Xiaotan Sanjie decoction normalizes tumor permissive microenvironment in gastric cancer (Review)

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Abstract. Gastric cancer (GC) develops in a complex tissue environment, the tumor microenvironment (TME), which it relies on for persistent proliferation, migration, invasion and metastasis. Non-malignant stromal cell types within the TME are regarded as a clinical meaningful target with the lower risk of resistance and tumor relapse. Studies have revealed that the Xiaotan Sanjie decoction, which is formulated on the basis of the theory of phlegm syndrome, a Traditional Chinese Medicine concept, modulates released factors such as transforming growth factor-β from tumor cells, immune cells, cancer-associated fibroblasts, extracellular matrix, as well as vascular endothelial growth factor involved in the process of angiogenesis within the TME. Clinical studies have also shown that the Xiaotan Sanjie decoction is associated with favorable survival and quality of life. The present review aimed to interpret the hypothesis that Xiaotan Sanjie decoction has the ability to normalize the GC tumor cells by influencing functions of stromal cells within the TME. The possible association between phlegm syndrome and the TME in GC was discussed in the present review. Overall, Xiaotan Sanjie decoction may be suitable to be added to tumor cell-directed agents or emerging immunotherapies becoming a desirable modality in the management of GC and acquire improved outcomes for patients with GC.

Contents

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1. Introduction

Gastric cancer (GC) is one of the most common cancer type in China, and newly diagnosed cases increased from 403,000 in 2015 to 479,000 in 2020 (1). It remains the fourth leading cause of cancer mortality worldwide (2). A large portion of patients with GC do not respond to conventional therapies or are at a higher risk for recurrent disease after they received those interventions, such as perioperative chemotherapy or chemotherapy alone (3,4) and anti-HER2 agent trastuzumab in combination with chemotherapy (5).

Over the last decade, the tumor microenvironment (TME) has become a hot topic for overcoming treatment failure or resistance to current therapies for advanced cancer, including GC (6-8). Various studies have evidenced promising outcomes in patients with GC through targeting angiogenesis, immune suppression and normalization of the tumor-permissive environment (9-15). The Xiaotan Sanjie decoction, a traditional Chinese medicine (TCM) regimen, is composed of 11 traditional medicinal components (16), formulated according to the phlegm syndrome theory (17). Phlegm syndrome, a TCM term, is used to diagnose patients with diseases caused by phlegm (harmful products originated from dysfunctional body fluid circulation) characterized by symptoms and signs including lack of appetite, nausea, vomiting, feel of heavy body, oily looking skin on the face and a pale tongue (18,19). Phlegm syndrome is prevalent in patients with GC (17). Previous preclinical studies have shown that the Xiaotan Sanjie decoction has the ability to regulate levels of some cytokines, growth factors and receptors, such as interleukin-8 (IL-8) (20), transforming growth factor-β (TGF-β) (21), TGF-β receptor 2 (TGFBR2) (22) and CD44V6 (23) in the TME of GC. The Xiaotan Sanjie decoction shows favorable antitumor activities (24) and clinical outcomes (25) in patients with GC.

The TME may constitute the biological basis of phlegm syndrome in patients with GC. We hypothesized that TME

in GC may redefine the phlegm syndrome by way of current biomolecular approaches. A literature review was performed to explore the association between phlegm syndrome and the TME, and what roles treatment with the Xiaotan Sanjie decoction played in the management of patients with GC in regard to target components, including cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) and the erratic tumor vasculature within the TME. A preliminary literature search for the Xiaotan Sanjie decoction and TME related articles was performed on the PubMed (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (https://www.sciencedirect.com/), Google Scholar (https://scholar.google.com/) and CNKI (https://www.cnki.net/). The following key search terms and phrases were used in combination or separately: 'Xiaotan Sanjie', 'Jinlongshe' (hospital prepared formulation of Xiaotan Sanjie decoction), 'phlegm', 'phlegm syndrome', 'gastric cancer', 'tumor microenvironment', 'cancer-associated fibroblasts', 'extracellular matrix', 'transforming growth factor-β', 'tumor vasculature' and 'angiogenesis'. This may promote translation of TCM theories into modern molecular landscape.

2. Phlegm syndrome in patients with GC

For >2,000 years, TCM has established a tradition of interpreting diseases and making therapeutic decisions (26). TCM syndrome (pronounced 'Zheng' in Chinese), a TCM term, is a combination of the presentation, pathogenesis, site and development tendency of a disease at a specific stage during its course) is based on the gathering of general manifestations of patients through inspection, hearing, inquiry and taking pulse, which is the essential diagnostic process by which TCM physicians describe signs and symptoms and make a treatment plan (27,28). 'Phlegm syndrome' is an important type of 'syndrome' in TCM. Zhenheng Zhu, a famous TCM physician from the Yuan dynasty (1,279-1,368 AC), said that 9/10 diseases were caused by phlegm (29). TCM has two general types of phlegm: Internal and external (nasal discharge or sputum from respiratory tract) (30). In TCM it is considered that the internal phlegm will arise when the body's fluid metabolism is disturbed by intrinsic or extrinsic factors, such as *qi* deficiency, *qi* stagnation, stagnancy of dampness, climatic factors, emotional changes and improper diet (31). The internal phlegm may accumulate in Zang and Fu viscera to disrupt the normal functions of the organs and systems or circulate via meridians and collaterals to distant organs from its source (30). The characteristics of phlegm syndrome can be observed in numerous disorders, including poor general status, respiratory diseases, gastrointestinal disorders, cardiovascular diseases, overweight, neurological dysfunctions and cancer (31).

Numerous major risk factors can be observed in patients with phlegm syndrome and GC concurrently. Improper dietary behaviors take prominent part in the development of phlegm syndrome and GC, such as excessive consumption of pickled or salted food or roasted and greasy foods (17). Overeating itself is also a cause of phlegm (32). *H. pylori* infection increases the risk of GC; moreover, salted food consumption may further promote *H pylori* infection, and jointly participate in the development of GC (33). Aging, obesity and chronic inflammation are all commonly found in patients with phlegm syndrome and in patients with GC (32).

GC is characterized by heterogeneous pathology in regard to anatomical location and histological subtypes (33). GC may be detected in almost all parts of the stomach, especially in the lower region (34). GC cells may move from their original site to distant body parts by way of the blood or lymphatic vessels with advancing stages of the disease in patients with GC (35). A broad range of locations should be noted in the diagnostic process, including the abdominal cavity, liver, supraclavicular lymph node, ovaries and umbilical region and Blumer shelf (a mass in the perirectal pouch) (36). Correspondingly, phlegm syndrome presents as a dynamic evolutionary process similar to GC development (32). Phlegm can also be categorized into substantial and insubstantial. Substantial phlegm is visible and palpable, such as scrofula and nodules in the skin and muscles (29). When accumulating, the phlegm is substantial; when dispersing, the phlegm is insubstantial (32). Phlegm arising in the spleen can easily extend to or accumulate in almost all other parts of the body (31), which is referred to as 'phlegm evil flowing' in TCM (32). Phlegm may play an important role in the pathogenesis and metastases of GC. Accumulation of internal phlegm transforms from an insubstantial to a substantial phlegmatic nodule in the stomach, and a phlegmatic nodule may create a vicious phlegmatic environment in which it will release more phlegm to relocate to other parts of the body (32).

3. Composition of Xiaotan Sanjie decoction and TCM usage

The Xiaotan Sanjie decoction is prepared to relieve symptoms and signs of phlegm syndrome in patients with GC. The Xiaotan Sanjie decoction is mainly composed of *Pinelliae rhizome*, *Arisaematis rhizoma*, *Scorpio*, *Scolopendra*, baked Endothelium corneum gigeriae galli, prepared *Glycyrrhiza uralensis Fisch* and other natural products (Table I). *Pinelliae rhizoma* and *Arisaematis rhizoma* are the dominant ingredients to dry dampness and resolve phlegm, prevent nausea and vomiting, relieve pain and dissolve lumps and resolve masses. *Scorpio*, *Scolopendra* and baked Endothelium corneum gigeriae galli are second principal medicinal components to activate the meridians, relieve pain and eliminate phlegmatic nodules. The prepared *Glycyrrhiza uralensis Fisch* plays a coordinator role to direct other medicines to the sites where affected by phlegm, to reduce toxicity and to improve flavor (37). All of these natural products work synergistically together to improve overall physical status of the patients with GC, especially in patients with advanced disease (17). TCM usages, active compounds and antitumor effects of each component in the Xiaotan Sanjie decoction are described and summarized in a non-exhaustive list in Table I.

4. Effects of Xiaotan Sanjie decoction on TME in GC

Malfunctioned vascular structures and ECM create a hostile metabolic and mechanical TME that is characterized by hypoxia, low pH and high interstitial pressure (38). Tumors become infiltrated with immune and inflammatory cells (39-41), blood endothelial cells (42), lymphatic endothelial cells (6), CAFs (43), the ECM (44) and bone marrow-derived mesenchymal stem cells (8) within the

Table I. Ingredients of the Xiaotan Sanjie decoction.

Chinese name	Latin name	TCM usages	Active compounds	Antitumor effects
Ban-xia	*Pinelliae rhizoma*	Dry dampness and phlegm, resolve swelling, stop vomiting and dissipate nodulation (47)	Stigmasterol, pentadecanoic acid, licochalcone A, β-sitosterol (48)	Inhibition of PI3K-Akt signaling pathway, MAPK signaling pathway (48)
Nan-xing	*Ariaematis rhizoma*	Dry dampness and resolve phlegm, extinguish wind and stop spasms, resolve swelling and dissipate nodulation (117)	Alkaloids, polysaccharides, lectins, amino acids, fatty acids, sterols (117)	Activate T cells by upregulating Th1 (increase INF-γ and IL-2)/Th2 (decrease IL-10) cytokine ratio (117)
Fu-ling	*Poria cocos*	Ameliorating phlegm and edema; promoting urination (118)	Polysaccharides, pachyman (119)	Inhibit the growth of tumor cells (119)
Zhi-shi	*Aurantii fructus immaturus*	Eliminate accumulation and break up lumps, resolve phlegm (120)	Flavonoids, alkaloids, coumarins and volatile oils (121)	Enhances NK cell-mediated cytotoxicity (50)
Chen-pi	*Citri reticulatae pericarpium*	Rectifies qi and fortifies the spleen, dries dampness, dissolves phlegm (122)	Flavonoids, phenolic acids, fatty acids, hesperidin, nobiletin, tangeretin (123)	Downregulates the AKT/mTOR signaling pathway (124); activation of caspase-9 and Fas/Fas L (125); suppression of MAPK signaling pathway (126)
Quan-xie	*Scorpio*	Dispels wind-evil or stops endogenous wind; dissipates nodulation (81)	Scorpion venoms, peptides (81)	TGF-β1-induced EMT process (81); inhibition of proliferation, decreasing cell migration (51)
Wu-gong	*Scolopendra*	Extinguishes wind and stops spasms, counteracts toxic pathogens and dissipates nodulation, unblocks collateral and alleviates pain (53)	Venom, polysaccharide-protein complex (53)	Downregulates arachidonic acid-metabolic pathways in tumor-associated macrophages; enhancing the activities of NK cells, CTL and the ratio of Th1/Th2 cytokines, and increasing the percentages of $CD4^+$ T cells, B cells and NK cells (53)
Ji-nei-jin	*Galli gigerii* endothelium corneum	Indigestion, dyspepsia (84)	Proteins, polysaccharides (127)	Hydroxyl radical scavenging, Fe^{2+} chelating and lipid peroxidation inhibitory activities (127); downregulation of TNF-α, IL-1β, IL-6 (84)
Bei-mu	*Fritillariae cirrhosae bulbus*	Removing phlegm, resolve swelling and dissipate nodulation (128)	Steroidal alkaloids, saponins, terpenoids, and glycosides (129)	Mediates apoptosis through a STAT1 and STAT4-mediated co-regulatory network (130) downregulating TGF-β/SMAD signaling pathway (54)
Bai-jie-zi	*Sinapis semen*	Eliminating phlegm, resolve swelling and dissipate nodulation (55)	Sinalbin, sinapine, and sinapic acid (55)	Anti-fibrotic effect/regulation of TGF-β1/Smad, NF-κB and AKT signaling pathways, which reduces the excessive deposition of ECM (55)
Gan-cao	*Glycyrrhiza uralensis Fisch*	A unique 'guide drug' to enhance the effectiveness of other ingredients, to reduce toxicity, and to improve flavor (131)	Triterpenes, saponins, flavonoids, phenolic compounds, Isoliquiritigenin, glycyrrhizin, licorice polysaccharides (49)	Activate immune cells and stimulate secretion of ant-inflammatory cytokines, especially IL-7 (49), and downregulates expression of TNFα, IL-1 and IL-6 (85)

Th, T helper; NK, natural killer; EMT, epithelial-mesenchymal transition.

stroma. Crosstalk exists between tumor-associated stromal cells and tumor cells through signaling molecules to promote tumor invasion, metastasis, immunosuppression and to induce treatment resistance (45). Regulation of the active interaction between tumor cells and tumor-associated stromal cells (that interfere with IL-6 mediated crosstalk between tumor cells and CAFs) in the TME has shown promising antitumor effects in GC (46). The Xiaotan Sanjie decoction, a decoction that contains a plethora of phytochemical compounds (47-49), vitamins (50), and peptides (51-53) has demonstrated multiple actions on various soluble molecules, cytokines and growth factors released by parenchyma and stroma cells of GC. The Xiaotan Sanjie decoction shows activities on desmoplastic reactions (21,54,55), ECM formation and degradation (56,57), and tumor blood supply (58-61) through regulating these elements in the TME over the course of the GC progression.

Effects of the Xiaotan Sanjie decoction on CAFs. CAFs are a predominant stromal constituent within the TME and play a prominent part in tumor progression (62). The high proportion of CAFs was identified as a predictor of poor outcome in patients with GC in a meta-analysis (63). The fibroblast activation protein α (FAP) is highly expressed on CAFs and is rarely detected in normal stomach tissue. FAP upregulation has been reported as an indication for a worse prognosis in GC and has a significant effect on GC development, immunosuppression and drug resistance to immune checkpoint inhibitors (64). The Xiaotan Sanjie decoction downregulates FAP protein and mRNA expression in GC MKN-45 cells xenografted in nude mice (65).

TGF-β is a ubiquitous, pleiotropic cytokine that plays an important role in cancer development (66). Activation of the TGF-β signaling pathway is involved in gastric carcinogenesis in earlier and later stages; in addition, elevated serum TGF-β1 protein levels are predictors of lymph metastases and dissemination in the peritoneal cavity after gastrectomy (67). TGF-β plays an indispensable role in activation of resident quiescent fibroblasts, and differentiation of bone marrow-derived mesenchymal stem cells and adipose tissue-derived stem cells into CAFs (68-70). Inhibition of TGF-β signaling interrupts the differentiation of human MSCs to CAFs and abrogates their pro-tumorigenic function (71). TGF-β signaling includes a coordinated interaction between TGF-β receptor (TGFBR)1 and TGFBR2, which has been thoroughly described in the literature (66,72). TGF-β shows antitumor activities in the early stage and activity as a tumor promoter in the later stage of various cancer types, such as hepatocellular carcinoma, prostate cancer and GC (73,74). The antitumor activities of TGF-β are compromised by the loss or reduction of TGF-β receptor expression or of downstream signaling targets while the cancer progresses to an advanced stage (75,76). TGFBR2 gene is a putative tumor suppressor, and loss of function of TGFBR2 is closely correlated to progression in patients with GC (77-80). In an experimental study, the expression level of TGF-β was downregulated in serum of Xiaotan Sanjie decoction-treated nude mice with orthotopically transplanted GC tumors (21). The Xiaotan Sanjie decoction has been observed to exert antitumor effects by upregulating TGFBR2 *in vivo* and *in vitro* (22). Previous studies have suggested that the aqueous extracts of *Fritillariae cirrhosae bulbus* (54) and *Sinapis semen* (55), two herbal medicinal components of the Xiaotan Sanjie decoction, downregulate the activity of the TGF-β/SMAD signaling pathway. The aqueous extracts of scorpion (an animal medicinal product used in the decoction)-medicated serum significantly alleviates the TGF-β1-induced epithelial-mesenchymal transition (EMT) process (81). We hypothesize that the Xiaotan Sanjie decoction has the ability to decrease the formation of CAFs by interrupting the TGF-β signaling pathway.

Activated CAFs can secrete soluble molecules, including the upregulation of IL-6 in dysplastic stomach tissue, and is associated with GC development (46). IL-6 is a major mediator in cross-talking between tumor cells and CAFs in the TME (82). Notably, interruption of this interaction by genetic modification of IL-6 expression inhibits gastric tumor growth (46). In a Xiaotan Sanjie decoction-treated S180 tumor-bearing mice model, the expression levels of IL-6 decrease significantly in the tumor and adjacent tissues (83). Bioactive research has revealed that isolated compounds extracted from *Galli gigerii* endothelium corneum (84) and *Glycyrrhiza uralensis Fisch* (85), another two natural products in the Xiaotan Sanjie decoction, have the ability to downregulate expression of TNFα, IL-1 and IL-6.

The tumor-derived IL-8, also secreted by CAFs, actively participates in vascularity and tumorigenesis in gastric carcinoma cell lines *in vitro* (86). A meta-analysis concludes that IL-8 expression might be a poor prognosticator for GC (87). Overexpression of IL-8 located in CAFs is associated with resistance to cisplatin in patients with GC via NF-κB activation and ABCB1 upregulation (88). Ju *et al* (20) examined expression levels of IL-8 and its receptors in gastric tissue in S180 xenograft-bearing mice treated using the Xiaotan Sanjie decoction. The IL-8 protein level was observed to be markedly decreased in tumor xenografts and neighboring gastric tissue. In another study, the Xiaotan Sanjie decoction has shown positive effects on inhibiting progression and metastatic behavior of SGC-7901 GC cells through downregulation of IL-8 (89). The Xiaotan Sanjie decoction, in combination with platinum-based chemotherapy may be able to achieve predictable benefits for patients with GC in the clinical setting.

Effects of Xiaotan Sanjie decoction on ECM. An altered ECM, which is the supporting structure of the TME, has a notable impact on the aggressiveness of cancer cell (6,42). CAFs play predominant roles in the production of structural macromolecules of ECM (such as collagen, fibronectin and laminin) as well as in the secretion of enzymes (such as lysyl hydroxylases and metalloproteinases) to degrade these structural components (90). TGF-β is an enhancer in the process of constructing a stiffened ECM by the CAFs (91,92). As previously discussed, the Xiaotan Sanjie decoction has been shown to downregulate activities of CAFs and to interfere with TGF-β signaling pathway (21,22,54,55). Therefore, the recipe may alleviate the excessive deposition of components of ECM, such as collagen, fibronectin and laminin, as well as prevent degradation of structural macromolecules of the ECM.

Hyaluronic acid (HA), an important component in the ECM, is expressed in numerous cancer types, including GC (93). A HA-positive tumor is a predictor of advanced disease and poor survival rate (94,95). HA plays an important

role in limiting the delivery of therapeutic agents to tumor tissue (96,97). Hyaluronidase is associated with favorable anti-tumor effects in GC by degrading HA within the TME (98). Hyaluronidase activities have been found in venom extracted from Scorpion and Scolopendra, two natural animal products used in the Xiaotan Sanjie decoction (99,100).

CD44, a receptor for HA, collagen, fibronectin and growth factors, is a multifunctional receptor involved in cell-cell and cell-ECM interactions (101). High expression of CD44 variants on GC cells is associated with local tumor growth and metastatic spread in patients with GC (102). The HA-CD44 interaction has been suggested to induce uncontrolled proliferation, migration and drug resistance in various tumor types including metastatic breast tumor, ovarian tumor and GC in cellular studies (103). An animal study found significant differences in CD44V6 expression between the Xiaotan Sanjie decoction group and control group in a MKN-45 GC nude mouse model (23). Another study further confirmed the link between downregulation of expression of CD44V6 and the Jinlongshe formulae (Hospital-prepared Xiaotan Sanjie decoction) treatment (104).

Destruction of ECM and basement membrane barriers is a prerequisite for the metastasis of GC (105). The Xiaotan Sanjie decoction has shown the ability to prevent MMPs from degrading the ECM and its basement membrane in a MKN-45 GC nude mouse model (56). In an animal study, Sprague-Dawley rats were used to prepare the Xiaotan Sanjie decoction drug serum. The drug serum significantly inhibited the proliferative, metastatic and invasive ability of the human GC cell line SGC-7901. Protein and gene expression levels of MMP-9 were downregulated in this experiment (57).

Effects of Xiaotan Sanjie decoction on tumor vasculature. Increased vascularity and neoangiogenesis provide oxygen and nutrients for tumor growth and expansion with advancing cancer stages (15). VEGF and its receptor (VEGFR) are important elements to form a new blood vessel network. Activated CAFs serve as an important VEGF promoter that establish an abnormal vascular condition in the TME (106). In a study on stomach biopsy of 20 cases with GC, the effects of the Xiaotan Sanjie decoction on microvessel density (MVD) and VEGF-A/VEGFR-2 activities were evaluated in histopathological samples of GC and adjacent tissue. At 6 months, MVD and VEGF-A/VEGFR-2 expression levels were significantly decreased in samples from patients treated with the Xiaotan Sanjie decoction (58). Animal studies have also shown that the Xiaotan Sanjie decoction downregulates expression of VEGF, kinase insert domain receptor, VEGF-D protein and mRNA in comparison with 5-fluorouracil group in tumor xenografts mice to inhibit tumor metastasis (59,60). Xiaotan Sanjie decoction has also shown inhibition of the formation of vasculogenic mimicry, a distinct tumor microcirculation model that does not depend on endothelial cells (61).

5. Xiaotan Sanjie decoction is associated with favorable survival and quality of life in GC

The Xiaotan Sanjie decoction has been used to treat GC with good efficacy and safety profile for >20 years (17,32). The Xiaotan Sanjie decoction improves quality of life more compared with chemotherapy in patients with advanced GC who had undergone the subtotal or total gastrectomy proceedure (107-109). The Xiaotan Sanjie decoction has shown satisfactory outcomes in clinical studies that evaluated the effects of the decoction in combination of chemotherapy or other Chinese medicinal formulations on quality of life and overall survival in patients with advanced GC (110-113). In a clinical study, among patients with stage III and IV GC, those who were treated with the Xiaotan Sanjie decoction in combination with chemotherapy (Etoposide, Calcium Folinate and 5-Fluorouracil) had longer overall survival and 3-year survival compared with those who received chemotherapy only (110). In another study, efficacy of Xiaotan Sanjie decoction combined with Huangqi injection and Huachansu injection (both are traditional Chinese patent medicine) were observed in patients with advanced GC. The results showed that TCM can improve Karnofsky performance score, NK cell activity and CD3 and CD4 cells counts more compared with those of chemotherapy (5-Fluorouracil, Oxaliplatin, Vincristine, Cisplatin, Mitomycin) (111). The Xiaotan Sanjie decoction has been shown to have a well-established safety profile, provide an enhanced quality of life, improve tumor response and prolong survival time and Karnofsky performance score in patients with GC (112,113). Therefore, Xiaotan Sanjie decoction may be a promising candidate for use in collaboration with conventional treatment regimens as an alternative method to delay cancer progression.

6. Summary and perspectives

The TME in GC is a complex ecosystem that consists of newly formed blood and lymphatic vessels and diversified stromal cell types embedded in a modified ECM (8). Targeting the TME has revealed promising survival outcomes by inhibition of VEGF signaling pathway or PD1 signaling pathway in patients with GC (9-11). However, there is a gap between the complete understanding of the underlying molecular mechanisms of a plethora of interconnected molecules and pathways in the TME in GC and exactly how metastatic GC leads to death. More pivotal molecular pathways or cell types need to be revealed in the TME in GC to develop innovative therapeutic regimens.

For thousand years, Chinese physicians have used traditional natural medicine to treat a plethora of diseases, including GC. TCM formulations have notable effects on multiple targets and seldomly cause the occurrence of undesirable effects (26,28). In addition, they may provide long-term benefits for patients with GC (19). The therapeutic effect of TCM formulations on tumors has been demonstrated in multiple pathways, providing reasonable evidence for the ability to restore abnormal TME in GC back into balance (32). For >20 years, models have been established based on phlegm syndrome theory for GC (17). The biochemical properties of the TCM term 'phlegm' in GC may be partly described in modern medical language by way of a series of preclinical studies.

Contaminated phlegm is likely to be an important pathological product in the development of GC (114). The hypothesis regarding symptoms, signs and molecular profiles stems from the clinical and experimental observation that the TME in GC can share commonalities with phlegm

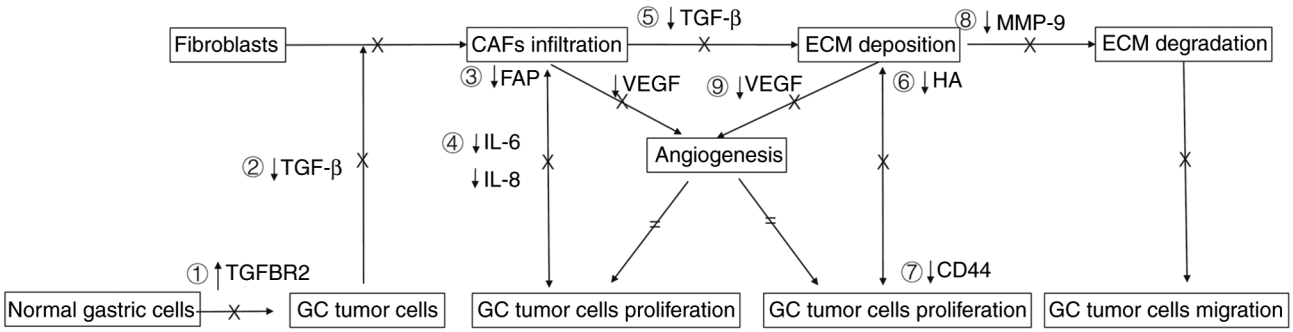

Figure 1. Schematic diagram showing interplay between the Xiaotan Sanjie decoction and the components in the tumor microenvironment. The Xiaotan Sanjie decoction has been demonstrated to have multiple effects on initiation, proliferation and migration of gastric cancer by: (1) Upregulating TGFBR2 to normalize the antitumor action of the TGF-β/SMAD signaling pathway; (2) interrupting the expression of TGF-β to decrease the formation of CAFs; (3) downregulating expression of FAP; (4) interfering with crosstalk between CAFs and tumor cells by downregulating IL-6 and IL-8; (5) alleviating deposition of ECM by blocking activities of CAFs by downregulating TGF-β; interrupting HA-CD44 interaction between the ECM and tumor cells by (6) degrading HA and (7) downregulating expression of CD44V6; (8) downregulating expression of MMP9 to prevent degradation of ECM and its basement membrane; and (9) decreasing the expression level of VEGF to inhibit angiogenesis. TGFBR2, TGF-β receptor type 2; CAFs, cancer-associated fibroblasts; FAP, fibroblast activation protein α; ECM, extracellular matrix; HA, hyaluronic acid; MMP9, matrix metallopeptidase 9; VEGF, vascular endothelial growth factor; GC, gastric cancer.

syndrome (17,32,114). A TCM decoction, Xiaotan Sanjie decoction, has been formulated to treat the phlegm syndrome in patients with GC (17,32). As discussed, the Xiaotan Sanjie decoction has shown activities on CAFs (21,54,55,65), ECM (23,56,57,99,100,104) and the tumor blood supply (58-61) within the TME during tumorigenesis, growth and migration of GC in preclinical studies.

The Xiaotan Sanjie decoction inhibits GC initiation by upregulating TGFBR2 to normalize the antitumor action of the TGF-β/SMAD signaling pathway (22). At subsequent stages, the Xiaotan Sanjie decoction has revealed the ability to decrease the formation of CAFs through interruption of the expression of TGF-β (21). In the single-component studies, the aqueous extracts of *Fritillariae cirrhosae bulbus* (54) and *Sinapis semen* (55), two herbal medicinal compositions of Xiaotan Sanjie decoction, suppress the protumorigenic activity of TGF-β/SMAD signaling pathway. In addition, the aqueous extracts of scorpion-medicated serum significantly alleviates the TGF-β1-induced EMT process (81). The Xiaotan Sanjie decoction interferes with crosstalk between CAFs and tumor cells by downregulating IL-6 (83) and IL-8 (20,89) to inhibit tumor proliferation. Isolated compounds extracted from *Galli gigerii* endothelium corneum (84) and *Glycyrrhi za uralensis Fisch* (85), another two natural products in the Xiaotan Sanjie decoction, have the ability to downregulate expression of IL-6. Furthermore, the Xiaotan Sanjie decoction alleviates the development of deposition of ECM by blocking the activities of CAFs. The Xiaotan Sanjie decoction interrupts HA-CD44 interaction between ECM and tumor cells by degrading HA (99,100) and downregulating expression of CD44V6 (23,104). The Xiaotan Sanjie decoction has also been revealed to potentially target angiogenesis by downregulating the expression level of VEGF to exert antitumor effects (58-60). During advanced stages, the Xiaotan Sanjie decoction has demonstrated effects on GC tumor cell migration by preventing the degradation of the ECM and its basement membrane (56,57). The possible mechanisms of antitumor activities of the Xiaotan Sanjie decoction are summarized in Fig. 1.

The Xiaotan Sanjie decoction improves survivorship and quality of life in patients with advanced GC in clinical studies. However, it is difficult to compare these clinical outcomes to studies conducted to observe efficacy and safety of synthetic drugs or biological products in patients with GC because the sample size of clinical studies using the decoction is relatively small. Well-designed, prospective, large-scale clinical trials should be conducted to find the most appropriate niche of the Xiaotan Sanjie decoction in the treatment of patients with GC. However, a preliminary conclusion may be drawn that the Xiaotan Sanjie decoction targets CAFs, ECM and angiogenesis in the TME, and thereby the decoction prepared a preferable physical condition for chemoradiation therapy or immune therapy. Advanced technologies, including synthetic biology and scalable spatial analysis of the TME (115,116), are enabling novel methods for finding and exploiting the medicinal value of natural products. Therefore, this has the potential to define the conclusive role of the Xiaotan Sanjie decoction in the treatment of GC.

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Authors' contributions

PKW and XQY developed the concept, designed the study and revised the manuscript. DZS collected the literature and

wrote the draft. All authors have read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

References

1. Cao W, Chen HD, Yu YW, Li N and Chen WQ: Changing profiles of cancer burden worldwide and in China: A secondary analysis of the global cancer statistics 2020. Chin Med J (Engl) 134: 783-791, 2021.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
3. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, *et al*: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355: 11-20, 2006.
4. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, *et al*: Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. Lancet 393: 1948-1957, 2019.
5. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, *et al*: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376: 687-697, 2010.
6. Sounni NE and Noel A: Targeting the tumor microenvironment for cancer therapy. Clin Chem 59: 85-93, 2013.
7. Quail DF and Joyce JA: Microenvironmental regulation of tumor progression and Metastasis. Nat Med 19: 1423-1437, 2013.
8. Oya Y, Hayakawa Y and Koike K: Tumor microenvironment in gastric cancers. Cancer Sci 111: 2696-2707, 2020.
9. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, Dos Santos LV, Aprile G, Ferry DR, *et al*: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383: 31-39, 2014.
10. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, Chen JS, Muro K, Kang WK, *et al*: Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390: 2461-2471, 2017.
11. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, *et al*: Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 4: e180013, 2018.
12. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, *et al*: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 15: 1224-1235, 2014.
13. Zheng YB, Cao FY, Liu KJ, Gan HF, He XB and Tong SL: Value of normalization window of tumor vasculature in neoadjuvant chemotherapy for patients with unresectable gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 15: 55-58, 2012 (In Chinese).
14. Sasaki A, Nakamura Y, Togashi Y, Kuno H, Hojo H, Kageyama S, Nakamura N, Takashima K, Kadota T, Yoda Y, *et al*: Enhanced tumor response to radiotherapy after PD-1 blockade in metastatic gastric cancer. Gastric Cancer 23: 893-903, 2020.
15. Jain RK: Normalizing tumor microenvironment to treat cancer: Bench to bedside to biomarkers. J Clin Oncol 31: 2205-2218, 2013.
16. Yan B, Liu L, Zhao Y, Xiu LJ, Sun DZ, Liu X, Lu Y, Shi J, Zhang YC, Li YJ, *et al*: Xiaotan Sanjie decoction attenuates tumor angiogenesis by manipulating Notch-1-regulated proliferation of gastric cancer stem-like cells. World J Gastroenterol 20: 13105-13118, 2014.
17. Shi J and Wei PK: The phlegm theory of gastric cancer. Zhong Xi Yi Jie He Xue Bao 9: 581-587, 2011 (In Chinese).
18. State Administration of Traditional Chinese Medicine: Criteria for Diagnosis and Evaluation of Therapeutic Effect on Diseases and Syndromes in Traditional Chinese Medicine. Nanjing University Press, Nanjing, pp9-11, 1994.
19. Sun DZ, Jiao JP, Ju DW, Ye M, Zhang X, Xu JY, Lu Y, He J, Wei PK and Yang MH: Tumor interstitial fluid and gastric cancer metastasis: An experimental study to verify the hypothesis of 'tumor-phlegm microenvironment'. Chin J Integr Med 18: 350-358, 2012 (In Chinese).
20. Ju DW, Wei PK, Lin HM, Sun DZ, Yu S and Xiu LJ: Effects of Xiaotan Sanjie Decoction on expressions of interleukin-8 and its receptors in gastric tumor xenografts and gastric tissue adjacent to the tumor in mice. Zhong Xi Yi Jie He Xue Bao 8: 74-79, 2010 (In Chinese).
21. Yu X, Zhao Y, Wei P, Chen M, Jing J, Zhong L, *et al*: Effects of Xiaotan Sanjie decoction on serum expression levels of IL-8 and TGF-β in gastric tumor xenografts in nude mice. Chin Arch Tradit Chin Med 36: 2382-2385, 2018 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2018&filename=ZYHS201810021&v=8GUmiMviuOMeRswXcUcanzXDS%25mmd2Bixowvul5WOa%25mmd2BraRlfuEWfwqoBiKhPNA6nOO6Ea
22. Ye M, Jiao J, Zhang X, *et al*: Xiaotan Sanjie decoction inhibit MKN-45 human gastric cancer cells by upregulating TGFβRII in vivo and in vitro. Chin J Clin 11: 596-601, 2017 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2017&filename=ZLYD201704014&v=SSyny61gLr%25mmd2BD7csH5ElmOXxnrufLyl1TFMCFLEq%25mmd2BKRZiigitzRn%25mmd2FLZPmCZon7uwML
23. Wang J, Wei P, Li Y and Xu L: Effects of Xiaotan Sanjie decoction on expression of CD44V6 in MKN-45 human gastric cancer nude mouse model. J Chengdu Univ Tradit Chin Med 27: 20-21, 2001 (In Chinese).
24. Gui MW, Wei PK, Lu Y, Guo W, Qin ZF and Sun DZ: Effects of Xiaotan Sanjie Decoction-containing serum on proliferation and apoptosis of human gastric cancer cells MKN-45. Zhong Xi Yi Jie He Xue Bao 8: 250-255, 2010 (In Chinese).
25. Liu X, Xiu LJ, Jiao JP, Zhao J, Zhao Y, Lu Y, Shi J, Li YJ, Ye M, Gu YF, *et al*: Traditional Chinese medicine integrated with chemotherapy for stage IV non-surgical gastric cancer: A retrospective clinical analysis. J Integr Med 15: 469-475, 2017.
26. Sun DZ, Li SD, Liu Y, Zhang Y, Mei R and Yang MH: Differences in the origin of philosophy between Chinese Medicine and Western medicine: Exploration of the holistic advantages of Chinese medicine. Chin J Integr Med 19: 706-711, 2013 (In Chinese).
27. World Health Organization: WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region, World Health Organization, Western Pacific Region, 2007. https://asiantherapies.org/wp-content/uploads/2021/10/WHO-Terminology-Manual-1.pdf
28. Lu A, Jiang M, Zhang C and Chan K: An integrative approach of linking traditional Chinese medicine pattern classification and biomedicine diagnosis. J Ethnopharmacol 141: 549-556, 2012.
29. Clavey S: Phlegm: Aetiology and symptomatology. In: Fluid Physiology and Pathology in Traditional Chinese Medicine. Churchill Livingstone Elsevier, London, pp265-312, 2003.
30. Meng Q: Basic Thoery of Traditional Chinese Medicine. China Press of Traditional Chinese Medicine, Beijing, 2005.

31. Greenwood MT: Dysbiosis, Spleen Qi, phlegm, and complex difficulties. Med Acupunct 29: 128-137, 2017.
32. Yue X and Wei P: Phlegm as the target of gastric cancer. Ti Erh Chun I Ta Hsueh Hsueh Pao 39: 1297-1301, 2018.
33. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC and Lordick F: Gastric cancer. Lancet 396: 635-648, 2020.
34. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, *et al*: Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 167-192, 2022.
35. Guner A and Yildirim R: Surgical management of metastatic gastric cancer: Moving beyond the guidelines. Transl Gastroenterol Hepatol 4: 58, 2019.
36. Andreoli TE: Cecil essentials of medicine. Elsevier, Philadelphia, PA, pp440-441, 2010.
37. Shi J, Qin Z, Wang X, *et al*: Clinical observation of TCM treatment of dispersing phlegm and eliminating stagnation on postoperative gastric carcinoma. Chin J Info Tradit Chin Med 18: 14-17, 2011 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2011&filename=XXYY201110010&v=WYxc3H1bWPb2I7WrEYpn3%25mmd2Bq7b0lH46oPvMqfiqxL2Kfg7dCZ%25mmd2FVE4dYKAbMYdugZR
38. Hsu PP and Sabatini DM: Cancer cell metabolism: Warburg and beyond. Cell 134: 703-707, 2008.
39. Gajewski TF, Meng Y, Blank C, Brown I, Kacha A, Kline J and Harlin H: Immune resistance orchestrated by the tumor microenvironment. Immunol Rev 213: 131-145, 2006.
40. Fox JG and Wang TC: Inflammation, atrophy, and gastric cancer. J Clin Invest 117: 60-69, 2007.
41. Bockerstett KA and DiPaolo RJ: Regulation of gastric carcinogenesis by inflammatory cytokines. Cell Mol Gastroenterol Hepatol 4: 47-53, 2017.
42. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
43. Sun H, Wang X, Wang X, Xu M and Sheng W: The role of cancer-associated fibroblasts in tumorigenesis of gastric cancer. Cell Death Dis 13: 874, 2022.
44. Noël A, Gutiérrez-Fernández A, Sounni NE, Behrendt N, Maquoi E, Lund IK, Cal S, Hoyer-Hansen G and López-Otín C: New and paradoxical roles of matrix metalloproteinases in the tumor microenvironment. Front Pharmacol 3: 140, 2012.
45. Bussard KM, Mutkus L, Stumpf K, Gomez-Manzano C and Marini FC: Tumor-associated stromal cells as key contributors to the tumor microenvironment. Breast Cancer Res 18: 84, 2016.
46. Kinoshita H, Hirata Y, Nakagawa H, Sakamoto K, Hayakawa Y, Takahashi R, Nakata W, Sakitani K, Serizawa T, Hikiba Y, *et al*: Interleukin-6 mediates epithelial-stromal interactions and promotes gastric tumorigenesis. PLoS One 8: e60914, 2013.
47. Bai J, Qi J, Yang L, Wang Z, Wang R and Shi Y: A comprehensive review on ethnopharmacological, phytochemical, pharmacological and toxicological evaluation, and quality control of *Pinellia ternata (Thunb.)* Breit. J Ethnopharmacol 298: 115650, 2022.
48. Song S, Huang W, Lu X, Liu J, Zhou J, Li Y and Shu P: A network pharmacology study based on the mechanism of *Citri Reticulatae Pericarpium-Pinelliae Rhizoma* in the treatment of gastric cancer. Evid Based Complement Alternat Med 2021: 6667560, 2021.
49. Ayeka PA, Bian Y, Githaiga PM and Zhao Y: The immunomodulatory activities of licorice polysaccharides (*Glycyrrhiza uralensis Fisch.*) in CT 26 tumor-bearing mice. BMC Complement Altern Med 17: 536, 2017.
50. Park A, Yang Y, Lee Y, Jung H, Kim TD, Noh JY, Lee S and Yoon SR: *Aurantii Fructus Immaturus* enhances natural killer cytolytic activity and anticancer efficacy in vitro and in vivo. Front Med (Lausanne) 9: 973681, 2022.
51. Ding J, Chua PJ, Bay BH and Gopalakrishnakone P: Scorpion venoms as a potential source of novel cancer therapeutic compounds. Exp Biol Med (Maywood) 239: 387-393, 2014.
52. Rapôso C: Scorpion and spider venoms in cancer treatment: State of the art, challenges, and perspectives. J Clin Transl Res 3: 233-249, 2017.
53. Zhao H, Li Y, Wang Y, Zhang J, Ouyang X, Peng R and Yang J: Antitumor and immunostimulatory activity of a polysaccharide-protein complex from *Scolopendra subspinipes mutilans L.* Koch in tumor-bearing mice. Food Chem Toxicol 50: 2648-2655, 2012.
54. Bokhari AA and Syed V: Inhibition of transforming growth factor-β (TGF-β) signaling by *Scutellaria baicalensis* and *Fritillaria cirrhosa* Extracts in endometrial cancer. J Cell Biochem 116: 1797-1805, 2015.
55. Cao S, Zheng B, Chen T, Chang X, Yin B, Huang Z, Shuai P and Han L: Semen Brassicae ameliorates hepatic fibrosis by regulating transforming growth factor-β1/Smad, nuclear factor-κB, and AKT signaling pathways in rats. Drug Des Devel Ther 12: 1205-1213, 2018.
56. Xiao Y, Wei P, Li Y, He J, Xu L and Qin Z: Influence of Xiaotan Sanjie decoction on the expression of matrix metalloproteinase and inhibitor in Gastric Carcinoma. Hubei J Tradit Chin Med 34: 8-10, 2005.
57. Ju D, Xiu L, Sun D, Lu Y and Wei P: Effects of Xiaotan Sanjie decoction on invasive ability of human gastric cancer cell line SGC-7901. Chin J Woman Child Health Res 27: 343-344, 2016 (In Chinese).
58. Tang J, Wei P and Zhang Y: Effects of Xiaotan Sanjie decoction on microvessel density and expression level of VEGF-A/VEGFR-2. World J Integr Tradit Western Med 10: 346-349, 2015.
59. Xu L, Su X, Chen Y and Wei P: Xiaotan Sanjie decoction down-regulate expression level of VEGF, KDRmRNA in orthotopic human gastric carcinoma in nude mice. World Chin J Digest 12: 3, 2004 (In Chinese).
60. Pang B, Wei P, Mao Z and Li Y: Effects of Xiaotan Sanjie Decoction on expression levels of VEGF-D in MKN45 xenografts in nude mice. Chin J Inf Tradit Chin Med 18: 42-44, 2011 (In Chinese).
61. Zhou W, Li YJ and Wei PK: Effects of xiaotan sanjie decoction on vasculogenic mimicry of human gastric cancer xenografts in nude mice. Zhongguo Zhong Xi Yi Jie He Za Zhi 31: 532-536, 2011 (In Chinese).
62. Kumar V, Ramnarayanan K, Sundar R, Padmanabhan N, Srivastava S, Koiwa M, Yasuda T, Koh V, Huang KK, Tay ST, *et al*: Single-cell atlas of lineage states, tumor microenvironment, and subtype-specific expression programs in gastric cancer. Cancer Discov 12: 670-691, 2022.
63. Gu J, Wang C, Xu X, Zhao L, Zhou J, Bai C and Sun Z: Immunohistochemical detection of cancer-associated fibroblasts in gastrointestinal cancer as a potential prognostic biomarker of survival: Meta-analysis. Transl Cancer Res 9: 6629-6638, 2020.
64. Wen X, He X, Jiao F, Wang C, Sun Y, Ren X and Li Q: Fibroblast activation Protein-a-positive fibroblasts promote gastric cancer progression and resistance to immune checkpoint blockade. Oncol Res 25: 629-640, 2017.
65. Yu Z, Zhao Y, Hu X, Shao Z, Jiang Z, Lu Y, Xiao Z, Pang B, *et al*: Effects of Xiaotan Sanjie decoction on expression of fibroblast activation protein α in gastric cancer MKN-45 cells xenografted in nude mice. Chin Arch Tradit Chin Med 28: 331-334, 2010 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2010&filename=ZYHS201002050&v=CTYLMbKoZXwaH0%25mmd2FV8SFqFzODQhR2nxC%25mmd2FPoPnpAkNeO7fQrS0ZGsv7vUfMkTs49D0
66. French R, Feng Y and Pauklin S: Targeting TGFβ signaling in cancer: Toward context-specific strategies. Trends Cancer 6: 538-540, 2020.
67. Saito H, Tsujitani S, Oka S, Kondo A, Ikeguchi M, Maeta M and Kaibara N: An elevated serum level of transforming growth factor-beta 1 (TGF-beta 1) significantly correlated with lymph node metastasis and poor prognosis in patients with gastric carcinoma. Anticancer Res 20: 4489-4493, 2000.
68. Evans RA, Tian YC, Steadman R and Phillips AO: TGF-β1-mediated fibroblast-myofibroblast terminal differentiation-the role of smad proteins. Exp Cell Res 282: 90-100, 2003.
69. Yang L, Chang N, Liu X, Han Z, Zhu T, Li C, Yang L and Li L: Bone marrow-derived mesenchymal stem cells differentiate to hepatic myofibroblasts by transforming growth factor-β1 via sphingosine kinase/sphingosine 1-phosphate (S1P)/S1P receptor axis. Am J Pathol 181: 85-97, 2012.
70. Jotzu C, Alt E, Welte G, Li J, Hennessy BT, Devarajan E, Krishnappa S, Pinilla S, Droll L and Song YH: Adipose tissue derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor derived factors. Cell Oncol (Dordr) 34: 55-67, 2011.
71. Calon A, Tauriello DV and Batlle E: TGF-beta in CAF-mediated tumor growth and metastasis. Semin Cancer Biol 25: 15-22, 2014.
72. Piek E, Heldin CH and Ten Dijke P: Specificity, diversity, and regulation in TGF-beta superfamily signaling. FASEB J 13: 2105-2124, 1999.
73. Massagué J, Seoane J and Wotton D: Smad transcription factors. Gene Dev 19: 2783-2810, 2005.
74. Elliott RL and Blobe GC: Role of transforming growth factor Beta in human cancer. J Clin Oncol 23: 2078-2093, 2005.

75. Pickup M, Novitskiy S and Moses HL: The roles of TGFβ in the tumour microenvironment. Nat Rev Cancer 13: 788-799, 2013.
76. Bierie B and Moses HL: TGF-β and cancer. Cytokine Growth Factor Rev 17: 29-40, 2006.
77. Park K, Kim SJ, Bang YJ, Park JG, Kim NK, Roberts AB and Sporn MB: Genetic changes in the transforming growth factor beta (TGF-beta) type II receptor gene in human gastric cancer cells: Correlation with sensitivity to growth inhibition by TGF-beta. Proc Natl Acad Sci USA 91: 8772-8776, 1994.
78. Nadauld LD, Garcia S, Natsoulis G, Bell JM, Miotke L, Hopmans ES, Xu H, Pai RK, Palm C, Regan JF, *et al*: Metastatic tumor evolution and organoid modeling implicate TGFBR2 as a cancer driver in diffuse gastric cancer. Genome Biol 15: 428, 2014.
79. Kim SH, Lee SH, Choi YL, Wang LH, Park CK and Shin YK: Extensive alteration in the expression profiles of TGFB pathway signaling components and TP53 is observed along the gastric dysplasia-carcinoma sequence. Histol Histopathol 23: 1439-1452, 2008.
80. Pak KH, Kim DH, Kim H, Lee DH and Cheong JH: Differences in TGF-β1 signaling and clinicopathologic characteristics of histologic subtypes of gastric cancer. BMC Cancer 16: 60, 2016.
81. Yan YQ, Xie J, Wang JF, Shi ZF, Zhang X, Du YP and Zhao XC: Scorpion inhibits epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma. Exp Biol Med (Maywood) 243: 645-654, 2018.
82. Karakasheva TA, Lin EW, Tang Q, Qiao E, Waldron TJ, Soni M, Klein-Szanto AJ, Sahu V, Basu D, Ohashi S, *et al*: IL-6 mediates cross-talk between tumor cells and activated fibroblasts in the tumor microenvironment. Cancer Res 78: 4957-4970, 2018.
83. Ju D, Wei P, Sun D, Lin H and Yu S: Effects of Xiaotan Sanjie decoction on IL-6 gene expression in tumor and adjacent tissues of S180 tumor-bearing mice model. Chin J Integr Dig 15: 284-288, 2008 (In Chinese).
84. Li S, Zheng M, Zhang Z, Peng H, Dai W and Liu J: Galli gigeriae endothelium corneum: Its intestinal barrier protective activity in vitro and chemical composition. Chin Med 16: 22, 2021 (In Chinese).
85. Yu JY, Ha JY, Kim KM, Jung YS, Jung JC and Oh S: Anti-Inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin and liquiritigenin, in BV2 cells and mice liver. Molecules 20: 13041-13054, 2015.
86. Kitadai Y, Takahashi Y, Haruma K, Naka K, Sumii K, Yokozaki H, Yasui W, Mukaida N, Ohmoto Y, Kajiyama G, *et al*: Transfection of interleukin-8 increases angiogenesis and tumorigenesis of human gastric carcinoma cells in nude mice. Br J Cancer 81: 647-653, 1999.
87. Wang Z, Hou Y, Yao Z, Zhan Y, Chen W and Liu Y: Expressivity of Interleukin-8 and gastric cancer prognosis susceptibility: A systematic review and meta-analysis. Dose Response 19: 15593258211037127, 2021.
88. Zhai J, Shen J, Xie G, Wu J, He M, Gao L, Zhang Y, Yao X and Shen L: Cancer-associated fibroblasts-derived IL-8 mediates resistance to cisplatin in human gastric cancer. Cancer Lett 454: 37-43, 2019.
89. Shi J and Wei PK: Xiaotan Sanjie decoction inhibits interleukin-8-induced metastatic potency in gastric cancer. World J Gastroenterol 21: 1479-1487, 2015.
90. Lynch MD and Watt FM: Fibroblast heterogeneity: Implications for human disease. J Clin Investig 128: 26-35, 2018.
91. Voloshenyuk TG, Landesman ES, Khoutorova E, Hart AD and Gardner JD: Induction of cardiac fibroblast lysyl oxidase by TGF-β1 requires PI3K/Akt, Smad3, and MAPK signaling. Cytokine 55: 90-97, 2011.
92. Najafi M, Farhood B and Mortezaee K: Extracellular matrix (ECM) stiffness and degradation as cancer drivers. J Cell Biochem 120: 2782-2790, 2019.
93. Huang J, Zhang L, Wan D, Zhou L, Zheng S, Lin S and Qiao Y: Extracellular matrix and its therapeutic potential for cancer treatment. Signal Transduct Target Ther 6: 153, 2021.
94. Balazs EA, Laurent TC and Jeanloz RW: Nomenclature of hyaluronic acid. Biochem J 235: 903, 1986.
95. Setälä LP, Tammi MI, Tammi RH, Eskelinen MJ, Lipponen PK, Agren UM, Parkkinen J, Alhava EM and Kosma VM: Hyaluronan expression in gastric cancer cells is associated with local and nodal spread and reduced survival rate. Br J Cancer 79: 1133-1138, 1999.
96. Eikenes L, Tufto I, Schnell EA, Bjørkøy A and De Lange Davies C: Effect of collagenase and hyaluronidase on free and anomalous diffusion in multicellular spheroids and xenografts. Anticancer Res 30: 359-368, 2010.
97. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, Feig C, Nakagawa T, Caldwell ME, Zecchini HI, *et al*: Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 62: 112-120, 2013.
98. Zhao R, Cui Y, Zheng Y, Li S, Lv J, Wu Q, Long Y, Wang S, Yao Y, Wei W, *et al*: Human Hyaluronidase PH20 potentiates the antitumor activities of Mesothelin-specific CAR-T cells against gastric cancer. Front Immunol 12: 660488, 2021.
99. Wright RP, Chan TK, Honetschlager L, Howell DE and Odell GV: Enzymes and toxins of the scorpion venom Palamneus gravimanus. Toxicon 15: 197-205, 1977.
100. González-Morales L, Pedraza-Escalona M, Diego-Garcia E, Restano-Cassulini R, Batista CV, Gutiérrez Mdel C and Possani LD: Proteomic characterization of the venom and transcriptomic analysis of the venomous gland from the *Mexican centipede Scolopendra viridis*. J Proteomics 111: 224-237, 2014.
101. Naor D, Sionov RV and Ish-Shalom D: CD44: Structure, function, and association with the malignant process. Adv Cancer Res 71: 241-319, 1997.
102. Chen Y, Fu Z, Xu S, Xu Y and Xu P: The prognostic value of CD44 expression in gastric cancer: A meta-analysis. Biomed Pharmacother 68: 693-697, 2014.
103. Misra S, Heldin P, Hascall VC, Karamanos NK, Skandalis SS, Markwald RR and Ghatak S: Hyaluronan-CD44 interactions as potential targets for cancer therapy. FEBS J 278: 1429-1443, 2011.
104. Zhang S, Wei P, He J, Xiao Y, Chen G, Gu J, *et al*: Effects of Jinlongshe formula on tumor proliferation and metastases and expression of cell adhesion molecules in MKN-45 human gastric cancer nude mouse model. Tumor 25: 519-524, 2006. https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2006&filename=ZZLL200606006&v=s1YASjhB7tsvRqd%25mmd2F%25mmd2BMg%25mmd2Fq8XnD2Vn96oB%25mmd2BffZf4A4Bh7qvD40ECTEqijOPzzUCyqD
105. Lukaszewicz-Zając M, Mroczko B and Szmitkowski M: Gastric cancer- The role of matrix metalloproteinases in tumor progression. Clin Chim Acta 412: 1725-1730, 2011.
106. Fukumura D, Xavier R, Sugiura T, Chen Y, Park EC, Lu N, Selig M, Nielsen G, Taksir T, Jain RK and Seed B: Tumor induction of VEGF promoter activity in stromal cells. Cell 94: 715-725, 1998.
107. Zhao Y, Wang X, Lu Y, Liu X, Xiu L, Yue X, *et al*: Xiaotan Sanjie decoction on quality of life in patients with advanced gastric cancer. Ti Erh Chun I Ta Hsueh Hsueh Pao 37: 1333-1337, 2016 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2017&filename=DEJD201611003&v=kQr6y0QoJCwsnabe8RyD3I5ziphgCCMRnPcPGOv3wTJP8Apz2l2jK77cElywgR16
108. Wu F, Qin Z, Zhang C, Yan B, Shen W and Wei P: Effects of Jinlongshe formulae on quality of life in patients with gastric cancer after gastric resection. Chin J Integr Tradit Western Med Digest 20: 289-292, 2012 (In Chinese).
109. Shi J, Qin Z, Wang X, Zhang Y, Zhang C, Wang D, *et al*: Xiaotan Sanjie decoction in patients with gastric cancer after gastric resection. Chin J Info Tradit Chin Med 18: 14-17, 2011 (In Chinese). https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFD2011&filename=XXYY201110010&v=WYxc3H1bWPb2I7WrEYpn3%25mmd2Bq7b0lH46oPvMqfiqxL2Kfg7dCZ%25mmd2FVE4dYKAbMYdugZR
110. Li X and Wei P: Jinlongshe formulae in advanced gastric cancer. Hubei J Tradit Chin Med 23: 3-5, 2001 (In Chinese).
111. Xu L, Chen Y, Liu Y, Qin Z, Li J, Shi J, *et al*: Efficacy of Xiaotan Sanjie decoction combined with Huangqi injection and Huachansu injection in patients with stage IV gastric cancer. J Chengdu Univ Tradit Chin Med 28: 7-9, 2005 (In Chinese). https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLTlOAiTRKgchrJ08w1e7F1IFNsBV5UtixLZQlfT5Bp4RioHTO7MFcAQH76h6XVw4s4ZTzR4S80OigHx_bgBm&uniplatform=NZKPT
112. Sun DZ, Jiao JP, Zhang X, Xu JY, Ye M, Xiu LJ, Zhao Y, Lu Y, Liu X, Zhao J, *et al*: Therapeutic effect of Jinlongshe granule on quality of life of stage IV gastric cancer patients using EORTC QLQ-C30: A double-blind placebo-controlled clinical trial. Chin J Integr Med 21: 579-586, 2015 (In Chinese).
113. Liu X, Xiu LJ, Jiao JP, Zhao J, Zhao Y, Lu Y, Shi J, Li YJ, Ye M, Gu YF, *et al*: Traditional Chinese medicine integrated with chemotherapy for stage IV non-surgical gastric cancer: A retrospective clinical analysis. J Integr Med 15: 469-475, 2017.
114. Sun DZ, Ju DW, He J, Lu Y, Wu F, Li C and Wei PK: Tumor interstitial fluid and postoperative recurrence of tumors: An experimental study for verifying hypothesis of 'Tumor-phlegm Microenvironment'. Chin J Integr Med 16: 435-441, 2010 (In Chinese).

115. Koelzer VH, Sirinukunwattana K, Rittscher J and Mertz KD: Precision immunoprofiling by image analysis and artificial intelligence. Virchows Archiv 474: 511-522, 2019.
116. Lin L and Wang LV: The emerging role of photoacoustic imaging in clinical oncology. Nat Rev Clin Oncol 19: 365-384, 2022.
117. Qi CY, Wang J, Wu X, He SR, Zhang Q, Wu JH and Zhao CB: Botanical, traditional use, phytochemical, and toxicological of *Arisaematis rhizoma*. Evid Based Complement Alternat Med 2021: 9055574, 2021.
118. Wang Y, Li T, Zhao Y, Zhang J and Liu H: Contents of some metabolites in the peel and flesh of the medicinal mushroom *Wolfiporia cocos* (F.A. Wolf) *Ryvarden et Gilb.* (*Higher Basidiomycetes*). Int J Med Mushrooms 14: 79-83, 2012.
119. Bian C, Xie N and Chen F: Preparation of bioactive water-soluble pachyman hydrolyzed from sclerotial polysaccharides of *Poria cocos* by hydrolase. Polym J 42: 256-260, 2010.
120. Wagner H, Püls S, Barghouti T, Staudinger A and Melchart D: Chromatographic Fingerprint Analysis of Herbal Medicines. Springer, Vienna, pp31-44, 2018.
121. Duan L, Guo L, Liu K, Liu EH and Li P: Characterization and classification of seven citrus herbs by liquid chromatography-quadrupole time-of-flight mass spectrometry and genetic algorithm optimized support vector machines. J Chromatogr A 1339: 118-127, 2014.
122. Hao EW, Su ZX, Gong YL, Du ZC, Yang X, Huang CT, Hou XT and Deng JG: Analysis on application law of dampness-removing traditional Chinese medicines in treatment of coronavirus disease 2019. Chin Herb Med 13: 518-524, 2021 (In Chinese).
123. Song L, Xiong P, Zhang W, Hu H, Tang S, Jia B and Huang W: Mechanism of *Citri Reticulatae Pericarpium* as an anticancer agent from the perspective of flavonoids: A review. Molecules 27: 5622, 2022.
124. Moon JY and Cho SK: Nobiletin Induces protective autophagy accompanied by ER-stress mediated apoptosis in human gastric cancer SNU-16 cells. Molecules 21: 914, 2016.
125. Dong Y, Cao A, Shi J, Yin P, Wang L, Ji G, Xie J and Wu D: Tangeretin, a citrus polymethoxyflavonoid, induces apoptosis of human gastric cancer AGS cells through extrinsic and intrinsic signaling pathways. Oncol Rep 31: 1788-1794, 2014.
126. Yu W, Xie X, Yu Z, Jin Q and Wu H: Mechanism of hesperidin-induced apoptosis in human gastric cancer AGS cells. Trop J Pharm Res 50: 2363-2369, 2019.
127. Xiong Q, Li X, Zhou R, Hao H, Li S, Jing Y, Zhu C, Zhang Q and Shi Y: Extraction, characterization and antioxidant activities of polysaccharides from *E. corneum gigeriae galli*. Carbohydr Polym 108: 247-256, 2014.
128. Chen T, Zhong F, Yao C, Chen J, Xiang Y, Dong J, Yan Z and Ma Y: A systematic review on traditional uses, sources, phytochemistry, pharmacology, pharmacokinetics, and toxicity of *Fritillariae Cirrhosae Bulbus*. Evid Based Complement Alternat Med 2020: 1536534, 2020.
129. Wang D, Chen X, Atanasov AG, Yi X and Wang S: Plant resource availability of medicinal *Fritillaria* species in traditional producing regions in Qinghai-Tibet plateau. Front Pharmacol 8: 502, 2017.
130. Li R, Zhang Y, Wang Y, Huang K, Yang Q, Zhang T, Xie K, Li J and Zhao Q: Aqueous extract of *Fritillariae cirrhosae* induces cellular apoptosis through activation of STATs-mediated immunomodulation. J Ethnopharmacol 261: 112338, 2020.
131. Wang X, Zhang H, Chen L, Shan L, Fan G and Gao X: Liquorice, a unique 'guide drug' of traditional Chinese medicine: A review of its role in drug interactions. J Ethnopharmacol 150: 781-790, 2013.