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REVIEW

Matching traditional Chinese medicine and western medicine-based research: Advanced nutraceutical development for proactive gastric cancer prevention

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Abstract

Gastric cancer (GC), the third leading cause of cancer-related death globally, is complex and heterogeneous. This review explores multidisciplinary investigations of traditional Chinese medicine (TCM) combined with Western medical practices, emphasizing the development of nutraceuticals for cancer prevention.

Using advanced analytical chemistry and food chemistry techniques, this study investigated how TCM components may be optimized for nutraceutical development. Focusing on molecular interactions with GC pathways, particularly the NF-κB, PI3K/Akt, and Wnt/β-catenin pathways, we examined the effects of TCM polyherbal formulas, extracts, and isolated compounds. These agents modulate apoptosis and cellular proliferation, underscoring their potential in preventive strategies. The convergence of nutraceutical and medicine food homology studies highlights a significant shift towards integrating TCM-derived compounds in a preventive health framework. This approach aims not only to enhance efficacy and reduce side effects but also to champion a preventive paradigm using personalized medicine to advance proactive health maintenance and disease prevention. The combination of TCM and western medical practices offers promising avenues for future research and practical applications in GC prevention.

Key Words: Traditional Chinese medicine; Precision medicine; Molecular network; Phytochemistry; Food chemistry; Nutraceuticals; Gastric cancer

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Core Tip: This review highlights the integration of traditional Chinese medicine and western medicine-based studies in the development of nutraceuticals for gastric cancer (GC) prevention. This review focuses on molecular interactions within GC pathways, emphasizing a proactive approach to enhancing treatment efficacy and advancing preventive health strategies.

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INTRODUCTION

Gastric cancer (GC) is a significant health challenge worldwide, with varying prevalence rates across different regions and sexes. GC represents the fifth most common cancer globally and the third leading cause of cancer-related deaths. Notably, the highest incidence rates are observed in Eastern Asia, Eastern Europe, and South America. In these regions, GC accounts for up to 42% of all cancer cases, with a higher prevalence among males than females. Despite advancements in cancer treatments, survival rates for GC patients remain low, underscoring the importance of primary and secondary prevention strategies[1].

The aetiology of GC is multifaceted, with over 80% of cases linked to *Helicobacter pylori* (*H. pylori*) infection. Additionally, factors such as family history, diet, lifestyle choices, genetics, socioeconomic status, and other environmental aspects contribute to GC development. Dietary factors play a pivotal role. The consumption of fruits and vegetables offers protection, whereas broiled and charbroiled animal meats, along with salt-preserved and smoked foods, are likely to increase the risk of GC.

Pathologically, GC is classified into two main types on the basis of the World Health Organization and Lauren classification: The intestinal type, which is more prevalent in high-risk regions and older populations, and the diffuse type, which is more common in women and younger patients. The progression to invasive gastric carcinoma involves a series of histopathological changes, starting with atrophic gastritis and progressing to intestinal metaplasia, dysplasia, and finally carcinoma.

The treatment of GC is stage dependent, with a focus on surgical methods such as resection, endoscopic mucosal resection, and submucosal dissection for the early stages and the incorporation of chemotherapy, including fluorouracil-based regimens, for more advanced cases. These treatments, although effective, may be enhanced through integration with vegetal substances traditionally used in traditional Chinese medicine (TCM). The first step, in this sense, is to investigate data from the scientific literature to establish new possible interventions aimed at reducing the incidence of GC in addition to improving the outcomes of patients undergoing surgery and chemotherapy.

Several TCM formulations[2,3], phytocomplexes[4,5] and phytochemicals[6,7] have been developed. *In vitro*, several mechanisms have been shown to act against several cancer types, including GC[8,9]. Moreover, several plant extracts could be explored for their potential to mitigate the side effects of chemotherapeutic agents[10,11]. To further understand the mechanisms of action of TCM in the treatment of GC, we explored in detail the pharmacological effects and mechanisms of specific Chinese herbs and their components. The aim of this review is to explore the potential of these integrative approaches for reducing the incidence of GC, reflecting a shift towards identifying nutraceuticals that can preemptively manage health. This approach draws from the western concept of nutraceuticals, which focuses on preventing diseases using food-derived substances that offer health benefits. Concurrently, it aligns with the Chinese concept of medicine food homology, which emphasizes the dual use of food to promote health and prevent illness. This

synthesis of Western and Eastern approaches offers a unique pathway for enhancing cancer prevention strategies through the development of effective nutraceuticals that target GC.

Aetiology and pathogenesis of GC

GC is significantly influenced by microbial agents such as *H. pylori* and Epstein-Barr virus (EBV), which disrupt the cellular signalling pathways critical for cancer development. *H. pylori*, a recognized carcinogen, is found in approximately 90% of GC patients and alters pathways such as JAK/STAT, interferon regulatory factor, and NF-κB. EBV modifies the JAK/STAT and NF-κB pathways, affecting the immune response and cellular apoptosis and proliferation mechanisms. These pathogens also influence the c-Junproto-oncogene signalling pathway, TGF-β cascade, and PI3K pathway, thereby playing complex roles in GC pathogenesis and highlighting the need for targeted therapeutic strategies[12].

Additionally, environmental and dietary factors affect GC risk through epigenetic mechanisms. Pollutants, such as heavy metals and cigarette smoke, along with dietary habits, such as high salt intake and alcohol consumption, induce DNA methylation and histone modifications, contributing to GC development. These insights emphasize the impact of lifestyle on genetic expression and cancer risk[13-15]. Exposure to several pollutants results in an increase in the expression of several phlogogenic proteins and the subsequent activation of inflammatory pathways, leading to the sustained release of cytokines, such as TNF-α, IL-1β, and IL-6, and the stimulation of these pathways is related to mechanisms involved in GC onset and progression. This inflammatory pattern is also induced by a diet characterized by a high consumption of red meat, likely due to the high amount of saturated fatty acids and a low intake of vegetal-based foods. Indeed, several polyphenols are associated with a lower GC risk, at least in part, because of their ability to counteract oxidative stress and low-grade inflammation.

These risk factors have a greater impact on genetically predisposed patients. Advancements in genetics have identified mutations in genes such as *PALB2*, *BRCA1*, *BRCA2*, *CDH1*, and *CTNNA1*, linking them to increased GC risk. These genes are involved in DNA repair, cell adhesion, and epithelial integrity, which are crucial in cancer progression. Geographic variations in these genetic mutations suggest differences in susceptibility among populations, necessitating personalized approaches to treatment[16-19].

Emerging therapeutic targets

Recent advances in understanding GC at the molecular level have identified several key targets that could be pivotal for the development of preventive strategies. Below is a detailed description of the main targets, highlighting their roles in potential prevention mechanisms: (1) Wnt/β-catenin signalling pathway: Central to cell proliferation and survival, disruption of this pathway may reduce the risk of cancer cell growth from the beginning stages[20]. Inhibitors targeting WNT ligand interactions, such as WNT974 (LGK974) and vantictumab (OMP-18R5), have shown promising results; (2) Oxidative stress biomarkers (MDA, SOD, and GSH-PX): These biomarkers are critical for maintaining the cellular redox balance. Monitoring and modulating these biomarkers could help prevent oxidative stress-related DNA damage, a known risk factor for cancer initiation. Enhancing antioxidant defence systems in high-risk populations might serve as a preventive measure[21,22]; (3) Programmed death-ligand 1 (PD-L1): By modulating immune evasion mechanisms early on, targeting PD-L1 could increase immune surveillance and eliminate potentially cancerous cells before they proliferate. This approach is particularly relevant in the development of vaccines or immunomodulatory agents that prime the immune system against neoplastic cells[23]; (4) Hypoxia-induciblefactor-1 (HIF-1): Targeting HIF-1 to prevent its ability to adapt cancer cells to low-oxygen conditions could inhibit early adaptations that promote cancer progression. Preventive strategies could include agents that normalize tumour oxygenation or disrupt the function of HIF-1, thereby deterring cancer cell survival in hypoxic tumour microenvironments; (5) Epidermal growth factor receptor (EGFR): Given that EGFR is involved in the early stages of cellular transformation and proliferation, EGFR inhibitors could be used in high-risk individuals to prevent initial cellular changes that lead to cancer; (6) Interferon-gamma receptor (IFNGR) and toll-like receptor 4 (TLR4): Both are involved in immune response regulation. Enhancing the function of these receptors might help boost innate and adaptive immune responses against early cancerous changes, providing a preventive advantage[24]; and (7) Nutritional and immunological parameters: Parameters such as albumin and immunoglobulins reflect the general health and immune status of an individual. Optimizing these parameters through dietary and lifestyle interventions could strengthen the body's natural defences against cancer initiation and progression[25,26].

The modulation of these targets may affect the early stages of cancer development. In particular, the investigation of food and vegetal extract-derived compounds endowed with the ability to modulate the abovementioned targets within specific molecular networks may lead to the development of methods that are able to decrease the risk of cancer risk and the side effects of chemotherapeutic drugs. This proactive approach is aligned with the principles of network pharmacology (NP) and the concept of medicine food homology, emphasizing the use of food-derived compounds and dietary interventions to maintain health and prevent disease.

Perspective of TCM on GC

TCM may offer an integrative approach to treating diseases, including GC. TCM views the human body as an interconnected system where an individual's health is strongly affected by the environment. This perspective extends to understanding diseases such as GC, where imbalances within this system, rather than isolated pathogenic factors, are considered the root cause of illness. From the TCM perspective, the pathogenesis of tumors is associated with health deficiencies, with the presence of pathogenic factors serving as indicators. The characteristic feature of its pathogenesis is a "mixture of deficiency and excess".

In TCM, GC is the result of a disturbance in the balance between yin and yang and an obstruction or depletion of *qi* within the body.

In TCM, chemically characterized phytocomplexes and mixtures of these extracts are used within a system based on TCM syndrome differentiation. Plants are administered according to a millenary experience-based system for which it is necessary to combine tumour staging, antitumour treatment methods, and clinical manifestations to identify deficiencies in *qi*, blood, yin, and yang in the patient and alterations in organ function[27-29].

The current approach of TCM in the treatment of GC involves the administration of herbal formulations, phytocomplexes and dietary styles in addition to pharmacological treatments. This approach may enhance the efficacy or reduce the toxicity of medicines.

The role of NP in GC treatment

NP is an interdisciplinary approach that combines pharmacology with complex biological networks to study the interactions between drugs and molecular targets. This method allows for understanding how TCM drugs influence various molecular targets and biological pathways simultaneously rather than focusing on a single target. NP is particularly useful for studying the multitarget mechanisms of TCM formulas, which often contain many active ingredients that act on multiple cellular pathways. For example, the active components in formulas such as Banxia Xiexin Decoction (BXD) and Sijunzi Decoction (SJZD) influence targets such as TP53, MAPK1, VEGFA, and AKT1 by modulating pathways such as the PI3K/AKT and HIF-1α pathways to exert antitumour and anti-inflammatory effects. Using NP tools, researchers can map the interactions between TCM components and molecular targets related to GC, offering new opportunities for drug discovery and optimization of existing treatments. This integrative approach is promising for addressing the complexity and heterogeneity of GC, thereby improving the effectiveness and precision of therapies.

In this context, the possibility of employing advanced techniques in the fields of analytical and food chemistry allows the precise chemical characterization of food and vegetal matrices, including phytocomplexes. Moreover, the advent of NP has provided a modern platform for analysing the intricate interactions among TCM ingredients, disease targets, and biochemical pathways. NP employs high-throughput screening, computer simulations, and network database retrieval to visualize the effects and influences of drugs and natural compounds on the biological network, predict therapeutic targets, and clarify the mechanisms of action of TCM compounds. This contemporary approach aligns with TCM's multicomponent, multitarget methodology and offers a modern lens through which to understand and eventually validate traditional practices. TCM ingredients interact with various molecular pathway sand can influence gene expression, protein synthesis, and cellular signalling mechanisms involved in the progression of the disease. This interaction is crucial for understanding how TCM formulations may exert beneficial effects, eventually contributing to reducing tumour growth, improving immune responses and inducing the apoptosis of cancerous cells.

TCM FORMULATIONS IN GC TREATMENT

BXD

BXD includes *Pinellia ternate* (Thunb.) Makino, *Coptischinensis* Franch, and *Scutellaria baicalensis* Georgi. Recent clinical research on BXD has provided insightful data regarding its efficacy intreating GC[30]. The BXD dosage involves the preparation of a decoction with approximately 600 mL of water, which is then reduced by boiling to approximately 200 mL. This decoction is administered in two doses of 100 mL each, taken twice daily. The duration of treatment can vary, but it generally spans several weeks to months, with some clinical studies indicating treatments lasting up to six months. This regimen aims to maximize the therapeutic effects of anticancer drugs while decreasing some of their side effects. One study showed that BXD inhibits GC cell proliferation, invasion, and metastasis. This effect was attributed to the inhibition of the Wnt/β-catenin signaling pathway. This study revealed that with increasing BXD concentration, the clonogenic ability of GC cells was notably inhibited. Furthermore, BXD selectively promoted oxidative stress in cancer cells, impacting key oxidative stress indicators such as MDA, SOD, and GSH-PX and leading to apoptosis[31]. A study revealed the ability of BXD to inhibit the expression of PD-L1 in GC through multitarget and multi-pathway regulation of major oncogenes. This study revealed that BXD can target key molecules in the PD-L1 regulatory network, leading to the inhibition of PD-L1, HIF-1, EGFR, and TLR4 expression in GC cells. These effects resulted in reduced GC cell proliferation and increased apoptosis both *in vitro* and *in vivo*. These findings underscore the potential of BXD in GC prevention through its complex multitarget approach. Several BXD components collectively affect different targets, such as HIF-1, EGFR, IFNGR, and TLR4, in the PD-L1 regulatory network[32]. This multidirectional mechanism may offer a mixture that may be further studied in the field of GC prevention. In addition, recent research has demonstrated that BXD significantly reduces the expression of the long noncoding RNA TUC338 in GC cells. TUC338 is overexpressed in GC tissues, and its downregulation by BXD contributes to the suppression of cancer cell proliferation and metastasis. Moreover, BXD inhibits epithelial-to-mesenchymal transition (EMT) by increasing E-cadherin levels and decreasing N-cadherin and vimentin levels, effectively reversing EMT. These mechanisms collectively inhibit the migration and invasion of GC cells, highlighting the potential of BXD as a nutraceutical integrative approach for GC[33] (Table 1).

SJZD

SJZD is a polyherbal formulation consisting of *Panax ginseng* C.A. Meyer, *Atractylodes macrocephala* Koidz (Am-EE). (Atractylodes macrocephala Rhizoma), *Poriacocos* (Schw.) Wolf, and *Glycyrrhiza uralensis* Fisch. ex-DC. (Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle). SJZD has been clinically studied in GC patients. A meta-analysis[34] evaluated its efficacy and safety when combined with enteral nutrition (EN) in patients with GC. The study included 10 randomized controlled trials encompassing 688 patients. SJZD was administered either through a nasogastric or mesenteric tube in doses of 100 mL once a day, with one patient receiving 200 mL twice a day, starting within 24-48 hours of admission and

Table 1 Molecular mechanisms and clinical effects of traditional Chinese medicine formulas and plant components

TCM formulas	Plant components	Clinical studies outcome	*In vitro* studies outcome	Key molecular targets	Molecular mechanisms
Banxia Xiexin Decoction	Pinellia ternata, coptis chinensis, scutellaria baicalensis	-	Inhibits proliferation, invasion, metastasis of GC cells	Wnt/β-catenin, PD-L1, HIF-1, EGFR, TLR4	Inhibits Wnt/β-catenin pathway, induces oxidative stress, modulates apoptosis
Sijunzi Decoction	Panax ginseng, Atractylodes macro cephala, Poria cocos, Glycyrrhiza uralensis	Enhances immune function, improves nutritional status in GC patients	Affects cell lines like MKN-28 and HGC-27	TNF-α, IL-6, TP53, JUN, VEGFA, PI3K/AKT	Regulates PI3K/AKT pathway, induces apoptosis, reduces tumor growth
Xiang-Sha-Liu-Jun-Zi-Tang	Panax ginseng, Poria cocos, Atractylodes macro cephala, Pinellia ternata, Citrus reticulata, Aucklandia lappa, Villous Amomum, Glycyrrhiza uralensis	Enhances survival post-surgery and chemotherapy for GC	Phytochemical study identified 144 active ingredients	TP53, MMP9, TIMP1, MYC, TNF, IL-17 signaling	Targets TNF and IL-17 signaling pathways, induces apoptosis, inhibits proliferation
Jianpi Yangzheng Xiaozheng Decoction	Astragalus membranaceus, Codonopsis pilosula, Atractylodes macro cephala, Angelica sinensis, Paeonia lactiflora, Sparganium stoloniferum, Curcuma zedoaria, Citrus reticulata, Aucklandia lappa, Hedyotis diffusa, Salvia chinensis, Glycyrrhiza uralensis	Used in patients with advanced GC	Inhibits cancer cell proliferation	PD-L1, IL-6/JAK2/STAT3	Modulates immune response, decreases expansion of myeloid-derived suppressor cells
Shenqi Fuzheng Formula	Radix codonopsis, radix astragali	Improves quality of life and immune function in combination with chemotherapy	-	Not specified in detail	Enhances immune function, reduces chemotherapy side effects, improves patient outcomes

GC: Gastric cancer; TCM: Traditional Chinese medicine.

continuing for a duration of 6-9 days. The results revealed significant improvements in the SJZD/EN group compared with the EN group, including a shorter time to flatus, a shorter length of hospital stay, and a lower incidence of postoperative complications. Additionally, the SJZD/EN group presented higher albumin, prealbumin, transferrin, immunoglobulins, CD3+, CD4+, andCD4+/CD8+ levels than the EN group, indicating enhanced immune function and improved nutritional status. The study concluded that SJZD combined with EN offer significant clinical advantages in strengthening immune function, reducing postoperative complications, and improving body nutrition status in GC patients compared with standard EN. Using NP, 117 compounds were identified in SJZD, with 161 and 3288 potential targets in SJZD and GC, respectively, among which 123 targets overlapped. The key bioactive molecules included quercetin, kaempferol, formononetin, ginsenoside, and atractylenolide III, which target factors such as TNF-α, IL-6, TP53, JUN, and VEGFA. This study revealed that SJZD inhibits tumour growth and induces tumour cell apoptosis by regulating the PI3K/AKT pathway; downregulating the expression of VEGFA, iNOS, COX-2, and Bax/Bcl2; and inhibiting p-PI3K and p-AKT expression. *In vivo* mouse experiments revealed that SJZD treatment for 21 days led to smaller and lighter tumours compared with the control group, indicating significant inhibition of tumour growth[35,36]. Another study demonstrated that SJZD inhibited SGC-7901 cell proliferation in a time- and concentration-dependent manner, inducing an increase in the G1/G0 phase population and a decrease in the G2/M and S phase populations. Importantly, SJZD induced apoptosis through upregulation of the proapoptotic protein Bax and downregulation of the anti-apoptotic protein Bcl-2, highlighting a mechanism involving both cell cycle arrest and apoptosis[37]. The effects of SJZD-treated rat serum on the proliferation of MKN-28 and HGC-27 gastric carcinoma cell lines were also investigated. The ability of SJZD to induce GC cell apoptosis was also observed *in vivo* due to a plethora of mechanisms involving the upregulation of Bax, caspase-3, and PARP and the downregulation of Bcl-2. Recent studies have also highlighted the role of exosomal miRNAs in mediating the anticancer effects of SJZD. SJZD downregulates miR-151a-3pin plasma and saliva exosomes, which are enriched in extrinsic apoptotic signalling pathways. This modulation may serve as a non-invasive marker for GC diagnosis and prognosis. Additionally, SJZD increases miR-184 expression in saliva but decreases its expression in plasma, influencing epithelial cell migration and apoptosis. SJZD also regulates key signaling pathways, including the PI3K/Akt, MAPK, HIF-1, and FoxO pathways, contributing to its multi-target therapeutic potential[38]. This study highlighted the nutraceutical potential of SJZD in gastric carcinoma through the induction of apoptosis and cell cycle arrest in addition to its effects on the immune system[39].

Xiang-Sha-Liu-Jun-Zi-Tang

Xiang-Sha-Liu-Jun-Zi-Tang (XSLJZT), derived from Si-Jun-Zi-Tang, contain seight botanicals, including *Panax ginseng* C.A. Meyer (or *Codonopsis pilosula*Franch. in modern practice), *Poria cocos* (Schw.) Wolf, *Atractylodesmacrocephala* Koidz., *Pinellia ternate* (Thunb.) Makino, *Citrusreticulata* Blanco peel, *Aucklandia lappa* Dence Radix, *VillousAmomum* Lour. Fruit, and *Glycyrrhiza uralensis* Fisch. ex-DC.

A comprehensive study[40] investigated the effects of herbal medicine on patients with GC in Taiwan. The results revealed that the administration of XSLJZT, provided at a daily dose of 4.4 g with an average duration of administration of 13.0 days, significantly improved survival among GC patients. XSLJZT has also been previously reported in Japanese clinical studies to alleviate symptoms related to cancer, particularly after gastrectomy and in cases of cancer cachexia. The effectiveness of this formula may be attributed to its ability to stimulate ghrelin secretion by blocking the serotonin 2b/2c receptor pathway and enhancing ghrelin receptor activity. These mechanisms suggest a potential role in alleviating cancer-related symptoms and improving patient well-being. A recent study provided an in-depth understanding of the mechanisms through which XSLJZT affects GC treatment[41]. A phytochemical investigation revealed 144 active ingredients among the XSLJZT components, which were then subjected to comprehensive NP, revealing 123 potential targets. By mapping the interactions between the active ingredients of XSLJZT and GC-related targets, NP enables the elucidation of complex mechanisms underlying the efficacy of the formula. Furthermore, this study employed molecular docking techniques, revealing that the main active ingredients of XSLJZT, including quercetin, stigmasterol, and naringenin, exhibit strong binding affinities to key GC targets. Quercetin had the lowest total binding energy and significant activity against TP53, MMP9, TIMP1, and MYC, which are integral to GC pathogenesis. Therefore, quercetin may play a crucial role in the efficacy of the formula, targeting essential pathways such as the TNFα and IL-17 signalling pathways. In addition, quercetin was found to directly reduce the expression of the genes *TP53*, *MMP9*, and *TIMP1* and *MYC*, *CCL2*, *CXCL2*, *LIF*, *MMP3*, and *JUNB*, thereby modulating the disease process. The study concluded that XSLJZT, through its component quercetin, acts as a multicomponent, multitarget, and multi pathway agent in GC cells[41]. NP reveals how XSLJZT components, such as quercetin, interact with a broad range of molecular targets, facilitating a multifaceted therapeutic approach. This method not only validates the traditional uses of XSLJZT but also provides a scientific basis for its efficacy in modern medical practice. The mechanisms of action of this formula involve the inhibition of cancer cell proliferation, the induction of apoptosis, and the modulation of key molecular pathways involved in GC pathogenesis, including the TNF and IL-17 signaling pathways[42], suggesting its potential in GC prevention.

Jianpi Yangzheng Xiaozheng decoction

The Jianpi Yangzheng Xiaozheng (JPYZXZ) decoction is an empirical formula based on TCM theory. With the functions of "*tonifying qi*, invigorating the spleen, and eliminating stasis," JPYZXZ is used in GC patients with syndromes such as spleen–kidney yang deficiency and blood stasis obstruction[43]. It is composed of *Astragalus membranaceus* Bunge (Astragalus Root), *Codonopsis pilosula* Franch., Am-EE, *Angelicasinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall. (white peony root), *Sparganium stoloniferum* (Buch. -Ham. ex Graebn.) Buch. -Ham. ex Juz., *Curcumazedoaria* (Christm.) Roscoe, *Citrus reticulata* Blanco (TangerinePeel), *Aucklandia lappa* Dence (Costustoot), *Hedyotis diffusa* Willd., *Salvia chinensis* Benth., and *Glycyrrhiza uralensis* Fisch. ex-DC. (raw liquorice). These herbs are combined in a specific formulation, with the largest quantity being astragalus root, to potentially enhance the effects in patients with advanced GC, with a focus on improving fatigue and survival outcomes. In one study, patients consumed JPYZXZ decoction in the form of granules at a precise dosage of 150 mL twice a day for at least 6 months. Each dose is prepared by dissolving one packet of granules in 150 mL of boiling water, which is administered once in the morning and once in the evening. Clinically, the decoction has shown benefits such as reducing chemotherapy-associated side effects such as leucopenia, thrombocytopenia, and gastrointestinal reactions and improving the overall quality of life in patients[44]. *In vitro* and *in vivo* studies revealed that JPYZXZ inhibited the proliferation of cancer cells through mechanisms involving the modulation of the IL-6/JAK2/STAT3 pathway and PD-L1 expression, which play crucial roles in cancer progression and the immune response. JPYZXZ decreases the expression of GC-derived exosomal PD-L1, impacting the tumour microenvironment and influencing tumour-infiltrating immune cells, particularly myeloid-derived suppressor cells (MDSCs). By inhibiting the delivery of exosomal PD-L1 from GC cells to bone marrow cells, JPYZXZ decreases the expansion of MDSCs, thereby reducing the levels of various immunosuppressive factors and reshaping the immunosuppressive TME. This research highlights the potential of JPYZXZ in controlling MDSC differentiation in GC and suggests a novel integrative approach involving the targeting of PD-L1[45]. Another study compared JPYZXZ with its components Jianpi Yangzheng decoction (JPYZ) and Xiao Zheng San Jie decoction and reported that JPYZXZ was more effective than either component alone in inhibiting the progression of GC both *in vitro* and *in vivo*. The decoction significantly reduced tumour weight and was particularly effective at inhibiting the EMT in GC. However, JPYZ was more effective at inducing phenotypic changes in macrophages from M2 to M1, highlighting the complexity of the mechanisms involved in the anticancer effects of JPYZXZ[43]. Furthermore, a metabolomic study focused on the role of JPYZXZ in GC treatment alongside chemotherapy. The study involved patients with GC undergoing chemotherapy with or without JPYZXZ. The results showed that combining JPYZXZ with chemotherapy led to a lower risk of common chemotherapy-associated side effects, such as leucopenia, thrombocytopenia, and gastrointestinal reactions. Moreover, patients in the treatment group had a greater quality of life. This study revealed significant differentially abundant metabolites in GC patients post chemotherapy that are involved in various metabolic pathways. JPYZXZ influences these pathways, suggesting its role in reducing adverse drug reactions and improving quality of life by correcting specific metabolic deficiencies and inhibiting gluconolactone metabolism, representing a potential antitumour mechanism[46]. In an animal study, JPYZXZ demonstrated significant tumour inhibition in a subcutaneously transplanted GC model. The mechanism involves the activation of apoptosis and autophagy-related factors. Specifically, JPYZXZ upregulated Bax and Fas while downregulating Bcl-2, CyclinD1, D2, and D3, as evidenced by reverse-transcription PCR results. Western blot analysis further revealed increased expression of cleaved-PARP, Beclin-1, and LC3B II, with concurrent downregulation of procaspase-3, procaspase-8, and procaspase-9. These findings indicate that JPYZXZ exerts its antitumour effects through the induction of apoptosis and autophagy, contributing to its overall efficacy in GC treatment[47].

Shenqi Fuzheng formula

Shenqi Fuzheng (SF) is a polyherbal formulation consisting of Radix Codonopsis (*Codonopsispilosula* Franch.) and Radix Astragali (*Astragalus membranaceus* Bunge). This polyherbal formulation is traditionally known for its ability to strengthen the body and nourish *qi* and *blood*. It is commonly used in the context of GC with the syndrome of dual deficiency of *qi* and *blood*[48]. SF injection (SFI), when used in conjunction with chemotherapy for the treatment of GC, has demonstrated several notable improvements in patient outcomes, as evidenced by a comprehensive evaluation through 11 systematic reviews and meta-analyses. The dosage of SFI generally used was 250 mL per day administered *via* intravenous infusion, with treatment courses varying from 10 to 21 days per cycle, depending on the specific chemotherapy regimen. Common chemotherapy regimens include combinations such as gemcitabine + cisplatin, vinorelbine + cisplatin, and paclitaxel/albumin paclitaxel + cisplatin, among others[49]. First, combination therapy has been shown to increase the overall response rate and disease control rate, crucial indicators of treatment effectiveness in managing the disease. In addition, patients receiving SFI with chemotherapy have reported improved quality of life, underscoring the treatment's impact beyond disease control to encompass overall well-being. Furthermore, the therapy increased CD4+/CD8+ levels, suggesting an increase in immune function. Additionally, one of the significant benefits of this combined therapy is the reduction in the occurrence of gastrointestinal reactions and neurotoxicity, which are common side effects of cancer chemotherapy, increasing patient comfort and compliance during treatment[50]. SF, when combined with chemotherapy, yielded positive results in terms of quality-of-life improvements, as well as incomplete and partial remission efficacy rates. Additionally, it was effective in reducing adverse events such as nausea, vomiting, oral mucositis, leucopenia, and myelosuppression. Importantly, SF also aids in maintaining body weight, which is important for patients undergoing cancer treatment. A systematic review and meta-analysis presented a comprehensive analysis of the efficacy of SFI combined with chemotherapy in treating advanced GC. The meta-analysis included 15 trials and revealed that, compared with chemotherapy, the combined treatment of SFI and chemotherapy significantly improved the objective response rate in patients. Additionally, combination therapy also significantly increased the Karnowski performance status (KPS) scores, indicating an improvement in the patient's quality of life (OR = 3.74, 95%CI: 2.66-5.27, $P < 0.05$). The study concluded that SFI, when used alongside chemotherapy, may enhance clinical efficacy and improve performance status in patients with advanced GC[51,52].

HERBAL COMPOUNDS AND THEIR MECHANISMS IN GC TREATMENT

Some Chinese herbal medicines are used in multiple formulas. Among them, 12 formulas contained *Glycyrrhiza uralensis* Fisch, whereas 11 formulas contained Am-EE. Other Chinese herbal medicines with high repetition rates include *Panax ginseng* C.A. Mey., *Poria cocos* F.A. Wolf, and *Zingiber officinale* Roscoe, all of which are included in 7 formulas. Next, we update the current knowledge on the pharmacological relationship between these frequently used Chinese herbal medicines and their components in the treatment of GC (Table 2).

Glycyrrhiza uralensis Fisch

In TCM, *Glycyrrhiza uralensis* Fisch is believed to have a neutral nature and a sweet taste. It is traditionally known to have several effects, such as pain relief, antispasmodic, and even anticancer properties. A *Glycyrrhiza uralensis* Fisch. extract induces apoptosis in the human GC cell line MGC-803[53] through several mechanisms involving increased plasma membrane permeability, increased levels of intracellular free calcium ions, decreased mitochondrial transmembrane potential, and cyclosporin a inhibition[54]. In a clinical trial, the administration of 150 mL of a modified decoction containing *Glycyrrhiza uralensis* daily for three months, when combined with chemotherapy, significantly improved clinical symptoms, enhanced quality of life and reduced gastrointestinal complications in patients with GC[55]. Moreover, glycyrol, a compound derived from *Glycyrrhiza uralensis*, effectively triggers apoptosis in human Jurkat cells *via* the *Fas-FasL*/caspase-8 pathway, independent of p53, highlighting its potential for broad application in targeting cancer cell apoptosis pathways. This p53-independent pathway suggests that this *Glycyrrhiza*-derived compound may be further studied as an inducer of apoptosis in GC, as confirmed by techniques including laser scanning confocal microscopy, agarose gel electrophoresis, and flow cytometry, which collectively demonstrate the apoptotic "ladder" pattern and time- and dose-dependent chromatin condensation in treated cells[56] (Figure 1).

Am-EE

Am-EE has a sweet and bitter taste and a warm nature. It enters the spleen and stomach meridians. It strengthens the spleen, harmonizes the middle burner, dries dampness, and promotes diuresis. It is mainly used to treat symptoms such as deficiency of the spleen and stomach *qi*, abdominal pain and discomfort after eating, and pregnancy oedema. An ethanolic extract of Am-EE, which contains atractylenolide-1 and -2, demonstrated significant anti-inflammatory effects in gastritis models, suggesting its potential in GC chemoprevention. Am-EE effectively reduces key inflammatory markers and modulates the Akt/IκBα/NF-κB pathway, highlighting its role in mitigating gastritis-related pathways that can lead to GC[57]. Several compounds extracted from this plant have been extensively researched for their potential anticancer effects against GC. Among these compounds, atractylenolide I, which is isolated from the rhizome of *Atractylodes macrocephala*, has dose- and time-dependent inhibitory effects on the viability of three human GC cell lines, including HGC-27, MGC-803, and MKN-45. In MGC-803 GC cells, atractylenolide I induce apoptosis and inhibits the *Notch* signaling pathway, affecting the activity of key proteins such as Notch1, Hes1, Hey1, and Jagged1[47]. A clinical trial demonstrated the ability of this compound to reduce appetite loss, improve KPS, and inhibit proteolysis-inducing factor proteolysis in patients with GC cachexia[58]. Another clinical trial explored the efficacy of a formulation containing

Table 2 Molecular mechanisms and clinical effects of compounds isolated from Chinese plants

Plant name	Active molecules	Clinical data	*In vitro* studies	Molecular targets	Biological effects
Glycyrrhiza uralensis	Glycyrol	Not specified	Induces apoptosis in MGC-803 and Jurkat cell lines	Fas-FasL/caspase-8 pathway, p53 independent	Enhances plasma membrane permeability, increases intracellular calcium, reduces mitochondrial potential
Atractylodes macrocephala	Atractylenolide I, II, III	Reduces appetite loss, improves Karnofsky performance	Affects viability of HGC-27, MGC-803, MKN-45 cells	Notch signaling, Ras/ERK, PI3K/Akt pathways	Induces apoptosis, inhibits inflammation, modulates immune responses
Panax ginseng	Ginsenosides (Rg3, others)	Enhances immune function, improves survival rates	Inhibits cell proliferation and enhances apoptosis	PI3K/AKT/mTOR, Fas-FasL pathways	Modulates chemoresistance, enhances immune function, reduces inflammation
Zingiber officinale	6-gingerol, 6-shogaol	Reduces GC risk, enhances antioxidant activity	Affects apoptosis in GC cell lines	Various cellular pathways (including Fas-FasL)	Induces apoptosis, inhibits inflammation, reduces oxidative stress, improves mitochondrial function
Scutellaria baicalensis	Baicalin, scutellarein	Not specified	Induces apoptosis in AGS cells	PIK3CB, CIP2A, ESR1, fos	Modulates cellular apoptosis pathways, downregulates critical proteins for cancer cell survival
Citrus reticulata	Polymethoxyflavones	Associated with reduced risk of GC	Induces apoptosis in human GC cells SNU-668	Bcl-2, Bax, CASP-3, RARβ, caspase pathways	Regulates apoptosis-related genes

GC: Gastric cancer.

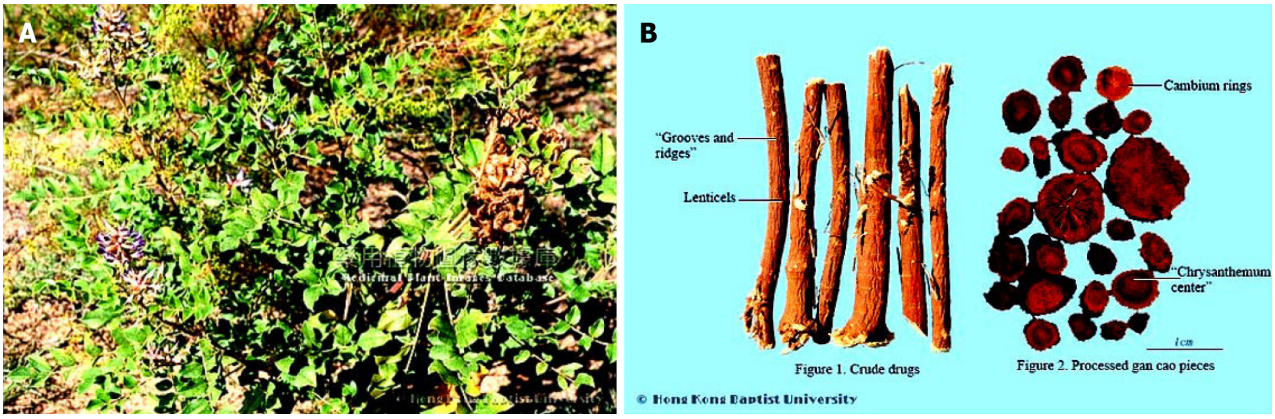

Figure 1 *Glycyrrhiza uralensis* Fisch. A: Living plants; B: Image of the dried root from which the raw drug is obtained.

Atractylodes macrocephala in preventing chemotherapy-induced mucositis, highlighting its supportive role in GC treatment [59]. A similar compound, atractylenolide II, induced apoptosis in HGC-27 and AGS cancer cells, affecting molecular pathways, specifically the Ras/ERK and PI3K/Akt pathways, by reducing the levels of p-ERK and p-Akt[60]. Another related compound, atractylenolide III, inhibits gastric precancerous lesions (GPLs)[61]. Indeed, the administration of atractylenolide III to rats with GPLs improved their overall condition, including increased energy levels, improved mobility, better appetite, and a reduction in diarrhoea. Additionally, AT-III partially preserved the body weight of these rats, countering the weight loss typically associated with GPLs. Histopathological examination of the gastric mucosa revealed that AT-III treatment effectively inhibited or even reversed dysplasia in the mucosa, preventing the progression of precancerous lesions. This activity was evidenced by a significant reduction in the incidence of GPLs in the AT-III-treated groups compared with the model group. Furthermore, AT-III demonstrated its ability to address microvascular abnormalities in the gastric mucosa of GPL rats. This led to a reduction in micro vessel dilation, basal lamina thickening, and vascular lumen occlusion in the model rats. Among the treatment groups, the high-dose AT-III group presented the most substantial improvement in micro vessel morphology. AT-III treatment also significantly reduced the density of CD34+ micro vessels, indicating its capacity to curtail new blood vessel formation in GPLs in rats. This effect was associated with a decrease in the protein expression of VEGF-A and HIF-1α, both of which are integral in angiogenesis. Additionally, AT-III downregulated DLL4, a protein closely associated with angiogenesis. This downregulation occurred in both rats with GPLs and human GC cell lines. The reduction in DLL4 suggested a mechanism for the observed antiangiogenic effects of AT-III (Figure 2).

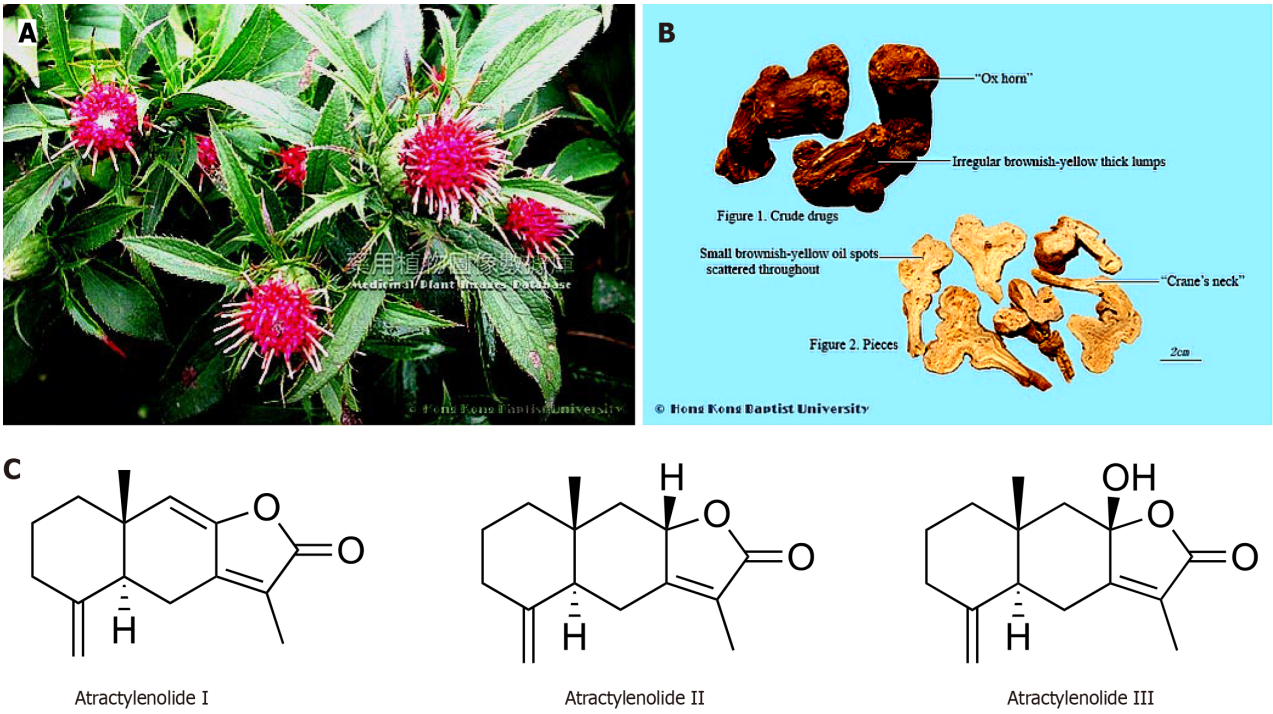

Figure 2 *Atractylodes macrocephala* Koidz. A: Whole plants; B: Image of the root from which the crude drug is obtained; C: Main phytochemicals.

Panax ginseng C.A. Meyer

In TCM, *Panax ginseng* C.A. Meyer is believed to tonify primordial *qi*, consolidate the pulse to relieve desertion, invigorate the spleen to benefit the lungs, promote fluid production to relieve thirst, and calm the mind to enhance intelligence. It is regarded as the "king of tonics" and is commonly used in formulas that strengthen body resistance. Studies suggest that the effects of ginseng in patients affected by GC vary by type and dosage. A clinical study investigated the effects of red ginseng on postoperative patients with stage III GC. The patients consumed 4.5 g per day of red ginseng powder (Korea Ginseng Corporation, Seoul, Korea) in capsule form, which was administered orally for the first six months after surgery. Red ginseng is associated with significant immunomodulatory effects and improved survival rates. Red ginseng powder helps restore CD4 T lymphocyte levels and inhibits CD3 depression during postoperative chemotherapy, suggesting a role in enhancing immune function weakened by cancer treatment[62]. American ginseng (*Panax quinquefolius*) at 2000 mg daily has been shown to significantly improve fatigue and overall well-being over 8 weeks[63]. In contrast, Asian ginseng (*Panax ginseng*) at 800 mg daily for 29 days did not significantly improve fatigue in GC patients, with no notable benefits for lower doses in short-term trials[64]. Another study reported an inverse association between ginseng consumption and the risk of GC[65]. According to these data, a more recent meta-analysis[66] revealed that ginseng consumption is associated with a significant reduction in the risk of developing various types of cancer, including GC. Specifically, a 16% overall lower risk of cancer was detected in individuals who consumed ginseng, suggesting a potential protective effect against this specific cancer type. The clinical effects of *Panax ginseng* may be due to its ability to modulate key biochemical and cellular processes involved in tumour development and progression, particularly in GC. This includes its significant impact on reducing the production and effects of hydrogen sulphide (H_2S) in vascular endothelial cells. By decreasing the expression of enzymes responsible for H_2S synthesis, such as cystathionine β-synthase and cystathionine γ-lyase, Korean red ginseng extract (KRGE) attenuates both the proinflammatory and proangiogenic impacts of H_2S, which are crucial for cancer growth. Furthermore, the extract reduces the levels of inflammatory mediators, such as COX-2 and iNOS, and angiogenic factors, such as IL-8, HIF-1α, VEGF, IL-6, and MMPs, thereby potentially inhibiting tumour growth and metastasis. KRGE also impacts cell signaling pathways, notably inactivating H_2S-activated signals such as p38 and Akt, leading to a decrease in angiogenic factor expression and the proliferation of endothelial cells[67]. Another extract from ginseng roots obtained through an enzymatic fortification process using laminarinase and pectinase has demonstrated notable anticancer properties against GC cells[68]. This extract, known as the enzymatically fortified ginseng extract (FGX), is derived from *Panax ginseng* root butanolic extract (GBX) and is characterized by an increased content of specific ginsenosides such as Rh1, Rg3 (R), Compound K, and Rh2, which are known for their antitumoral activities. FGX has shown strong antiproliferative and proapoptotic effects on KATO3 human GC cells. Compared with GBX, GBX inhibits cell proliferation in a concentration-dependent manner and induces apoptosis more effectively. The anticancer effects of FGX are attributed to its influence on several molecular mechanisms, including the increased expression of the proapoptotic protein Bax, the dephosphorylation and hence inactivation of key signaling proteins such as mTOR and PKB, and the reduction in IκBα levels, suggesting NF-κB activation, leading to apoptotic pathways in cancer cells.

Ginsenosides, key phytochemicals in *Panax ginseng*, constitute a diverse group of steroidal saponins known for their spectrum of biological activities. Chemically, they are classified into various types, with 35 distinct ginsenosides identified to date. These include 22 protopanaxadiol (PDD)-type compounds, 12 protopanaxatriol-type compounds, and a

unique oleanane-type ginsenoside Ro. During ginseng processing, for example, in the transformation of white to red ginseng, specific ginsenosides such as 20 (S)-ginsenoside Rg3, Rh2, Rs1, Rs2, Rs3, Rs4, Rg5, notoginsenoside-R4, 20 (R)-ginsenoside Rg2, 20 (R)-ginsenoside-Rh1, ginsenoside Rh4, and F4 are formed, with malonyl ginsenosides Rb1, Rb2, Rc, and Rd being unique to white ginseng.

Ginsenoside Rg3, which is isolated from *Panax ginseng*, has shown promise in modulating chemoresistance in GC cells. A study by Wang *et al*[69] demonstrated its role in overcoming cisplatin resistance, a common hurdle in treating advanced GC. This compound enhances the chemosensitivity of AGS resistant to cisplatin, mainly through the upregulation of miR-429, the targeting of SOX2 and the modulation of the PI3K/AKT/mTOR signaling pathway[69,70]. Moreover, it inhibits angiogenesis in GPLs. It attenuated gastric intestinal metaplasia and dysplasia in rats with MNNG-ammonia compound-induced GPLs and reduced VEGF protein expression and CD34+ micro vessel density, potentially involving the downregulation of GLUT1 and GLUT4[71]. In addition, this compound significantly decreased the proliferation rates and invasion capabilities of the SGC-7901 GC cell line, suggesting its potential to inhibit metastasis. Rg3 treatment resulted in cell cycle arrest, altered the cell distribution in the G1 and G2 phases, and modulated key signaling proteins, notably increasing the levels of the tumour suppressors PTEN and P53 and decreasing the levels of the p-PI3K and AKT proteins[72]. Rg3 also notably inhibited HIF-1α and VEGF expression under hypoxic conditions in BGC823 GC cells, suggesting the downregulation of VEGF by inhibiting HIF-1α and thus affecting tumour angiogenesis and growth [73]. Another study highlighted its impact on *TRPM7* channels, indicating its role in inducing apoptosis in gastric and breast cancer cells[74]. The stereochemistry of ginsenoside Rg3 is significant, with the 20 (S)-Rg3 epimer showing greater anticancer activity than 20 (R)-Rg3. This difference is reflected in their interaction with ion channels, which are crucial for the regulation of Na^+ channels[75]. Furthermore, Rg3 inhibits fucosyltransferase IV in *H. pylori CagA*-treated GC cells, affecting the transcription factors *SP1* and *HSF1* and inducing apoptosis by modulating these effects[76]. In addition, 20 (S)-PDD from *Panax ginseng* also has diverse molecular mechanisms against cancer. PDD hampers HGC-27 cell proliferation and induces autophagy without significant apoptosis, disrupting lysosomal and mitochondrial function[77,78].

F2 is another ginsenoside that has potential in GC treatment. A study highlighted the role of F2 in inducing apoptosis in GC cells through ROS accumulation and ASK-1/JNK pathway activation. Another study revealed the ability of F2 to inhibit SGC7901 cells through autophagy-related pathways[79,80]. Similarly, ginsenoside Rb1 was effective against GPLs in rats, reversing intestinal metaplasia and dysplasia and influencing the β-catenin/TCF4 interaction[81].

Rh1 and CK also showed efficacy against GC. Rh1 inhibited cell proliferation, migration, and invasion in xenograft models *via* the TGF-β/Smad pathway[82]. Ginsenoside CK, unlike Rb1, suppressed HGC-27 cell proliferation and induced apoptosis, impacting cell cycle proteins and the PI3K/AKT/NF-κB pathway[83].

Polysaccharides derived from *Panax ginseng* roots, notably PGPW1 and PGP2α, as well as red ginseng polysaccharide, exhibit anti tumour effects. These polysaccharides have distinct chemical compositions. PGPW1, with a molecular weight of approximately 3.5×10^5 Da, comprises glucose, galactose, mannose, and arabinose. In contrast, PGP2α, an acidic protein-polysaccharide, has a lower molecular weight of approximately 3.2×10^4 Da and includes galactose, arabinose, glucose, and galacturonic acid at specific molar ratios. The anti tumour mechanisms of these polysaccharides are multifaceted. PGPW1 impedes tumor cell migration in HGC-27 human GC cells by impairing cell motility and modulating the expression of proteins associated with tumor metastasis. Specifically, PGPW1 suppresses Twist and AKR1C2 proteins while increasing NF1 protein levels, consequently hindering EMT, a pivotal process in tumour invasion and metastasis[84]. Conversely, PGP2α potently inhibited HGC-27 cell proliferation and viability, with pronounced effects at higher concentrations (up to 400 μg/mL) after 48 hours of treatment. This polysaccharide induced apoptosis in HGC-27 cells, as indicated by characteristic apoptotic morphological changes and a dose-dependent increase in the number of apoptotic cells. Additionally, PGP2α induced G2/M phase cell cycle arrest, suggesting its role in impeding cell cycle progression. At the molecular level, PGP2α influences the expression of Bcl-2 family proteins, augmenting the proapoptotic protein Bax while reducing the antiapoptotic proteins Bcl-2 and Bcl-xl and thus promoting apoptosis. The activation of caspases, notably caspase-3, caspase-9, and PARP, further corroborated the involvement of the mitochondria-mediated intrinsic apoptotic pathway. Furthermore, extrinsic death receptor-mediated pathways were implicated through increased *Fas/Fas* ligand expression and reduced levels of pro-caspase 8 and bid in PGP2a-treated cells[51].

Red ginseng polysaccharide inhibited AGS cell proliferation and viability. This polysaccharide induced apoptosis and promoted ferroptosis by inhibiting the PI3K/Akt pathway and downregulating Aquaporin 3, a protein involved in cancer progression. Ferroptosis induction is characterized by elevated ROS levels, increased Fe^{2+} levels, and altered expression of key ferroptosis regulators, underscoring its potential as a therapeutic approach in cancer treatment[85] (Figure 3).

Poria cocos F.A. Wolf

In TCM, *Poria cocos* F.A. Wolf is a mushroom that has a sweet and bland taste, a neutral nature, and the ability to promote diuresis and leach out dampness, strengthening the spleen. In TCM, *Poria cocos* is considered a tonifier of the *spleen* that benefits *qi* in patients with chronic illness who are thin and weak, have a low appetite, or experience fatigue and diarrhoea. An ethanolic extract of *Poria cocos*, which is rich in triterpenoids, impacts crucial signaling pathways, such as the MAPK and PI3K-Akt pathways, which are vital for cell proliferation and survival, resulting in substantial antiproliferative effects on MKN45 GC cells both *in vitro* and *in vivo*[86]. Collectively, these findings underscore the potential of *Poria cocos* as a nutraceutical source in GC prevention. Triterpenoids are potentially involved in the anticancer effects of *Poria cocos* against GC cells.

Pachymyc acid (PA) inhibits the growth of the GC cell lines SGC-7901 and MKN-49P and induces cell cycle arrest in the G1 and G2/M phases while suppressing the G0 phase. PA also triggers apoptosis through a mitochondrial pathway, as indicated by changes in mitochondrial morphology and the activation of apoptosis-related proteins such as caspase-3, PARP, Bcl-2, and Bax[87]. Additionally, the effects of PA are also induced by the modulation of the JAK2/STAT3

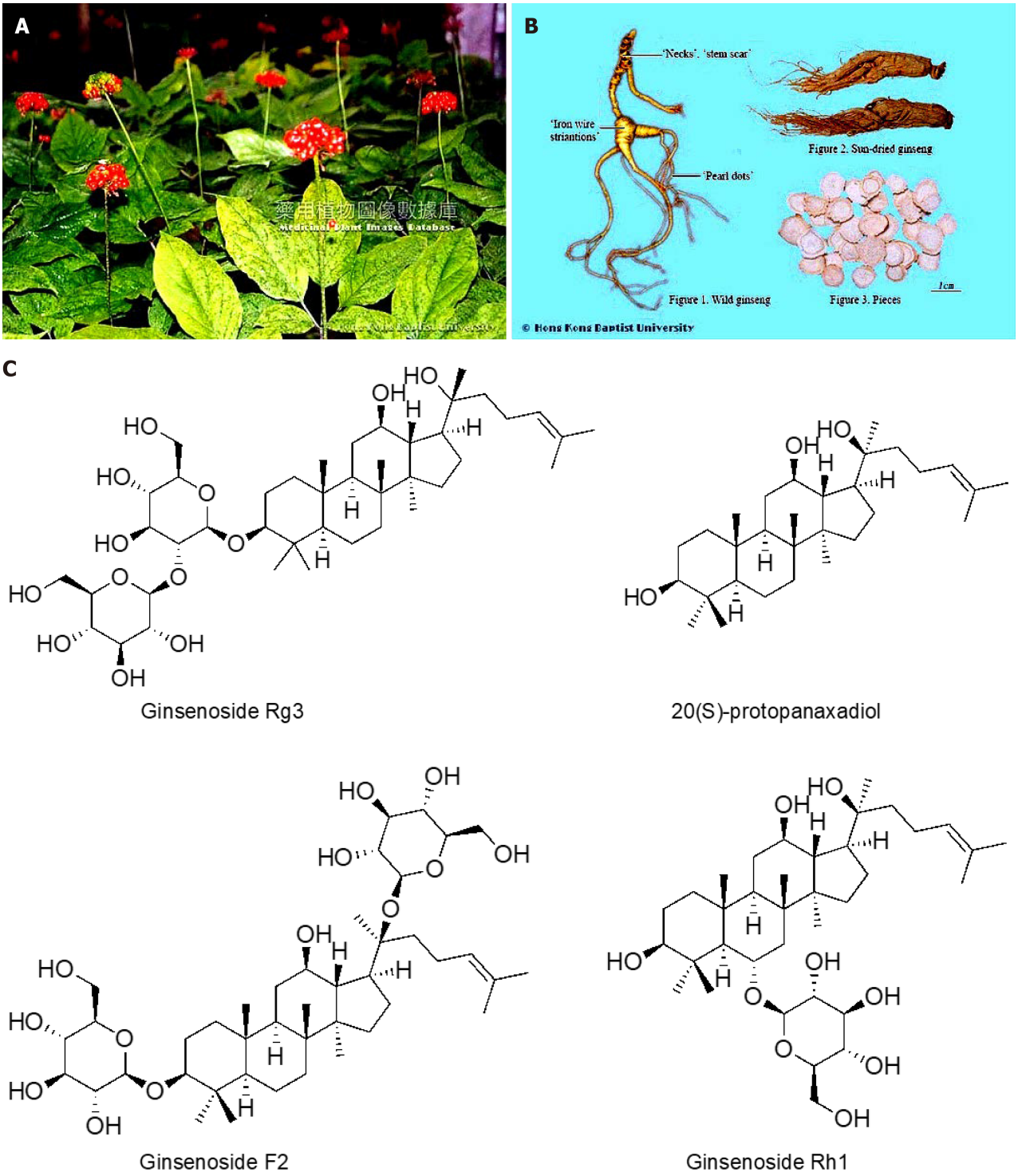

Figure 3 *Panax ginseng* C.A. Mey. A: Whole plants; B: Image of the root from which the crude drug is obtained; C: Main phytochemicals.

signaling pathways[88]. Furthermore, a recent study[89] provided a comprehensive view of the impact of PA on GC cell invasion and metastasis. These findings confirmed the inhibitory effect of PA on cell viability, adhesion, and migration. Research has also demonstrated that PA effectively reduces the dynamic migration of GC cells and alters the expression of EMT-related proteins such as E-cadherin, N-cadherin, and vimentin along with decreasing the expression of metastasis-related proteins such as MMP-2, MMP-9, and TIMP1. These findings suggest that PA may inhibit GC cell invasion and migration by affecting EMT processes and MMP activity (Figure 4).

Zingiber officinale Roscoe

In TCM, ginger, scientifically known as *Zingiber officinale* Roscoe, is considered an element with a slightly warm nature and a pungent taste. According to TCM theory, ginger is believed to target the lung, stomach, and spleen meridians. Traditionally, ginger is said to induce sweating to release the exterior, dispel cold, and alleviate pain. Ginger is also thought to promote digestion, increase appetite, and support the nourishment of the spleen and stomach. These effects

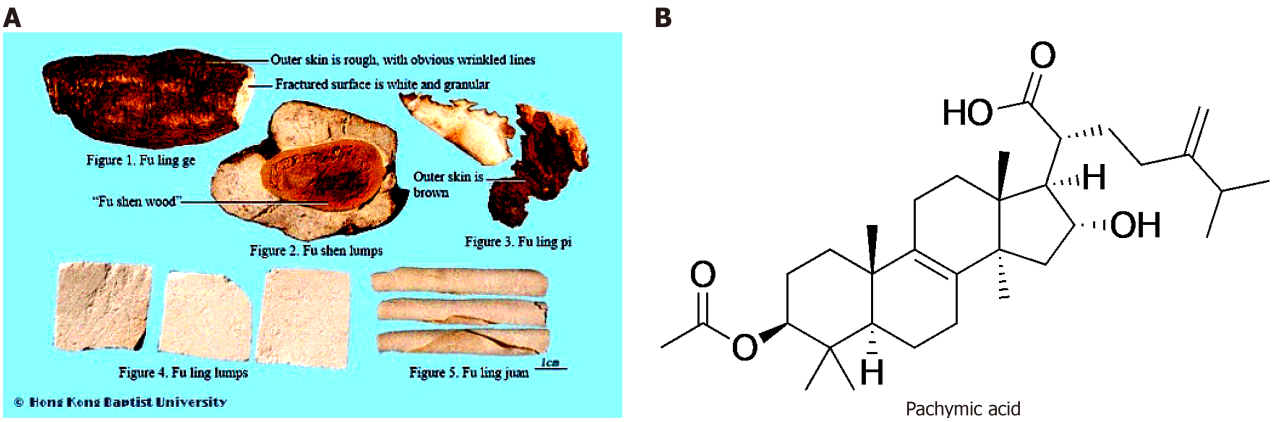

Figure 4 *Poria cocos* F.A. Wolf. A: Image of the root from which the crude drug is obtained; B: Pachymic acid.

are traditionally associated with improved immune function and a reduced occurrence of cancer, reflecting cultural beliefs rather than scientific evidence. The anticancer properties of aqueous ginger extract (AGE) were investigated. In Wistar rats with GC induced by N-nitroso N-methyl urea, AGE reduced the expression of GC markers such as gastrin, as well as markers of oxidative stress and inflammation. Additionally, AGEs enhanced the activity of antioxidant enzymes such as SOD, catalase, GST, GPx, and GR and reduced lipid peroxidation, indicating a decrease in oxidative stress. Histopathological analysis also revealed a reduction in cancerous lesions and an improvement in the gastric epithelium. These findings suggest that AGEs represent potentially promising dietary agents for the prevention of gastric carcinoma because of their antioxidant and anti-inflammatory properties[90]. According to these data, the administration of ginger extract to gerbils infected with *H. pylori* led to a significant reduction in both acute and chronic inflammation as well as the degeneration of epithelial cells, erosion, and cryptitis. This effect was achieved through a multifaceted mechanism that included the inhibition of cyclooxygenase-2 activity, suppression of the NF-κB transcriptional response, and a reduction in the release of proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α[91,92]. Consistent with these data, ginger extract significantly reduced the area of gastric ulcers and mitigated the histological damage induced by acetic acid in rats. The phytocomplex demonstrated antioxidative properties by reducing the levels of xanthine oxidase, myeloperoxidase, and malondialdehyde in the ulcerated gastric mucosa, underscoring its potential as a gastroprotective and chemopreventive agent[93].

The anticancer properties of several ginger compounds have been investigated. Among these compounds, 6-gingerol and 6-shogaol affect GC cell viability in distinct ways. In studies involving human GC cell lines, including HGC, AGS, and KATO III cells, 6-gingerol enhanced the TRAIL-induced reduction in viability by increasing TRAIL-induced caspase-3/7 activation and downregulating the expression of *cIAP1*, a protein that suppresses caspase-3/7 activity, through the inhibition of TRAIL-induced NF-κB activation. Conversely, 6-shogaol alone reduced GC cell viability by damaging microtubules and inducing mitotic arrest, a mechanism independent of caspase-3/7 activation. These findings suggest that 6-gingerol and 6-shogaol from ginger offer promising options for developing novel nutraceutical strategies against GC[93]. Additionally, 8-paradol, another phenolic compound isolated from ginger, was studied for its anticancer effects against GC[94]. This compound exhibited significant cytotoxicity against AGS cells and induced apoptosis through several processes, including morphological alterations, membrane damage, nuclear fragmentation, chromatin condensation, and DNA fragmentation. The apoptotic effects are accompanied by increased expression of proapoptotic proteins such as Bax and cytochrome c and caspases such as caspase-9 and caspase-3 while reducing the levels of the antiapoptotic protein Bcl-2[50].

Additionally, proteomic analysis revealed that 8-paradol treatment altered the expression of numerous proteins linked to mitophagy and autophagy signaling pathways. These findings suggest a complex interplay between fatty acid metabolism and the autophagy machinery, implicating mitophagy as the primary mechanism behind AGS cell apoptosis induced by 8-paradol.

The study also revealed that 8-paradol promotes PINK1/Parkin-mediated mitophagy in AGS cells. Treatment with 8-paradol resulted in mitochondrial dysfunction, characterized by fragmented mitochondria and diminished mitochondrial function. This dysfunction triggers the PINK1/Parkin pathway, which is essential for enhancing mitophagy, as indicated by increased PINK1 and Parkin expression in the treated cells (Figure 5).

Scutellaria baicalensis Georgi

Scutellaria baicalensis Georgi, known in TCM for its bitter taste and cold nature, is traditionally believed to perform several functions, including clearing heat and dispelling dampness, treating heat fires and removing toxic substances, promoting haemostasis, and preventing miscarriage. It is often chosen as the preferred TCM remedy because of its heat-clearing and detoxifying properties[30].

This plant presents a complex array of bioactive molecules that may synergistically contribute to its anticancer properties. Several plant extracts have been shown to target and regulate a range of cellular processes predominantly through the modulation of critical protein expression. Treatment with *Scutellaria baicalensis* leads to significant changes in several proteins that play key roles in cancer cell behaviour. Specifically, the protein PIK3CB, which is crucial for cell

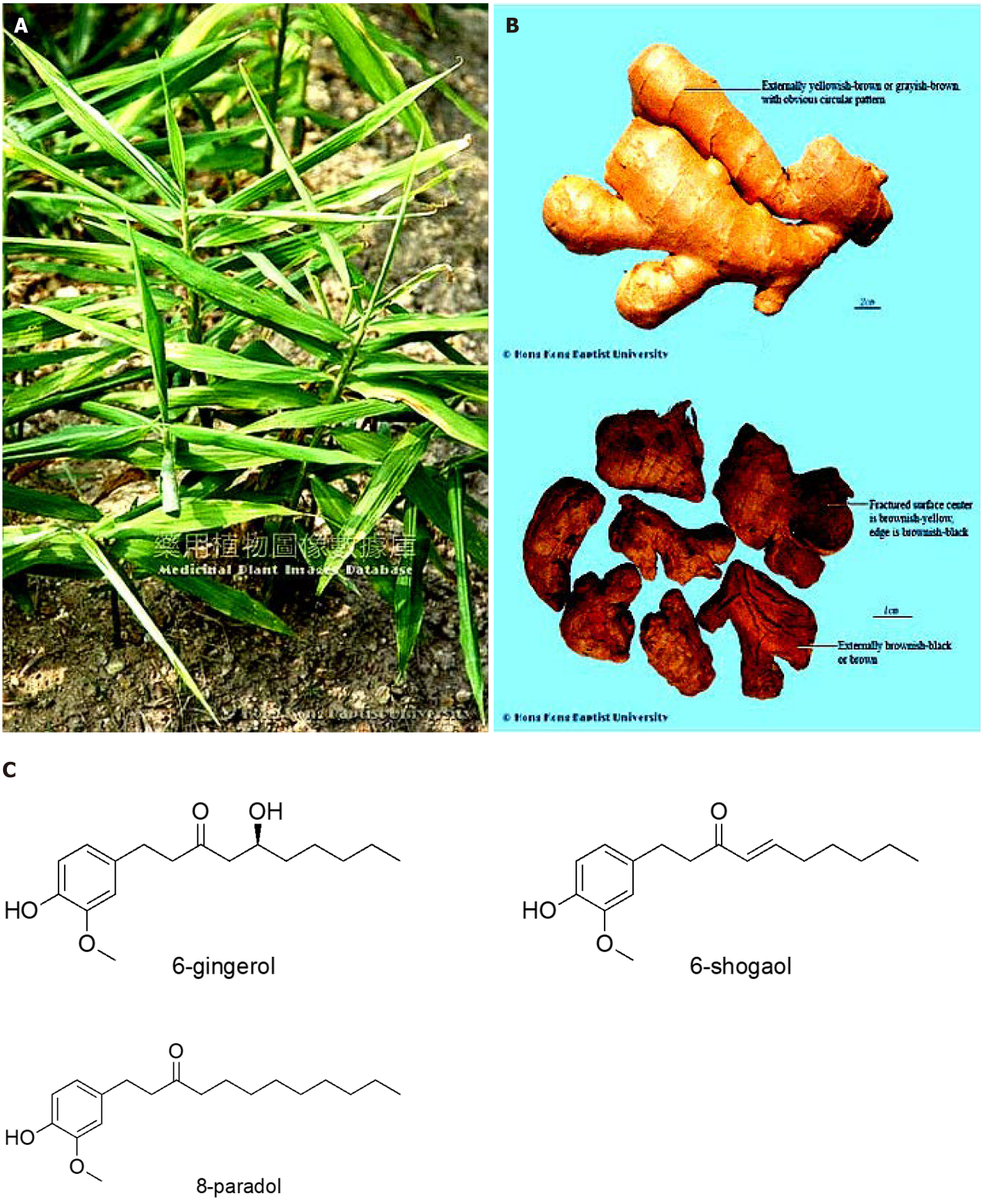

Figure 5 *Zingiber officinale* Roscoe. A: Whole plants; B: Image of the root from which the crude drug is obtained; C: Main phytochemicals.

survival and proliferation through the PI3K/AKT signaling pathway, is downregulated. This reduction may disrupt the pathway, potentially decreasing cancer cell growth and increasing cell death. Additionally, the oncoprotein CIP2A, known for its ability to suppress the tumour suppressor protein phosphatase 2A (PP2A), is also downregulated. This allows PP2A to be reactivated, enhancing cell death and inhibiting tumour growth and resistance to treatments that induce apoptosis[95]. A flavonoid-rich extract of *Scutellaria baicalensis* has significant efficacy against GC cells. This extract induces apoptosis in AGS human GC cells in a concentration-dependent manner. The apoptotic process is primarily mediated through the mitochondrial pathway, as evidenced by the disruption of the mitochondrial membrane potential and caspase cascade activation. The extract caused an increase in the Bax/Bcl-xL ratio, indicating mitochondrial

membrane permeabilization and the release of cytochrome c into the cytosol. This release triggers the formation of the apoptosome, leading to the activation of caspase-9, which subsequently activates the executioner caspase-3. The subsequent cascade of events includes the cleavage of *PARP*, a key DNA repair enzyme, indicating the final stages of apoptosis. This detailed mechanism highlights the specific action of the flavonoid-rich extract in inducing apoptosis through mitochondrial disruption in GC cells[96]. The flavonoids baicalin and scutella rein, which are isolated from *Scutellaria baicalensis*, target specific genes involved in cancer progression. These flavonoids interact with genes such as ESR1 and *fos,* which are critical for regulating cell proliferation, differentiation, and apoptosis. ESR1, the gene encoding estrogen receptor alpha, plays a role in various cancers. The *fos* gene, which is part of the activator protein-1 (AP-1) complex, is crucial for regulating inflammatory responses and cellular processes such as proliferation and apoptosis. The influence of flavonoids on the *fos* gene can lead to changes in AP-1 activity, thereby affecting the expression of genes that govern essential cellular functions. This gene-targeting action of flavonoids is pivotal in disrupting key signaling pathways involved in the survival and proliferation of GC cells, contributing significantly to the anticancer effects of *Scutellaria baicalensis*[97,98]. In conclusion, the anticancer effects of *Scutellaria baicalensis* flavonoid-rich extracts and isolated flavonoids result from their combined effects on various molecular targets and pathways (Figure 6).

Citrus reticulata Blanco

Several studies have shown that a high intake of citrus fruits is associated with a reduced risk of GC[99,100]. In TCM, *Citrus reticulata* Blanco, commonly known as mandarin orange, is traditionally used for its ability to regulate chi (vital energy), improve digestion, and clear phlegm. It is often prescribed for its soothing properties, particularly in treating abdominal discomfort and enhancing lung health. Some studies have suggested that these compounds have anticancer effects in experimental models. This fruit induces apoptosis in SNU-668 human GC cells, affecting the expression of different apoptosis-related genes (Bcl-2, Bax, and Caspase-3)[101]. Additionally, polymethoxyflavones from *Citrus reticulata* have been studied for their anticancer potential, particularly against GC. These compounds inhibit cell proliferation and induce apoptosis by upregulating *RARβ*, activating caspase-3, caspase-9, and *PARP1* proteins, and increasing cleaved caspase-8 levels, further enhancing their anticancer efficacy[102] (Figure 7).

The exploration of anticancer effects through NP reveals a paradigm in which multiple molecular targets are modulated simultaneously by diverse classes of phytochemicals. Flavonoids, ginsenosides, and polymethoxyflavones represent key molecular classes that orchestrate broad-spectrum biological activities against GC.

This multitarget approach is reflective of the principles of NP, which aims to understand the synergistic effects of multiple compound interactions within biological networks. By targeting various pathways, these phytochemicals disrupt cancer progression at multiple points, potentially increasing the efficacy of pharmacological treatments and reducing the likelihood of resistance development.

These observations support the strategic development of nutraceuticals on the basis of NP and multicomponent analyses, providing a promising route for proactive GC prevention and emphasizing the need for a systematic exploration of TCM-and food-derived compounds within complex biological systems. This approach not only enhances the understanding of pharmacological networks but also supports the development of multiaction nutraceuticals in the field of cancer prevention (Figure 8).

COMBINING TCM, SURGERY, RADIOTHERAPY AND CHEMOTHERAPEUTIC DRUGS

Currently, surgical treatment remains an important treatment regimen for GC. However, surgery alone or in combination with radiotherapy and chemotherapy offers limited advantages in terms of enhancing patient quality of life. The use of TCM as an adjunct therapy may improve a patient's immune function and nutritional status and alleviate the side effects of radiotherapy and chemotherapy, such as nausea, vomiting, and poor appetite[29,103]. Specifically, GC surgery may produce symptoms such as shortness of breath, fatigue, weight loss, and mental fatigue. TCM formulas such as Shiquan Dabu decoction and Si Jun Zi decoction have been studied for their effects on digestion, nutritional status, and immune function[83]. Studies on various TCM formulas have revealed their potential synergistic effects with chemotherapy, potentially offering new pathways for effective cancer adjuvant treatments. For example, BXD regulates proteins associated with drug resistance and sensitivity in tumours, suggesting its potential to modify the response to chemo therapy in GC. Although the specific mechanisms are still being investigated, BXD is a classic TCM formula that is traditionally used to treat various gastrointestinal diseases, including GC[30,104]. SFI, when combined with chemotherapy, has shown promising effects on quality of life and remission rates and can reduce adverse events such as nausea, vomiting, and leucopenia in patients with advanced GC, as reported in a randomized controlled trial[35]. The effects of SJZD combined with EN have been studied inpatients with GC. The results suggest improvements in postoperative recovery, nutritional status, and immune function, highlighting the potential of SJZD in supporting patients undergoing cancer treatments[34]. JPYZXZ decoction alleviates GC progression by suppressing exosomal PD-L1, thereby reducing MDSC expansion in the tumour microenvironment. These findings indicate a potential role of JPYZXZ in remodelling the immunosuppressive tumour microenvironment, which could be beneficial when JPYZXZ is combined with chemotherapy[42,43].

Other formulas, such as AiDi, Hua Chan Su, Fufang Kushen and Shenqi Fuzheng, have been used in combination with chemotherapy. These TCM formulas are typically administered *via* injection, with doses varying on the basis of the specific formula. Studies indicate that these combinations may not only improve treatment outcomes such as response rates and quality of life but also reduce adverse reactions such as leucopenia, nausea, and vomiting[94]. With respect to polyherbal formulas in TCM, existing studies suggest that the synergistic effects observed with chemotherapeutic drugs

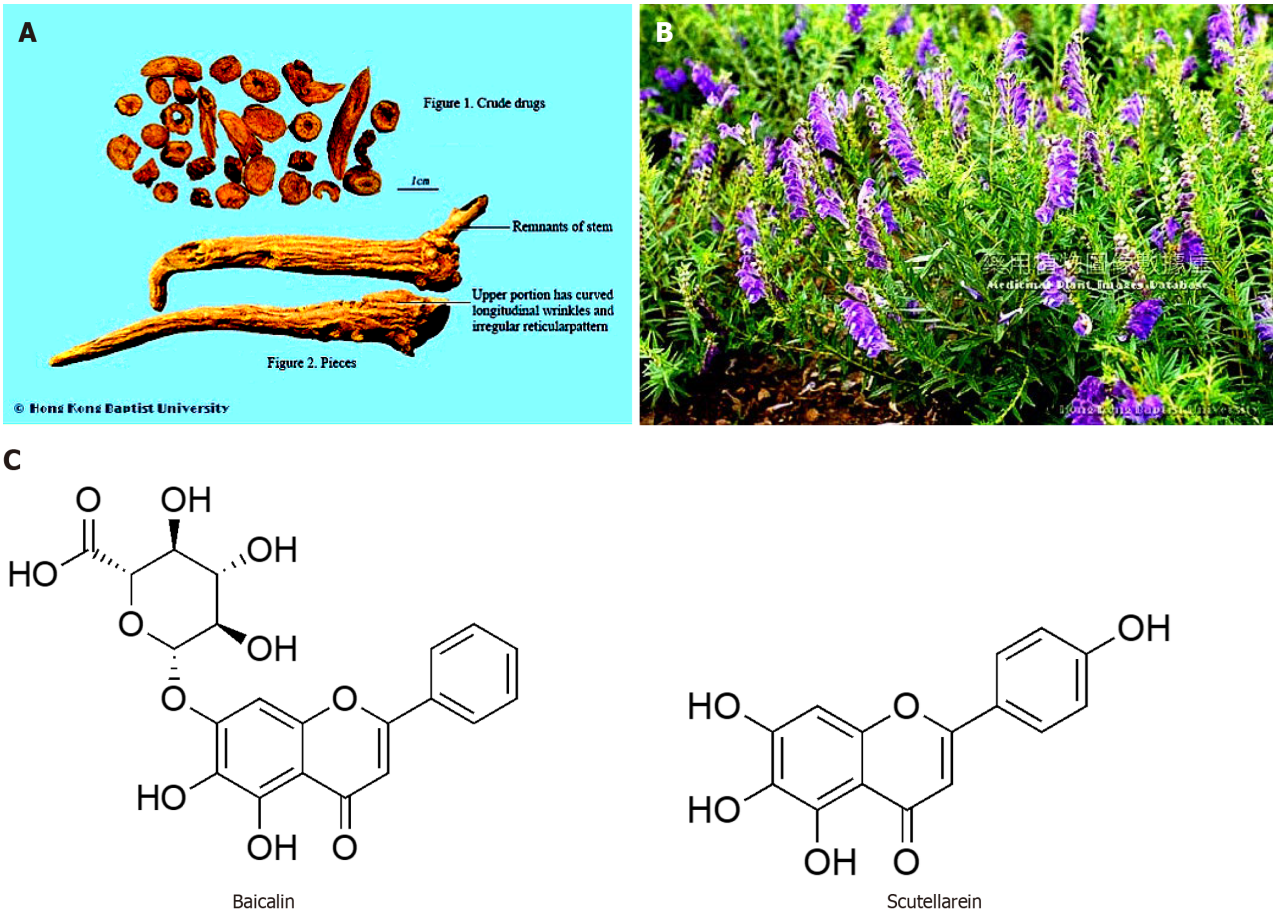

Figure 6 *Scutellaria baicalensis* Georgi. A: Whole plants; B: Image of the root from which the crude drug is obtained; C: Main phytochemicals.

in the treatment of GC are predominantly focused on minimizing side effects and enhancing the quality of life for patients rather than demonstrating a direct antitumour effect. However, it is important to note that potential synergy between the components of polyherbal formulas and chemotherapeutic drugs cannot be entirely excluded.

In this context, it has been demonstrated that an extract derived from *Panax ginseng* has a synergistic inhibitory effect on BGC823 cells when combined with 5-fluorouracil (5-FU). This phytocomplex not only has the potential to enhance the efficacy of 5-FU but also has protective effects against 5-FU-inducedtoxicity in mice, as observed in *in vivo* studies[105]. Several compounds in *Panax ginseng* increase chemotherapeutic drug efficacy in experimental models. Ginsenoside Rg3 sensitizes AGSR-CDDP cells to cisplatin-induced apoptosis *via* the targeting ofmiR-429[61]. A phytochemical isolated from *Scutellaria baicalensis* acts synergistically with an anticancer drug. Baicalein reverses hypoxia-induced resistance to 5-FU in GC AGS cells through the suppression of glycolysis and the PTEN/Akt/HIF-1α signalling pathway. The flavonoid baicalein inhibited glucose uptake and lactate production in AGS cells under hypoxic conditions, counteracting the enhanced glycolytic flux associated with drug resistance. In addition, baicalein attenuated the expression of key glycolysis-related enzymes, including hexokinase 2, lactated hydrogenase A and pyruvate dehydrogenase kinase 1, which are crucial for cancer cell survival and growth in hypoxic environments. Furthermore, this compound reduces HIF-1α protein levels and suppresses Akt phosphorylation by promoting PTEN accumulation, thus influencing the PTEN/Akt pathway, which is known to regulate hypoxic responses in tumour cells[6,106]. Another flavonoid named scutellarin inhibited AGS and SNU484 cell viability in a concentration-dependent manner through the downregulation of OFD1, VINC, HIP1R, and PIK3CB and increasing the expression of voltage-dependent calcium channel subunit α-2/δ-1, proto-oncogene vav 1, and synaptonemal complex protein 1[107]. [6]-Gingerol enhances the radiosensitivity of GC *via* G2/M phase arrest and apoptosis induction. This compound from ginger not only inhibited HGC-27 cell viability in a dose-dependent manner but also sensitized these cells to ionizing radiation (IR). Treatment with [6]-gingerol enhanced IR-induced cell cycle arrest at theG2/M phase and increased IR-induced apoptosis. Additionally, [6]-gingerol pretreatment following IR downregulated cyclinB1, cyclin A2, CDC2, and cyclin D1 expression; upregulated p27 mRNA expression; and induced the activation of caspase-9, caspase-3, and cytochrome c, which are key regulatory molecules in theapoptotic process[93]. A previous study[108] revealed that the combination of *Poriacocos* extracts with chemical agents such as oxaliplatin significantly hinders the migration and invasion of GC cells. This is achieved primarily through the inhibition of EMT, a critical process in cancer metastasis, and is further supported by changes in gene expression, such as the downregulation of EMT-related markers. The synergistic effects of Poria cocos extract and oxaliplatine resulted in a decrease in EMT-related miRNAs, such as Snail, Twist, Vimentin and N-cadherin, and an increase in E-cadherin.

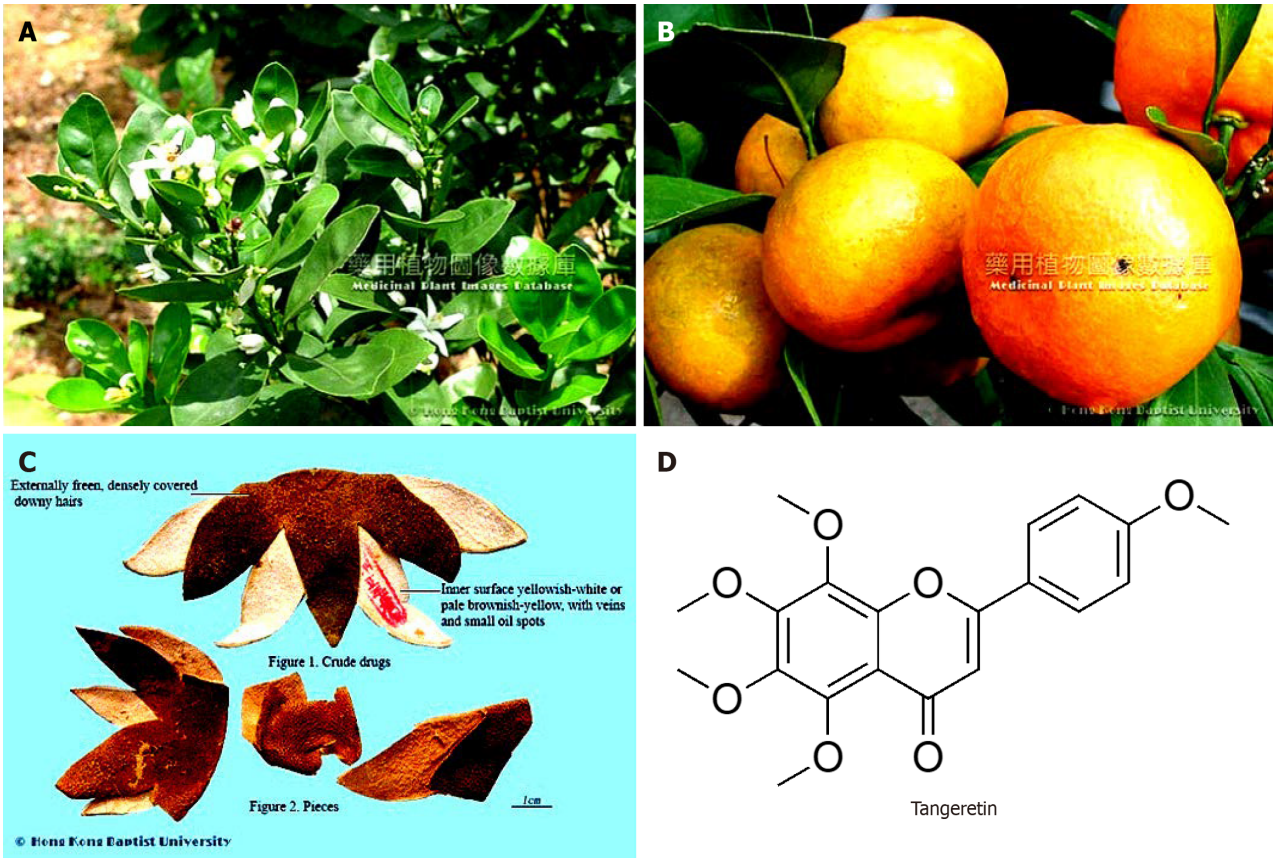

Figure 7 *Citrus reticulata* Blanco. A: Whole plants; B: Fruits; C: Image of the dried peels of citrus from which the crude drug is obtained; D: Tangeretin.

The integration of TCM with anticancer drugs such as chemotherapy and radiotherapy provide a compelling avenue for enhancing therapeutic outcomes and managing side effects. Research into various TCM formulations has demonstrated their potential in reducing adverse effects associated with anticancer treatments and potentially enhancing their efficacy.

Phytocomplexes derived from TCM herbs have shown promise in various studies, not only in alleviating symptoms and improving patients' quality of life but also in enhancing the effectiveness of chemotherapy and radio therapy agents. Compounds such as ginsenoside Rg3 from Panax ginseng and baicalein from *Scutellaria baicalensis* exemplify the potential of TCM-derived nutraceuticals to modify drug response pathways and counteract drug resistance mechanisms. These compounds engage in multifaceted interactions within various cellular signalling pathways, such as the PTEN/Akt/HIF-1α signalling axis, influencing crucial processes such as apoptosis, cell cycle regulation, and glycolysis under hypoxic conditions, and these processes are often heightened in tumour environments.

The potential of TCM phytocomplexes and isolated compounds to act as nutraceuticals in a supportive role during chemotherapy and radiotherapy may improve patient quality of life. These substances may offer a strategic advantage by employing a multicomponent–multitarget approach typical of NP, addressing multiple pathways involved in cancer progression and treatment resistance. By modulating key signalling pathways and reducing the metabolic adaptations of cancer cells, these nutraceuticals could enhance the efficacy of standard therapies and improve patient outcomes.

Ongoing research into these compounds could lead to innovative nutraceuticals that may favour the overall well-being of patients and decrease GC risk, embodying the concept of 'before drugs, beyond foods.

TCM AND WESTERN MEDICINE: POINTS OF CONTACT IN THE FUTURE

Personalized medicine

Recent advancements in personalized medicine for GC have significantly evolved, with a focus on targeted and immunotherapies based on specific molecular biomarkers. The incorporation of trastuzumab, a monoclonal antibody targeting HER2, has been a major improvement in treating metastatic GC, especially HER2-positive tumours. The use of immune checkpoint inhibitors such as nivolumab and pembrolizumab has shown consistent efficacy in patients with HER2-positive and PDL1-positive tumours[109]. Perioperative chemotherapy has become the standard treatment for resectable GC, with regimens such as FLOT being common in Western countries. Adjuvant chemotherapy is recommended for patients with stage II or III disease after surgery. Studies such as HER-FLOT and PETRARCA have investigated the efficacy of adding anti-HER2 therapies such as trastuzumab and pertuzumab to perioperative chemotherapy. Anti-VEGF therapies, including bevacizumab and ramucirumab, have been evaluated in the perioperative setting, with mixed results

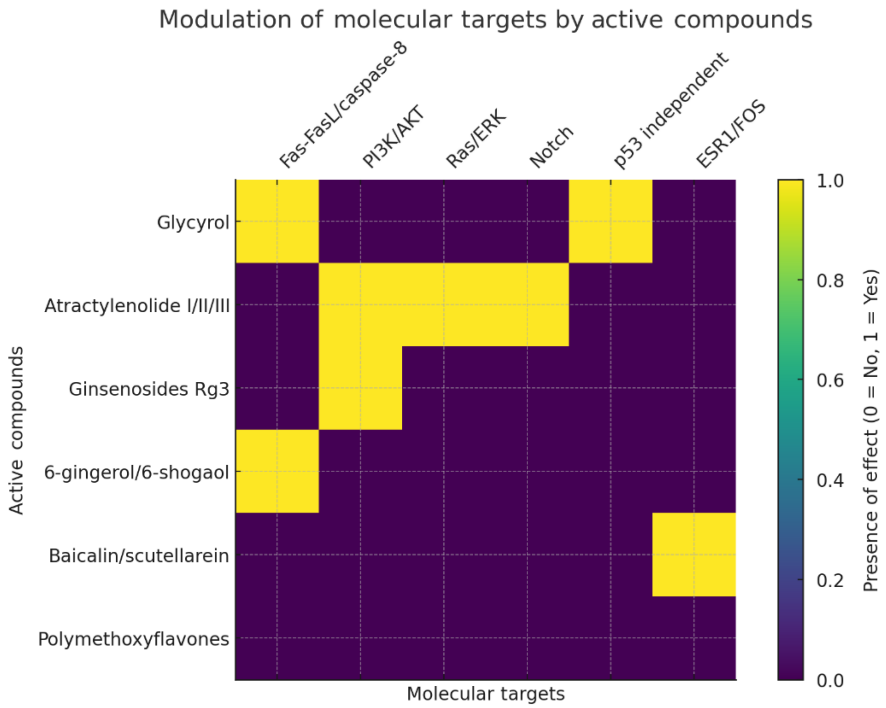

Figure 8 Heatmap of molecular target modulation by traditional Chinese medicine derived compounds. This heatmap illustrates the interaction between selected active compounds and specific molecular targets. Each row represents a different compound, while each column corresponds to a molecular target. The colour intensity in each cell indicates whether a particular compound modulates a specific target (brighter green for modulation, darker for no modulation). This visualization aids in identifying which compounds are involved in influencing molecular pathways, providing insights into their potential therapeutic roles in modulating cellular processes relevant to cancer treatment and prevention.

concerning overall survival. PD-1 inhibitors have been approved for first- and third-line treatment of unresectable/metastatic GC. For the dMMR/MSI-H subgroup, immunotherapy in the perioperative setting has shown promising results, potentially allowing patients who achieve a complete pathological response to avoid surgery. These developments underscore the importance of advanced diagnostic techniques and novel drugs for better characterizing molecular profiles and identifying new therapeutic targets in GC.

In parallel, TCM formulations such as BXD, which inhibits PD-L1, HIF-1, EGFR, and TLR4 expression, show potential synergies with these targeted therapies and may be studied in patients with specific features. Other formulations, such as SJZD, enhance immune responses and improve chemotherapy outcomes. In this context, the detailed molecular characterization of cancer cells from patients treated with TCM could reveal a predominant molecular pattern unique to these individuals. If this pattern is confirmed through rigorous scientific analysis, it would represent a pivotal point of contact between TCM-derived nutraceuticals and Western medical approaches. This intersection would not only validate the effectiveness of TCM-derived nutraceuticals in specific molecular contexts but also enhance the precision of personalized medicine by integrating diverse strategies to target GC more effectively.

CONCLUSION

The exploration of TCM polyherbal formulations in the context of GC presents a compelling avenue for scientific inquiry. The existing research, although promising, underscores the need for more rigorous, in-depth studies to substantiate the efficacy and mechanisms of TCM in this context to establish innovative research aimed at identifying nutraceuticals based on TCM herbs. This review aims to chart a new direction for research, advocating for a collaborative approach that merges TCM chemical and pharmacological profiling with the precision and systematic methodology characteristic of Western medicine.

Such an integrated research agenda could encompass several key areas. First, detailed chemical and molecular network analyses are needed. These studies should focus on how TCM active ingredients interact with GC pathways at the genetic and proteomic levels.

Second, personalization of TCM-derived nutraceuticals on the basis of individual patient profiles represents a significant step forward. By aligning TCM phytocomponents with the genetic and molecular characteristics of each patient's cancer, nutraceuticals may be tailored for maximum efficacy.

In addition, developing nutraceuticals based on TCM phytocomplexes or isolated compounds that synergize with anticancer drugs could enhance overall treatment efficacy while mitigating adverse reactions. This approach requires careful study of herb-drug interactions to optimize safety and therapeutic outcomes.

FOOTNOTES

Author contributions: Micucci M and Xiang BZ initiated the work and designed the idea; Kwan HY, Ting CM, and Battistelli M prepared and collected the material and data; Micucci M, Battistelli M, Mari M, Retini M, Burattini S, Abdullah FO, Okeke UJ, Gianfanti F, and Osman R wrote the paper. All the authors have read and approved the final manuscript. Micucci M and Xiang BZ are the corresponding authors. Micucci M is the corresponding author responsible for all contact and correspondence with the journal. Micucci M brings specialized knowledge in Food Chemistry, Phytochemistry, Nutraceuticals, and *in vitro* evaluation for the investigation of molecular mechanisms. Xiang BZ contributes his extensive expertise in clinical research, pharmacology, and pharmacological research applied to Traditional Chinese Medicine formulations. The combination of these distinct fields of knowledge ensures a comprehensive and multidisciplinary approach to our research. The collaboration between Micucci M and Xiang BZ ensures effective management of post-submission matters. Their joint efforts facilitate prompt and accurate responses to reviewers' and readers' queries, enhancing the overall quality and reliability of the manuscript. This effective communication is crucial for addressing diverse aspects of the research, from molecular mechanisms to clinical applications. The presence of co-corresponding authors enriches the analysis and presentation of our study. Micucci M's expertise in molecular mechanisms and phytochemistry, combined with Xiang BZ's clinical and pharmacological insights, offers a thorough and well-rounded examination of the research topic. This multidisciplinary perspective not only deepens the understanding for readers but also promotes broader scientific discussions.

Conflict-of-interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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