase; ERK, extracellular regulated protein kinases; FADD, Fas-associating protein with a novel death domain; GSK3, glycogen synthase kinase-3; IKK, inhibitor of kappa B kinase; LEF, lymphoid enhancer-binding factor; MEK, mitogen-activated protein; MMP, matrix metalloproteinases; Mtor, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NIK, NF-κB-inducing kinase; PI3K, phosphatidyqinositol-3 kinase; PIP2, phosphatidylinositol(4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKB, protein kinase B; PTEN, mutated in multiple advanced cancers 1; Raf, rapidly accelerated fibrosarcoma; RAS, Renin-angiotensin system; RIP, receptor-interacting protein; RSK, ribosomal S6 kinase; STAT3, signal transducer and activator of transcription 3; tBID, truncated Bid; TCF, T-cell factor; TCF-1, T cell factor 1; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TRAF, tumor necrosis factor receptor-associated factors; VEGF, vascular endothelial growth factor.

lating Bcl-2-associated X protein and P21—ultimately activating the cancer-suppressing P53 pathway through these coordinated molecular actions.[61]

Suppression of cancer cell invasion

Gastric cancer is a malignant cancer originating from epithelial tissue. Epithelial-mesenchymal transition (EMT), a critical pathological phenomenon in cancer development and metastasis, permeates the entire process of gastric cancer initiation, progression, and dissemination. Studies indicate that after six weeks of *S. diffusum* treatment, experimental rats exhibited significantly increased expression of the epithelial marker E-cadherin and decreased expression of mesenchymal markers (vimentin and N-cadherin) in gastric tissues. Hematoxylin and eosin staining results further confirmed that this treatment alleviated pathological damage in gastric mucosal cells, demonstrating *S. diffusu*'s multi-target reversal of gastric precancerous lesions.[62] Mechanistic research revealed that a TCM compound containing *S. diffusum* regulates the hTERT/MDM2-p53 signaling pathway to inhibit EMT in gastric cancer cells.[63] The core function of this pathway involves p53 protein inhibiting cancer metastasis by negatively regulating EMT-related factors while promoting MDM2 expression; the resulting p53-MDM2 complex upregulates E-cadherin expression through ubiquitination-mediated degradation of the transcription factor Slug, ultimately blocking the EMT process.[64,65] Another *in vitro* study revealed that quercetin suppresses the pro-metastatic urokinase-type plasminogen activator/urokinase-type plasminogen activator receptor system by inhibiting nuclear factor kappa-B (NF-κB), protein kinase C-δ, and extracellular regulated protein kinase 1/2 while activating AMPKα. This system drives gastric cancer cell invasion by regulating key effectors such as matrix metalloproteinases, the PAK1/LIMK1/cofilin signaling axis, focal adhesion kinase, TGF-β, and vascular endothelial growth factor (VEGF).[66]

Inhibition of tumor angiogenesis

Cancer cells can induce the growth of microvessels around the tumor, establishing blood circulation to generate tumor blood vessels, which are key to tumor growth because blood vessels support tumor invasion and metastasis. Therefore, the destruction of tumor vascularization is a hot topic in cancer treatment today.[67] VEGF is an important proangiogenic factor that contributes to angiogenesis

via COX-2 and has been shown to play a central role in key signaling pathways that promote tumor growth and metastasis.[68] This, in turn, provides nutrients to cancer cells. Moreover, activation of the PI3K/AKT signaling pathway facilitates tumor angiogenesis by upregulating the expression of VEGF.

The flavonoids in *S. diffusum* are primarily composed of quercetin and kaempferol. Quercetin significantly inhibits tumor angiogenesis, a mechanism involving the suppression of COX-2 and hypoxia-inducible factor-1α expression,[11] and functions by downregulating the expression of VEGF-C and its receptor VEGFR-3 in gastric cancer MGC-803 cells.[69] Kaempferol, in *in vitro* experiments, exhibits time-dependent inhibition of VEGF secretion and angiogenesis blockade. Mechanistic studies suggest both compounds likely influence angiogenesis through shared pathways: kaempferol reduces signal transducer and activator of transcription 3 phosphorylation levels, thereby downregulating NF-κB expression, while simultaneously suppressing VEGF expression via the proto-oncogene Myelocytomatosis viral oncogene homolog-P21 pathway[12]; quercetin's regulation of VEGF receptors may act synergistically with this mechanism.

Enhancement of immune function

Immunity is the ability of the body's immune system to distinguish "self" from "non-self" components and eliminate antigens, damaged cells, and cancer cells through immune responses, thereby sustaining health. Immunotherapy is an important means for the treatment of cancers. Experimental studies indicate that low-dose *S. diffusum* enhances the expression of cluster of differentiation (CD) 40 and CD86 on bone marrow-derived dendritic cells and promotes tumor necrosis factor-α and interleukin (IL)-6 production in a dose-dependent manner. When combined with antigens, *S. diffusum* strengthens specific memory T-cell responses, thereby maintaining anticancer efficacy even upon cancer recurrence.[70] On the immunomodulatory level, polysaccharides in *S. diffusum* indirectly eliminate cancer cells by increasing the number and activity of lymphocytes, macrophages, and natural killer cells. After binding to polysaccharide receptors on immune cell surfaces, they activate intracellular signaling pathways and stimulate cytokine secretion by macrophages. The resulting cascade effectively suppresses tumor cell growth, proliferation, migration, and invasion while regulating the body's immune response.[71] This effect may be related to the increase in the proportions of CD3, CD5, and cytokine-induced killer cells, the production of inflammatory cytokines, and the reduction in cytokine-induced killer cell apoptosis.[72] Beyond polysaccharides, phenolic acids demonstrate promising immunomodulatory properties in cancer therapy. Specifically, oleanolic acid functions as an epigenetic modulator that blocks the IL-1β/NF-κB/TET3 axis in gastric cancer cells, resulting in DNA hypomethylation and programmed cell death ligand 1 downregulation, thereby providing adjuvant therapeutic benefits.[73] Concurrently, ursolic acid suppresses nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 inflammasome activation and reduces pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor-α, ultimately inhibiting both proliferation and inflammatory responses in lipopolysaccharide-stimulated BGC-823 gastric cancer cells.[13] Furthermore, kaempferol enhances natural killer cell-mediated cytotoxicity and blocks tumor immune escape pathways by downregulating major histocompatibility complex class I chain-related protein A expression in gastric cancer SGC-7901 cells,[74] further expanding *S. diffusum*'s multi-target immunoregulatory network.

Future research directions

Currently, significant progress has been made in the active compounds of *S. diffusum* against gastric cancer and the mechanisms of combating gastric cancer, but there are still significant deficiencies. In the future, we can modify drugs based on these pathways and active compounds, which provides an unparalleled opportunity for the development of new anticancer compounds with different biological activities and limited systemic toxicity. For example, the methylated derivatives of quercetin have been proven to inhibit the migration and invasion of cancer cells, indicating that these modifications can endow enhanced anticancer properties.[75] After structural modification, ursolic acid shows higher efficacy and diverse targets and can inhibit the processes leading to cancer pathology. Like many natural medicinal compounds, the active compounds in *S. diffusum* have poor solubility, and the solvents have potential toxicity. For example, parenteral administration of ursolic acid is rarely used. The oral route, by adding it to the diet or drinking water, is of little use.[76] Structural modification of the drug can also enhance its solubility, absorption, low protein binding, and longer tissue accumulation time. Structural modification and nanoparticle formulations have also significantly improved the stability, solubility, and bioavailability of quercetin, enabling targeted drug delivery. In addition, multi-pathway synergy has always been a major advantage of TCM. Based on these pathways, more drug combinations can be developed in the future. Studies have shown that when naringenin and quercetin are used in combination, they show promising synergistic anticancer cell proliferation effects by increasing lipid peroxidation, inducing mitochondrial depolarization, inhibiting anti-apoptotic Bcl-2, and concomitantly activating caspase 3/7, which neither of the two single components can achieve in cancer treatment.[77]

Therefore, future research directions can be divided into three major categories. First, in terms of active compounds, more attention should be paid to the structural modification of drugs. This can not only make the drugs more stable but also enhance their anticancer effects. Second, in terms of drug action target pathways, more combinations of drugs with drugs and active compounds with immunotherapeutic drugs should be explored. Finally, in drug research and development, emphasis should be placed on the nanocarrier/liposome system and the self-microemulsifying drug delivery system to improve the utilization rate of components with strong anticancer activity but poor bioavailability.

Conclusions

The anticancer potential of natural products has garnered increasing recognition in recent years. Exemplifying modernized research in TCM, *S. diffusum* demonstrates significant anti-neoplastic efficacy in both preclinical and clinical studies, highlighting the considerable promise of rigorous multidisciplinary integration. This review synthesizes two critical insights: *S. diffusum* contains multiple bioactive constituents that combat gastric cancer through diverse mechanisms, and beyond conventional approaches like apoptosis induction, proliferation suppression, and angiogenesis inhibition, emerging evidence reveals *S. diffusum*'s therapeutic actions via ferroptosis modulation and telomerase interference. These findings underscore *S. diffusum*'s substantial untapped potential for gastric cancer management, particularly through synergistic combinations of active compounds to discover novel anticancer pathways. Such advancements provide crucial empirical validation for TCM principles while propelling the development of precision herbal oncology frameworks.

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Conflict of interest

We disclose that Jiang-Jiang Qin and Xiao-Qing Guan held editorial positions at *Oncology Advances* when this manuscript was submitted. The journal's recusal procedures ensured independent peer review. The authors have no other conflicts of interest to note.

Author contributions

Writing–original draft, investigation, data curation (YXZ), critical revision, funding acquisition (JJQ), writing–review & editing, and funding acquisition (XQG). All authors have made significant contributions to this study and have approved the final manuscript.

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