Emerging Potential of Naturally Occurring Molecules against Gastric Cancer: Insights Molecular Mechanism and Therapeutic Targets

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Abstract: Gastric cancer, also known as stomach cancer, is a cancer which develops from the lining of the stomach. Accumulated evidences and epidemiological studies have been indicated that natural products play an important role in gastric cancer prevention and treatment, although its mechanism of action did not elucidate yet. Particularly, experimental studies have been showed that natural products displayed a protective effect against gastric cancer via numerous molecular mechanisms such as suppression of cell metastasis, anti-angiogenesis, inhibition of cell proliferation, induction of apoptosis, and modulation of autophagy. Although chemotherapy remains the standard treatment for advanced gastric cancer along with surgery, radiation therapy, hormone therapy and immunotherapy, but its adverse side effects including neutropenia, stomatitis, mucositis, diarrhea, nausea, and emesis are well documented. Additionally, intake of naturally occurring phytochemicals could increase the efficacy of gastric chemotherapy and chemotherapeutics resistance. However, natural product structural stability and powerful bioactivity are important to develop novel treatments for gastric cancer that may minimize such adverse effects. Therefore, the purpose of this review is to summarize the potential therapeutic effects of natural products on prevention and treatment of gastric cancer with intensive molecular mechanisms of action, bioavailability, and safety efficacy.

Keywords: Gastric cancer; natural products; autophagy; apoptosis; angiogenesis; metastasis; chemo-resistance

1. Introduction
The incidence and mortality of cancer is growing worldwide, with estimated 19.3 million new cases and 10 million cancer deaths in 2020 [1]. Gastric cancer is the 5th most common neoplasm and the 4th leading cause of cancer death, which led to over one million new cases and an estimated 769,000 deaths in 2020 [1]. Clinically, to offer pertinent treatment, gastric carcinoma is classified as early or advanced stage [2]. Gastric carcinoma has multiple risk factors; genetics, *Helicobacter pylori* infection, gastric ulcer, gastroesophageal reflux disease (GERD), tobacco, smoking, alcohol, chemical exposure, diet, obesity, and so forth [3, 4]. Surgical resection, when possible, offers the best chances of cure for early gastric cancer [5]. Adjuvant or neoadjuvant chemotherapy may be beneficial in increasing the chance of successful resection or in decreasing the rate of recurrence and/or metastasis [6-8]. For patients with unresectable advanced gastric cancer, chemotherapy is a common...
choice. Conventional regimens are mostly based on cytotoxic agents including antimetabolites and platinum based anticancer drugs. However, these regimens cause severe side effects such as chemotherapy-induced peripheral neuropathy (CIPN), neutropenia, stomatitis, mucositis, diarrhea, nausea and emesis [9, 10]. Moreover, failure of first-line chemotherapy due to resistance is also an obstacle of gastric cancer treatment hampering the novel and effective therapies and imposing significant economic costs to patients [11]. Exposure to unrecoverable toxins, trauma, or infection can occur mutagenic chronic inflammatory response, leading to dysplasia [12]. Considering gastric cancer, *Helicobacter pylori* infection is a major risk factor of developing deleterious tumor microenvironments [13]. Nuclear factor kappa-B (NF-κB), c-Jun N-terminal kinase (JNK), and signal transducer activator of transcription 3 (STAT3), inflammatory cytokines, tumor necrosis factor (TNF), interleukin (IL)-1/6, tumor-derived cytokines such as fasciclin (Fas) ligand and vascular endothelial growth factor (VEGF) are major targets of regulation for prevention and treatment of gastric cancer [14-17]. Therefore, novel drug development against gastric cancer is strongly needed to further improve survival rates of this disease and lower the side effect of conventional therapies.

Epidemiological studies showed that natural dietary products decrease the risks of gastric cancer [18-21]. Extensive research was conducted to measure the value of natural products for prevention and treatment of gastric carcinoma, leading to the discovery of major phytochemicals with anti-cancer properties such as quercetin, silymarin, taurine, berberine, curcumin, and so forth [22-25]. However, few review articles included agents from animal or marine sources, which are also being studied with growing expectation [26, 27]. The same goes for traditional medicine, despite their wide use in clinical practice to combat various illnesses including cancer [28-31]. Especially, traditional Korean and Chinese medicine have used mixtures made from medicinal herbs, animals, or mineral resources. This review explored various single compounds or extracts isolated from biological resources, and traditional medicine in the form of mixtures that show anti-cancer properties, closely targeting gastric cancer. Efficacies and underlying mechanisms of the subjects are discussed as well as the major experimental models of each study.

2. Role of naturally occurring molecules in gastric cancer managements

Programmed cell death is an important process of cell suicide involved in a number of biological activities including morphogenesis, maintenance of tissue homeostasis, and harmful cell removal [32]. Since dysfunctional programmed cell death leads to several diseases, especially cancer, considering cell death is crucial for cancer treatment [32]. Various natural products are reported to suppress cancerous cell development by inducing cell death, apoptosis and autophagy [24]. Recent studies discovered that natural products can also trigger non-canonical cell death such as ferroptosis, necroptosis, and pyroptosis [33]. Among the studies discussed, one reported the occurrence of necrosis and another lipid peroxidation [34, 35]. Other studies mainly reported induction of apoptosis and/or autophagy. Due to their wide variety, apoptosis-inducing natural products were organized into three subgroups according to their modes of preparation: single compounds, extracts, or mixtures (decoctions).

2.1.1. Apoptosis-inducing natural molecules in gastric cancer

Apoptosis is the process of programmed cell death, characterized by distinct morphology: cell shrinking, membrane blebbing, chromatin condensation, and nuclear fragmentation [36, 37]. Several single compounds and extracts originated from plants, animals, fungi, and minerals showed apoptosis-inducing effects on gastric cancer cells and animal models have been presented in Figure 1 and Table 1. Yang *et al.* reported that berberine could inhibit the proliferation of SGC-7901 cells and induce apoptosis on a dose dependent manner [38]. *In vitro* models have been demonstrated that cyclovirobuxine D originated from *Buxux microphylla* Richardii. *Radix* (*Buxaceae*) induced apoptosis in MGC-803 and MKN-28 cells [39]. Both cell lines were treated 30, 60, 120 μM/L cyclovirobuxine D solutions for 48 h. GFG-3a, a glycoprotein isolated from the fungus *Grifola frondose*
Gray Mycelia (Meripilaceae), promoted apoptosis against SGC-7901 cells [40]. GFG-3a increased the expression levels of active caspases, p53 and Bcl-2 associated agonist of cell death (Bad). Kong et al. reported that melittin, a component of *Apis cerena* Fabricius venom (Apidae), induced caspase-dependent apoptosis by causing ROS formation and triggering mitochondrial membrane depolarization [41]. Expressions of caspase-3, cytochrome c, endonuclease G (Endo G), apoptosis inducing factor (AIF) and Smac/Diablo were upregulated in melittin-treated SGC-7901 cells. Wu et al. revealed that phenolic alkaloids of *Menispermum dauricum* DC. Rhizoma (Menispermaceae) induced apoptosis and suppressed gastric tumor growth by inducing apoptosis and inhibiting of oncogenic Kirsten rat sarcoma viral oncogene homolog (K-RAS) expression [42]. According to study by Zhang et al., berberine and d-Limonene showed anti-cancer effect synergistically [43]. Berberine was extracted from *Coptidis japonica* Makino rhizoma (Ranunculaceae), and d-limonene from *Evodiae rutacearpa* Bentham. Fructus (Rutaceae). They were combined at a ratio of 1:4, 20 and 80 µM each. Apoptotic rate of the combination of the two compounds was much higher (29.03%) compared to berberine-only-treated group (12.2%) and d-limonene-only-treated group (19.6%). Trifolirhizin, a compound isolated from *Sophora flavescens* Aiton Radix (Fabaceae), demonstrated apoptotic activity both in vitro and in vivo [44]. Trifolirhizin induced apoptosis of MKN-45 cells in vitro via EGFR-MAPK pathways and triggered G2/M phase cell cycle arrest by impacting CDC2/Cyclin B complex. Qian et al. discovered that Ginsenoside-Rh2 originated from *Panax ginseng* C.A.Mey Radix (Araliaceae) inhibits proliferation and induces apoptosis of SGC-7901 cells [45]. The ratio of Bcl-like protein 4 (Bax) to Bcl-2 (Bax/Bcl-2) was elevated following Ginsenoside-Rh2 treatment.

Figure 1. Schematic diagram of natural product-mediated apoptosis signaling pathways. FADD, Fas-associated proteins with death domain; TRAILR, TNF-related apoptosis-including ligand receptor; FASR, Fas receptor; tBid, truncated Bid; PARP, Poly ADP-ribose polymerase; APAF1, Apoptotic Protease Activating Factor 1; MOMP, Mitochondrial Outer Membrane Permeabilization; PIP2, Phosphatidylinositol-3,4-Bisphosphate; PIP3, Phosphatidylinositol-3,4,5-Triphosphate; PI3K, Phosphoinositide 3-kinase.

Tanshinone IIA, originated from *Salviae miltiorrhiza* Bunge. Radix (Lamiaceae), suppressed AGS gastric tumor cells via activation of tumor necrosis factor-alpha (TNF-α), Fas, p38, JNK, p53, p21, caspase-3, caspase-8 and inhibition of ERK [46]. The apoptotic activities of *Zingiber officinale* Roscoe Rhizoma (Zingiberaceae) against AGS cells were reported by Debjani et al. [47]. 100, 250 µM of [6]-gingerol treatment for 24 h to AGS cells.
generated reactive oxygen species and decreased ΔΨm, leading to induction of apoptosis. Perturbations of ΔΨm were associated with deregulation of Bax/Bcl-2 ratio at protein level, which led to upregulation of cytochrome c and triggered the caspase cascade. 2, 7-dihydroxy-3-methylanthaquinone (DDMN), a flavone isolated from *Hedyotis diffusa* Wild. Herba, induced caspase-dependent apoptosis of SGC-7901 gastric cancer cells [48]. 6, 7, 30-trimethoxy-3, 5, 40-trihydroxy flavone (TTF), extracted from *Chrysosplenium nudicaule* Ledeb. Herba, is a well known traditional Chinese medicine for digestive diseases [49]. TTF induced apoptosis on SGC-7901 cells treated at the dose of 2, 4, 8, 16, 32 μg/mL for 24, 48 and 72 h. Sun et al. observed that curcumin, isolated from *Curcuma longa* L. Rhizoma (Zingiberaceae), induced apoptosis of SGC-7901 and BGC-823 (5, 10, 15, 20, 40 μM for 24 h) cells by up-regulating microRNA-33b (miR-33b) expression [50]. Three human gastric cancer cell lines, SGC-7901, MGC-803, and BGC-823 were treated esculetin at dose of 12.5, 25, 50 μM for 24 h. Esculetin treatment triggered ROS formation, elevated caspase-3/9 activity and induced poly (ADP-ribose) polymerases (PARP) cleavage. Liu et al. reported that hydroxysafflor yellow A (HSYA) induces apoptosis of BGC-7901 cells via activation of pexoxisome proliferator-activated receptor gamma (PPARγ) signal [51]. Expressions of PPARγ and caspase-3 were elevated. Zhou et al. studied the efficacy of the combination of TRAIL and kuraririnone against gastric cancer cell line SGC-7901 [52]. Kuraririnone is a substance originated from *Sophora flavescens* Aiton Radix (Fabaceae). Kuraririnone (5 μM) for 24 h significantly enhanced TRAIL-induced apoptosis compared to single treatment by stimulating inhibition of Mcl-1 expression, cleavage of FLIP, and phosphorylation of STAT3. Wu et al. elucidated that licochalcone A (LicA) induced apoptosis by blocking the Akt signaling pathway and reducing hexokinase 2 (HK2) expression in MKN45 cells [53]. Notably, 25% of tumor cells were subjected to apoptosis at 60 μM. The apoptotic ability of ophiopogonin B, a compound isolated from *Ophiopogon japonicus* Radix, against SGC-7901 cells were suspected to be relevant with the JNK 1/2 and ERK1/2 signaling pathways [54]. Ophiopogonin B treatment activated phosphorylation of JNK1/2 and ERK 1/2, upregulated active caspase-3 and Bax expression levels and downregulated Bcl-2 expression levels. Xu et al. found that phloretin, a plant-derived natural product, is an important molecule for the treatment of gastric cancer. To investigate its apoptotic effect, 4, 8, 16 μM of phloretin was treated with AGS cells for 24 h. The apoptotic AGS cells increased from 1.25% in control to 46.3% at 40 μM doses of phloretin. Expression of Bax was increased in a dose-dependently while the expression of Bcl-2 decreased [55]. Podophlootoxin, extracted from *Linum album* Kotschya (Linaceae), induced apoptosis and downregulated zinc finger protein 703 oncogene expression according to a study by Akbari et al. [56]. When AGS cells were treated with different concentrations (200, 400, 600, 800 and 1000 μg/mL) for 24 h, apoptotic cell count was increased 44% in contrast to 2.70% in untreated AGS cells. Tsai et al. found that 7-acetylsinunaximol B (7-AB), discovered from *Sinularia sandensis* (Alysoniidae), shows anti-proliferative effect through apoptosis against human gastric carcinoma NCI-N87 cells [57]. In the study, the cells were treated with 4, 8, 16 μM 7-AB formula for 24 h. 7-AB treatment increased the expression of Bad, Bcl-like protein 11 (Bim), Bax, and cytochrome c, decreased the expression levels of phosphorylated Bad (p-Bad), myeloid cell leukemia-1 (Mcl-1), Bcl-xL, and Bcl-2 proteins. Apoptosis was induced by elevated levels of ROS and caspase-3 along with inhibition of Bcl-2, and loss of ΔΨm. Crotosic acid, isolated from *Actinidia colvata* Dunn. Radix (Actinidiaceae), was reported to inhibit proliferation of BGC-823 cells by downregulating the NF-kB pathway [58]. Crotosic acid inhibited phosphorylation of nuclear factor kappa B-alpha (αBxα), expression of p65, and nuclear translocation and DNA-binding activity of NF-kB. Upregulation of Bax and downregulation of Bcl-2 were also observed. Jung et al. found that curcuzedolaide, sesquiterpene components of *Curcuma zedoaria* Roscoe Rhizoma (Zingiberaceae) induced mitochondrial apoptosis of AGS cells [59]. AGS cells were treated with curcuzedolaide at the concentration of 100 μM and 200 μM for 24 h. Exposure to curcuzedolaide induced cleavage of PARP as well as caspase-8, caspase-9, and caspase-3, in a dose-dependent manner. Deacetylsovastratum, extracted from *Patrinia heterophylla* Bunge. (Caprifoliaceae), was treated to AGS and HGC-27 human gastric cancer cell lines for 24 h at
the dose of 4, 8, 16 μM/mL and 10, 20, 30 μM/mL, respectively [60]. Deacetylisovaltratum induced mitochondrial and caspase-dependent apoptosis. Li et al. demonstrated that elemene counters against gastric cancer via regulation of the ERK 1/2 signaling pathway [61]. Elemene is a sesquiterpenoid mixture extracted from a traditional herbal medicine Curcuma zedoaria Roscoe Rhizoma (Zingiberaceae). In an in vitro investigation, BGC-823 cells were treated with 20, 40, 80, 160 μg/mL elemene solution for 24 h. Moreover, Bak, Bax, and Cyclophilin D (CypD) expressions increased while Bcl-2, Bcl-xL and XIAP levels decreased. Grifolin, isolated from the mushroom Albatrellus confluens (Alb. & Schwein.) Kotl. & Pouzar (Albatellaceae), inhibited growth and invasion of gastric cancer cells by inducing apoptosis and suppressing the ERK1/2 pathway [62]. Liao et al. reported that N-butylidenephthalide (BP), a bioactive compound of Angelica Sinensis Diels Radix, activated the intrinsic apoptotic pathway of human gastric cancer cells AGS, NCI-N87 and TSGH-9201 [63]. Lyu et al. reported anticancer activities of paeonol, a principal active component found root bark of Paeonia suffruticosa Andr. Cortex (Paeoniaceae) and Cyndium paniculatum K. Schum Radix (Apocynaceae) [64]. Paeonol treatment (0.1, 0.2, 0.4 mg/mL for 48 h) inhibited proliferation, invasion, migration and induced apoptosis against BGC823 cells. The protein expression of matrix metalloproteinase (MMP)-2 and MMP-9 were attenuated in a concentration-dependent manner by paeonol. Pseudolaric acid B inhibited cell proliferation and induced apoptosis of SGC-7901/ADR cells, a multidrug-resistant gastric cancer cell line [65]. Pseudolaric acid B is a diterpene acid isolated from Pseudolarix, the dried root bark of Pseudolarix kaempferi Gorden Cortex (Pinaceae). The study revealed that p53 and Bax were activated while the expressions of P-glycoprotein (P-gp), cyclooxygenase 2 (COX-2), Bcl-2 and Bcl-xl were inhibited. Downregulation of phosphorylated Akt, Bcl-2 and upregulation of caspase-3 and Bax were detected. Thymol is a phenolic compound isolated from Thymus quinquecostatus Celak. (Lamiaceae) that possesses anti-inflammatory, anticancer, antibacterial, and more biological efficacies [66]. Thymol showed cytotoxicity on AGS cancer cells via intrinsic mitochondrial pathway when treated at doses of 100, 200, 400 μM for 6, 12 and 24 h. It upregulated Bax, PARP expressions and promoted cleavage of caspase-7, caspase-8 and caspase-9 and downregulated ΔΨm. The anticancer potencies of toosendanin (TSN), a triterpenoid extracted from Melia toosendan Sieb et Zucc Cortex et Fructus (Meliaceae), was discussed in two studies. According to Wang et al., SGC-7901 treated with 0.5 or 1 μM TSN solution for 24, 48 h demonstrated a dose-dependent increase of cells undergoing early apoptosis [67]. Following facilitation of microRNA 200a, or miR-200a, a microRNA that targets β-catenin, TSN inactivated the β-catenin pathway in SGC-7901 cells and subsequently induced apoptosis. Moreover, the compound inhibited migration, invasion and TGF-β1-induced epithelial-mesenchymal transition (EMT). Similarly, Zhou et al. reported that TSN inhibited cell proliferation and induced caspase-dependent apoptosis via the p38 MAPK signaling pathway [68]. Incarvillea compacta has been used to treat stomach disease in Tibet for many years. Incarvillea compacta Radix extract (5, 10, 20 μg/mL) was treated on EBV-positive AGS cells for 24 h. Apoptosis was induced by disruption of mitochondrial membrane potential, activation of Bax, and inactivation of Bcl-2. Arsenic sulfide, a compound of natural mineral realgar [69], induced apoptosis of human gastric cancer AGS and MGC-803 cells. Expression levels of p53 and murine double minute 2 (MDM2) expression were elevated, and proteins mediating the intrinsic pathway of apoptosis were regulated. Kapoor and Dharmesh reported that peptic oligosaccharide separated from Solanum lycopersicum L. (Solanaceae) induced apoptosis by suppressing galectin-3 expressions [70]. Additionally, several natural products retarded tumor growth in animal models (Table 2). Wu et al. revealed that phenolic alkaloids of Menispermum dauricum induced apoptosis and suppressed gastric tumor growth by inducing apoptosis and inhibiting onco- genic Kirsten Rat sarcoma viral oncogene homolog (K-RAS) expression [42]. Xenograft mice treated with trifolirhizin, DDMN or arsenic trioxide developed smaller tumors compared to the control group [44, 48, 69]. When BALB/C mice grafted with MFC mouse gas
tric cancer cells were treated curcumin solution every day for 60 days, expressions of interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), granzyme B, and perforin were upregulated while differentiated embryonic chondrocyte gene 1 (DEC1), hypoxia-inducible factor-1 alpha (HIF-1α), STAT3 and VEGF expressions were downregulated in the experimental group [71]. When MKN45 treated BALB/ca mice were treated with LicA, tumor growth was significantly inhibited in contrast to the vehicle group without LicA treatment [53]. Elemene retarded tumor growth in nude mice and showed better efficacy when synergized with PD98059 [61]. In a xenograft mouse model, mice treated with grifolin survived for a longer period compared to the control group [62].
Table 1. Apoptosis-inducing natural compounds in vitro.

| Classification       | Compound/ Extract | Source                        | Experimental Model | Dose; Duration | Efficacy        | Mechanism                                                                 | References |
|----------------------|-------------------|-------------------------------|--------------------|----------------|----------------|---------------------------------------------------------------------------|------------|
| Alkaloids            | Berberine         | (family: Ranunculaceae)       | SGC-7901           | 5, 10, 20 µM; 24, 48 h | Induction of apoptosis | ↑c-caspase-3, Bax ↓Bcl-2                                                  | [38]       |
| Alkaloids            | Cyclovirobuxine D | (family: Buxaceae) Buxus microphylla Richardii Radix | MGC-803, MKN-28 | 30, 60, 120 µM/L; 48 h | Induction of apoptosis  | ↑RBBP4, caspase-3, -8, p53, Bax ↓ΔΨm                                  | [39]       |
| Alkaloids            | GFG-3a            | (family: Meripilaceae) Grifola frondose (Diks.) Gray Mycelia | SGC-7901           | 100, 200 µg/mL; 24, 48 h | Induction of apoptosis | ↑caspase-3, cyt c, Endo G, AIF, Smac/Diablo, ROS ↓ΔΨm                  | [40]       |
| Alkaloids            | Melittin          | (family: Apidae) Apis cerena Fabricius venom | SGC-7901           | 4 µg/mL; 1, 2, 4 h | Induction of apoptosis | ↑Bax, caspase-3 ↓J-K-RAS                                             | [41]       |
| Alkaloids            | Phenolic alkaloids | (family: Menispermaceae) Menispermum dauricum DC. Rhizoma | SGC-7901           | 5, 10, 20 µM; 24h | Induction of apoptosis  | ↑ROS, caspase-3 ↑ΔΨm, Bcl-2                                            | [42]       |
| Alkaloids, Terpenoids | Berberine, d-Limonene | (family: Ranunculaceae) Coptidis japonica Makino Rhizoma | MGC-803           | (1) 20 µM; 24, 36, 48 h  | Induction of apoptosis  | ↑ROS, caspase-3 ↑ΔΨm, Bcl-2                                           | [43]       |
| **Fructus** |
|----------------|
| | **Flavonoids** |
| | **Trifolirhizin**  |
| | *(family: Fabaceae)* *Sophora flavescens* Aiton *Radix*  |
| | MKN-45  |
| | 20, 30, 40 µg/mL; 48 h  |
| | Induction of apoptosis  |
| | ↑caspase-9, -3, c-PARP, p53, p38  |
| | ↓EGFR, CDC2, cyclin B, ΔΨm  |
| | [44]  |
| | **Phytosterols** |
| | **Ginsenoside – Rh2**  |
| | *(family: Araliaceae)* *Panax ginseng* C.A. Mey *Radix*  |
| | SGC-7901  |
| | 5, 10, 20 µg/mL; 24, 48 h  |
| | Induction of apoptosis  |
| | ↑Bax ↓Bcl-2  |
| | [45]  |
| | **Phytosterols** |
| | **Periplocin**  |
| | *(family: Apocynaceae)* *Periplocae septium* Bunge.  |
| | SGC-7901, MGC-803, BGC-823  |
| | 50, 100, 200 ng/mL; 24, 48 h  |
| | Induction of apoptosis  |
| | ↑Mcl-1, c-caspase-3, EGR 1  |
| | ↓pro-Bid, p-ERK 1/2  |
| | [72]  |
| | **Phytosterols** |
| | **Tanshinone IIA**  |
| | *(family: Lamiaceae)* *Salviae miltiorrhiza* Bunge. *Radix*  |
| | AGS  |
| | 2.0, 3.7, 5.5 µg/mL; 24, 48 h  |
| | Induction of apoptosis  |
| | ↑Mcl-1, c-caspase-3, EGR 1  |
| | ↓pro-Bid, p-ERK 1/2  |
| | [46]  |
| | **Polyphenols** |
| | **[6]-Gingerol**  |
| | *(family: Zingiberaceae)* *Zingiber officinale* Roscoe *Rhizoma*  |
| | AGS  |
| | 100, 250 µM; 24 h  |
| | Induction of apoptosis  |
| | ↑cyt c, Bax ↓Bcl-2  |
| | [47]  |
| | **Polyphenols** |
| | **2,7-dihydroxy-3-methylanthaquinone (DDMN)**  |
| | *(family: Rubiaceae)* *Hedyotis diffusa* Wild *Herba*  |
| | SGC-7901  |
| | 10, 20, 40 µM; 48 h  |
| | Inhibition of proliferation  |
| | ↑Bax, Bad, caspase-3, -9, cyt c ↓Bel-xL, Bel-2  |
| | [48]  |
| | **Polyphenols** |
| | **6, 7, 30-trimethoxy-3, 5, 40-trihydroxy flavone (TTF)**  |
| | *(family: Saxifragaceae)* *Chrysosplenium nudicaule* Ledeb *Herba*  |
| | SGC-7901  |
| | 2, 4, 8, 16, 32 µg/mL; 24, 48, 72 h  |
| | Induction of apoptosis  |
| | ↑endogenous Ca2+ / Mg2+ dependent endonuclease  |
| | [49]  |
| | **Polyphenols** |
| | **Curcumin**  |
| | *(family: Zingiberaceae)* *Curcuma longa* L. *Rhizoma*  |
| | SGC-7901, BGC-823  |
| | 5, 10, 15, 20, 40 µM/L; 24 h  |
| | Induction of apoptosis  |
| | ↓XIAP ↑miR-33b  |
| | [50]  |
| Polyphenols                  | Esculetin                           | SGC-7901, MGC-803, BGC-823 | 12.5, 25, 50 μM; 24 h | Induction of apoptosis | ↑ROS, c-caspase-9, -3, c-PARP, cyt c, Bak, Bax, CypD ↓Bcl-2, Bcl-xL, XIAP |
|-----------------------------|-------------------------------------|----------------------------|------------------------|------------------------|-----------------------------------------------------------------------|
| Polyphenols                 | Hydroxysafflor Yellow A             | BGC-823                    | 100 μM; 48 h           | Induction of apoptosis  | ↑caspase-3, PPARγ                                                       |
| Polyphenols (combined with TRAIL) | Kurarinone                         | SGC-7901                   | 5 μM; 24 h             | Enhancement of TRAIL-induced apoptosis | ↓Mcl-1, c-FLIP, p-STAT3                                                 |
| Polyphenols                 | Licochalcone A                      | MKN-45, SGC-7901           | 15, 30, 60 μM; 24 h    | Inhibition of cell proliferation and tumor glycolysis | ↑c-caspase-3, c-PARP ↓Bcl-2, Mcl-1, HK2, p-Akt, p-ERK1/2, p-S6, p-GSK3β |
| Polyphenols                 | Ophiopogonin B                      | SGC-7901                   | 5, 10, 20 μM           | Induction of apoptosis  | ↑ROS, Bax, caspase-3 ↓p-ERK 1/2, p-JNK 1/2, ΔΨm, Bcl-2               |
| Polyphenols                 | Phloretin                           | AGS                        | 4, 8, 16 μM; 24 h      | Induction of apoptosis  | ↑Bax ↓Bcl-2                                                             |
| Polyphenols                 | Podophyllotoxin                     | AGS                        | 200, 400, 600, 800, 1000 μg/mL; 24 h | Induction of apoptosis  | ↓ZNF703                                                               |
| Terpenoids                  | 7-Acetylsinumaximol B               | NCI-N87                    | 4, 8, 16 μM; 24 h      | Induction of apoptosis  | ↑Bad, Bim, Bax, cyt c ↓p-Bad, Mcl-1, Bcl-2 |
| Terpenoids | Name | Family | Cells | Concentration | Induction | References |
|------------|------|--------|-------|---------------|-----------|------------|
| Terpenoids | Crosolic Acid | (family: Actinidiaceae) Actinidia valvata Dunn | BGC-823 | 20, 40, 80 μg/mL; 72 h | Induction of apoptosis | ↑Bax, smac, IxBa ↓Fas, Bcl-2, p65, p-IxBa, NF-κB [58] |
| Terpenoids | Curcuzedoalide / Methanol extract | (family: Zingiberaceae) Curcuma zedoaria Roscoe | AGS | 100, 200 μM; 24 h | Induction of apoptosis | ↑c-caspase-8, -9, -3, c-PARP [59] |
| Terpenoids | Deacetylisovaltratum | (family: Caprifoliaceae) Patrinia heterophylla Bunge. | (1) AGS (2) HGC-27 | (1) 4, 8, 16 μM; 24 h (2) 10, 20, 30 μM; 24 h | Induction of apoptosis | ↑p21, caspase-3, c-PARP ↓p-STAT3, procaspase-9, ΔΨm [60] |
| Terpenoids | Elemene | (family: Zingiberaceae) Curcuma zedoaria Roscoe | BGC-823 | 20, 40, 80, 160 μg/mL; 24 h | Induction of apoptosis | ↑Bax, p-ERK 1/2 ↓Bcl-2 [61] |
| Terpenoids | Grifolin | (family: Albatrellaceae) Albatrellus confluens (Alb. & Schwein.) Kotl. & Pouzar | BGC-823, SGC-7901 | 10, 50 μM; 48 h | Induction of apoptosis | ↑caspase-9, -3, CDKN2 ↓MEK1, MEKK3, MEK5 [62] |
| Terpenoids | N-butylideneephthalide | (family: Apiaceae) Angelica Sinensis Diels | AGS | 25, 50, 75 μg/mL; 24 h | Induction of apoptosis | ↑REDD1 ↓mTOR [63] |
| Terpenoids | Paeonol / extract | (family: Paeoniaceae) Paeonia suffruticosa Andr Root bark, (family: Apocynaceae) Cynanchum paniculatum K. Schum | BGC-823 | 0.1, 0.2, 0.4 mg/mL; 24, 48 h | Inhibition of proliferation, invasion, and migration Induction of apoptosis | ↓MMP-2, -9 [64] |
| Terpenoids | Pseudolaric acid B | (family: Pinaceae) Pseudolarax kaempferi Gorden Root bark | SGC-7901/ADR | 5, 10, 20 μM/L; 24 h | Induction of apoptosis | ↑p53, Bax | ↓P-gp, COX-2, Bcl-2, Bcl-xL |
|------------|------------------|-------------------------------------------------|--------------|-------------------|----------------------|-----------|-----------------|
| Terpenoids | Thymol | (family: Lamiaceae) Thymus quinquecostatus Celak Essential oil | AGS | 100, 200, 400 μM; 6, 12, 24 h | Induction of apoptosis | ↑Bax, c-PARP, caspase-8, caspase-7, caspase-9 | ↓ΔΨm |
| Terpenoids | Toosendanin | (family: Meliaceae) Melia toosendan Sieb et zucc Cortex or Fructus | SGC-7901 | 0.5, 1 μM; 48 h | Inhibition of invasion, migration and EMT | Induction of apoptosis | ↑E-cadherin | ↓β-catenin | ↑miR-200a |
| Terpenoids | Toosendanin | (family: Meliaceae) Melia toosendan Sieb et Zucc Cortex or Fructus | (1) AGS (2) HGC-27 | (1) 0.5, 1, 2 μM; 48 h (2) 0.5, 1, 2 μM; 36 h | Inhibition of proliferation | Induction of apoptosis | ↑c-caspase-3, -8, -9, c-PARP, Bax, p-p38 | ↓Bcl-2, Bcl-xL, Mcl-1, survivin, XIAP |
| Arsenic sulfide | Realgar | (family: Solanaceae) Solanum lycopersicum L. | AGS, MGC-803 | 0.31, 0.62, 1.25, 2.5, 5, 10 μM; 24, 48, 72 h | Induction of apoptosis | ↑p53, Bax, MDM2 | ↓ΔΨm, Bcl-2 |
| Pectic oligosaccharide | | (family: Solanaceae) Solanum lycopersicum L. | AGS | 10, 20, 30 μg/mL; 48 h | Induction of apoptosis | ↓Galectin-3 |

Bax, Bcl-2 like protein 4; ΔΨm, mitochondria membrane potential; c-caspase-3, cleaved caspase-3; Bcl-2, B-cell lymphoma 2; RBBP4, retinoblastoma-binding protein 4; Bad, Bcl-2 associated agonist of cell death; RUVBL1, RubA like AAA ATPase 1; NPM, Nucleophosmin 1; PI3K, Phosphoinositide 3-kinase; Akt1, protein kinase B 1; cyp c, cytochrome c; Endo G, endonuclease G; AIF, apoptosis inducing factor; ROS, reactive oxygen species; K-RAS, Kirsten rat sarcoma viral oncogene homolog; c-PARP, cleaved poly ADP ribose polymerase; EGFR, epidermal growth factor receptor; CDC2, cell division control protein 2; Mcl-1, Myeloid cell leukemia-1; EGR 1, Early growth response protein 1; p-ERK1/2, phosphorylated extracellular-signal-regulated kinase 1/2; TNF-α, tumor necrosis factor-alpha; Fas, fasciculin; p-JNK, phosphorylated Jun N-terminal protein kinase; Bcl-xL, B-cell lymphoma-extra large; XIAP, X-linked inhibitor of apoptosis protein; miR-33b, micro RNA-33b; IFN-γ, interferon gamma; DEC1, differentiated embryonic chondrocyte gene 1; HIF-1α, hypoxia-inducible factor-1 alpha; STAT3, Signal transducer and activator of transcription 3; VEGF, Vascular endothelial growth factor; c-caspase-9, cleaved caspase-9; CyP2D, Cyclophilin D; PPARγ, Peroxisome proliferator-activated receptor gamma; c-FLIP, Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; p-STAT3, phospho-STAT3 transducer and activator of transcription 3; HK2, hexokinase 2; p-S6, phosphorylated S6; p-SK3β, phosphorylated glycogen synthase kinase 3 beta; ZNF703, Zinc Finger Protein 703; Bin, Bcl-2-like protein 11; p-Bad, phosphorylated Bad; IκBα, inhibitor of nuclear factor kappa B-α; p-IκBα, phospho-inhibitor of nuclear factor kappa B-α; NF-κB, nuclear factor kappa-B; MEK1, mitogen activated protein kinase 1; MEKK3, mitogen activated protein kinase kinase 3;
| Classification | Compound/ Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | References |
|----------------|------------------|--------|-------------------|---------------|----------|-----------|------------|
| Alkaloids      | Phenolic alkaloids | (family: Menispermaceae) Menispermum dauricum DC. Rhizoma | Nude mice / SGC-7901 | 5, 10, 20 mg/kg/week; 3 weeks | Suppression of tumor growth | | [42] |
| Flavonoids     | Trifolirhizin     | (family: Fabaceae) Sophora flavescens Aiton. Radix | BALB/C nude mice / MKN-45 | 1-3 mg/kg; 3 weeks | Retardation of tumor growth | ↑c-caspase-3 ↓ΔΨm | [44] |
| Polyphenols    | 2,7-dihydroxy-3- methylanthraquinone (DDMN) | (family: Rubiaceae) Hedyotis diffusa Wild. Herba | nude mice / SGC-7901 | 40 mg/kg; 5, 10, 15, 20 days | Inhibition of gastric cancer cell growth | ↑Bax, Bad, c-caspase-3, -9, cyt c ↓Bcl-xL, Bcl-2 | [48] |
| Polyphenols    | Curcumin         | (family: Zingiberaceae) Curcuma longa L. Rhizoma | BALB/C mice / MFC | 20, 40, 60 μM/L/day; 60 days | Inhibition of tumor growth Induction of apoptosis Activation of immune cells | ↑IFN-γ, TNF-α, granzyme B, perforin ↓DEC1, HIF-1α, STAT3, VEGF | [71] |
| Polyphenols    | Licochalone A    | (family: Fabaceae) Glycyrrhiza glabra L. Radix | BALB/ca nude mice / MKN-45 | 10 mg/kg/day; 33 days | Inhibition of tumor growth | | [53] |
| Terpenoids     | Elemene          | (family: Zingiberaceae) Curcuma longa L. Rhizoma | BALB/c athymic nude mice / BGC-823 | 200 mg/kg/day; 15 days | Retardation of tumor growth | | [61] |
| Terpenoids     | Grifolin         | (family: Albatrellaceae) Albatrellus confluens (Alb. & | Balb/c nude mice / BGC-823, SGC- | 15 mg/kg; 2 days | Improvement of survival time | | [62] |
| Arsenic sulfide | Realgar | BALB/c-nu/nu mice / MGC-803 | 1, 2 mg/kg; 3 weeks | Induction of apoptosis | ↑p53 | [69] |
|----------------|---------|-----------------------------|-------------------|----------------------|------|------|

*c-caspase-3, cleaved caspase-3; ΔΨm, mitochondria membrane potential; Bax, Bcl-2 like protein 4; Bcl-2, B-cell lymphoma 2; Bad, Bcl-2 associated agonist of cell death; Bcl-xL, B-cell lymphoma-extra large; cyt c, cytochrome c; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor-alpha; DEC1, differentiated embryonic chondrocyte gene 1; HIF-1α, hypoxia-inducible factor-1 alpha; STAT3, Signal transducer and activator of transcription 3; VEGF, Vascular endothelial growth factor.*
2.1.2. Natural plant extracts inducing apoptosis in gastric cancer

Several have been studies demonstrated that natural product extracts of plant or animal sources induced apoptosis against gastric cancer cells and inhibited tumor growth of xenograft animals (Table 3, 4). Acetonic extracts of the endolithic fungus EL002332 isolated from *Rhizus nigrum* L. (Saxifragaceae) showed selective cytotoxicity against AGS human gastric cancer cells [74]. Liu et al. reported that the polyphenol-rich extract of *Rhizus nigrum* L. (Saxifragaceae), or black currant, induced apoptosis of MKN-45 cells via MAPK- and PI3K/Akt-mediated mitochondrial pathways [75]. *Euphorbia lanulata* Bunge. (Euphorbiaceae) ethanol and n-hexane extract was processed to 10, 20, and 40 μg/mL solutions and applied to SGC-7901 and ADR cells for 24 h [76]. The solution increased the expression of Bax, caspase-3, caspase-8, and caspase-9, and suppressed the expression of Bcl-2, thereby inducing apoptosis. Xie et al. reported that treatment of ethanololic extract of *Cordyceps cicaeae* (Miq.) Massae. (EEC), a member of the *Cordyceps* genus, induced death-receptor mediated and mitochondria-mediated apoptosis [77]. Hao et al. reported that ethanol extract of *Smilax glabra* Roxb. (Smilacaceae) induced apoptosis by regulating Akt-mediated signaling pathways [78]. The root extract of Chinese tonic herb *Astragalus cornus* mass L. *radix* (Cornaceae) contains astragalosides, flavonoids and polysaccharides [79]. Wang et al. demonstrated that *astragalus* induced apoptosis by inhibiting the IL-6/STAT3 signaling pathway. SGC-7901 gastric cancer cells treated with *astragalus* extract (AE) showed down-regulation of interleukin-6 (IL-6) and STAT3. To investigate the efficacy of AE in vivo, AE (60 or 120mg/kg, daily) was treated to mice implanted with SGC-7901 cells. Jeong et al. investigated that anticancer effects of *Saururus chinensis* (Lour.) Baill (Saururaceae) ethanol extract against gastric cancer cell line AGS and NCI-N87 via caspase-dependent apoptosis through mitochondria membrane depolarization and activates JNK and p38 [80]. Kim et al. reported that *Sophora flavescens* Ait. *Radix* (Leguminosae/Fabaceae) inhibited proliferation and induced apoptosis of AGS cells by mitochondrial- and caspase-dependent apoptosis [81]. Activation of Fas and FasL, and caspase-3 were detected. *Suertia muscotti* Franch. (Gentianaceae) extract showed anti-proliferative effect and induced mitochondria-dependent apoptosis via depolymerization of cytoskeletal filaments, disrupted ΔΨm, and increased cytoplasmic levels of ROS [82]. Hosseini et al. studied the apoptotic ability of *Cornus mas* L. *Bulbus* (Cornaceae) extract against AGS cells in comparison with mouse fibroblast cell line, L929 [34]. Ghasemi et al. treated *Urtia dioica* radix (Urticaceae) hydroalcholohic extract on MKN-45 cell line (32, 125, 500 μg/mL for 24 h) [35]. The extract induced apoptosis of tumor cells by inducing ROS formation and lipid peroxidation. Nagbere et al. reported that *Aster incises* Fisch. (Asteraceae) induced mitochondria-related apoptosis in AGS cells [83]. The expression levels of pro-apoptotic proteins such as Bak, BH3 interacting-domain death agonist (Bid), Bad, AIF, cytochrome c, cleaved caspases and cleaved PARP were significantly upregulated. Levels of anti-apoptotic proteins such as FLIP, Bcl-2 and Bcl-xL were lowered. Kustiawan et al. discovered that the methanol extract of *Trigona incisa* propolis represented cytotoxic activity to the human gastric cancer cell line, KATO-III [83]. Methanol extract of *Schizandra chinensis* Baill Fructus (Schisandraceae) was treated to AGS cells at the dose of 100, 200, 300, or 400 μg/mL for 24 h [84]. The extract induced apoptotic cell death and generated ROS via mitochondria- and caspase-dependent pathways, elevating Bax, caspase-3, and caspase-9 expressions and inhibiting Bcl-2 expression. It is suggested that c-Jun N-terminal kinase and p38 MAPK pathway is also involved. Study by Zhang et al. indicated that trichloromethane fractions of *Incarvillea compacta* Maxim. *Radix* (Bignoniaceae) inhibited the proliferation of EBV-positive AGS cells (AGS-EBV) by inducing EBV lytic replication and apoptosis [85]. Aqueous extract of *Euphorbia esula* Latex (Euphorbiaceae) promoted caspase dependent apoptosis regulated by Bax and Bcl-2 family [86]. 5, 10, 20, 40, 80, 160 mg/L extract was treated on SGC-7901 human gastric cancer cells for 24, 48 h. The activity of caspase-8 and caspase-3 increased 1.73-fold and 1.98-fold, respectively. Additionally, efficicicy of *Astragalus membraneus* Fisch. *Radix* (eguminosae/Fabaceae) was also studied in vivo model (Table 4) [79]. Xenograft nude mice injected SGC-7901 cells developed tumors of lesser size compared to mice only injected the vehicle.
| Compound/Extract                  | Source                  | Experimental Model | Dose; Duration | Efficacy                                      | Mechanism                              | Reference |
|----------------------------------|-------------------------|--------------------|----------------|----------------------------------------------|----------------------------------------|-----------|
| Acetone extract                  | EL002332                | AGS                | 5 µg/mL; 24 h  | Induction of apoptosis                        | ↑Myc, caspase-3, -5, c-PARP ↓Bcl-2       | [74]      |
| Black currant extract (family: Saxifragaceae) | Ribes nigrum L. | MKN-45             | 5, 10, 15, 20, 25 mg/mL; 12, 24, 48 h | Induction of apoptosis                       | ↑Bax, caspase-8, JNK/p38, Fas, FasL ↓ΔΨm, Bcl-2, p-Akt, p-ERK1/2 | [75]      |
| Ethanol and n-hexane extract (family: Euphorbiaceae) | Euphorbia lunulata Bunge. | SGC-7901, ADR | 10, 20, 40 µg/mL; 24 h | Inhibition of the proliferation, migration, and invasion | ↑Bax, caspase-3, -8, -9 ↓Bcl-2 | [76]      |
| Ethanol extract (family: Ascomycota) | Cordyceps cicadae (Miq.) Massee. | SGC-7901 | 200, 400, 800 µg/mL; 48 h | Induction of apoptosis                        | ↑Bax, caspase-3, -6, -8, AIF, p53, Fas ↓Bcl-2, PARP | [77]      |
| Ethanol extract (family: Smilaceae) | Smilax glabra Roxb. Rhizoma | SGC7901 | 10, 20, 30 µM /L; 24 h | Induction of apoptosis                        | ↑caspase-3, Bax ↓p-Akt, Bcl-2          | [78]      |
| Ethanol extract (family: Cornaceae) | Astragalus cornus mass L, radix | SGC-7901 | 25, 50, 100 µg/mL; 3 days | Induction of apoptosis                        | ↑Bax ↓IL-6, STAT3                      | [79]      |
| Ethanol extract (family: Saururaceae) | Saururus chinensis (Lour.) Baill. | AGS, NCI-N87 | 25, 50 µg/mL; 1, 3, 6, 24, 30, 48 h | Induction of apoptosis                        | ↑Bax, c-PARP, p-p38, p-JNK ↓ΔΨm, Bcl-2 | [80]      |
| Ethanol extract (family: Leguminosae/Fabaceae) | Sophora flavescens Ait. Radix | AGS | 20, 40, 60, 80, 100, 200 µg/mL; 24 h | Induction of apoptosis                        | ↑Fas, FasL, caspase-3                  | [81]      |
| Ethanol extract (family: Gentianaceae) | Swertia mussotti Franch. | MGC-803, BGC-823 | 300, 600, 900 µg/mL; 24 h | Induction of apoptosis                        | ↑ROS ↓ΔΨm                              | [82]      |
| Extraction Method                      | Plant Family                      | Plant Name                          | Cell Line | IC₅₀ Values | Induction of Apoptosis / Necrosis                                                                 | Ref. |
|---------------------------------------|-----------------------------------|-------------------------------------|-----------|-------------|------------------------------------------------------------------------------------------------|------|
| Ethanol, water extract                | (family: Cornaceae)               | Cornus mas L. Bulbus                | AGS       | IC₅₀ 5.44 mg/mL; 48 h  IC₅₀ 2.44 mg/mL; 72 h | Induction of apoptosis and necrosis                                                            | [34] |
| Hydroalcoholic extract                | (family: Urticaceae)              | Urtia dioica radix                  | MKN-45    | 32, 125, 500 µg/mL; 24 h | Induction of apoptosis                                                                         | [35] |
| Methanol extract                      | (family: Asteraceae)              | Aster incises Fisch. *              | AGS       | 80, 100, 140 µg/mL; 24 h | Induction of apoptosis                                                                         | [87] |
| Methanol extract                      | Propolis produced by              | Trigona incisa                      | KATO-III  | IC₅₀ 6.06 ± 0.39 µg/mL; 48 h | Induction of cytotoxicity                                                                       | [83] |
| Methanol extract                      | (family: Schisandraceae)          | Schizandra chinensis Baill Fructus  | AGS       | 100, 200, 300, 400 µg/mL; 24 h | Induction of apoptosis                                                                         | [84] |
| Trichloromethane fractions / Ethanol extract | (family: Bignoniaceae)          | Incarvillea compacta Maxim. Radix   | AGS-EBV   | 5, 10, 20 µg/mL; 24 h | Induction of lytic cytotoxicity and apoptosis                                                  | [85] |
| Water extract                         | (family: Euphorbiaceae)           | Euphorbia esula Latex               | SGC-7901  | 5, 10, 20, 40, 80, 160 mg/L; 24, 48 h | Induction of apoptosis                                                                         | [86] |

c-PARP, cleaved poly ADP ribose polymerase; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 like protein 4; Fas, fasciclin; FasL, Fas ligand; ΔΨm, mitochondria membrane potential; p-Akt1, phosphorylated protein kinase B1; p-Erk1/2, phosphorylated extracellular-signal-regulated kinase 1/2; AIF, apoptosis inducing factor; PARP, poly ADP ribose polymerase; IL-6, interleukin-6; STAT3, Signal transducer and activator of transcription 3; p-p38, phosphorylated p38; p-JNK, phosphorylated Jun N-terminal protein kinase; ROS, reactive oxygen species; Bid, BH3 interacting-domain death agonist; Bak, Bcl-2 antagonist/killer 1; cyt c, cytochrome c; Bcl-xL, B-cell lymphoma-extra large.*The part of the plant used in this was not mentioned in the study.
Table 4. Apoptosis-inducing natural product extracts *in vivo*.

| Compound/ Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | Reference |
|-------------------|--------|---------------------|----------------|----------|-----------|-----------|
| Ethanol extract   | (family: Leguminosae/Fabaceae) Astragalus membranaceus Fisch. Radix | nude mice / SGC-7901 | 60, 120 mg/kg; daily, for 3 weeks | Inhibition of tumor growth | ↓VEGF, IL-6 | [79] |

VEGF, Vascular endothelial growth factor; IL-6, interleukin-6
2.1.3. Apoptosis-inducing mixtures in gastric cancer

Four studies discussing decoctions or pills of TCM focused on the apoptosis-inducing abilities of the mixtures (Table 5, 6). Jinlong capsule (JLC) is an effective Traditional Chinese Medicine widely used to treat gastric cancer patients [88]. It was discovered that JLC induces mitochondrial apoptosis of MGC-803 and BGC-823 cells through a cascade-dependent pathway [89]. Xu et al. demonstrated that the TCM decoction Xiao Tan He Wei induces apoptosis against gastric tumors [90]. 1-Methyl-3-nitro-1-nitrosoguanidine (MNNG) was treated to wistar rats and GES-1 cells to induce precancerous lesions of gastric carcinoma in vivo and in vitro. The decoction induced apoptosis of GES-1 cells by inhibiting the NF-κB pathway and showed anti-metastatic efficacy to wistar rats via cell cycle arrest. Yangzhen Sanjie decoction is made from the medicinal herbs Astragalus membranaceus Fisch. Radix (Leguminosae/Fabaceae), Scutellariae barbata D. Don Herba (Lamiaceae), Arisaematis preparatum Fructus Swingle. (Rutaceae), Cremastreae pseudobulbus seu Pleiones. (Orchidaceae), Curcuma longa L. Rhizoma (Zingiberaceae) [91]. The decoction was diluted into a 10% serum and treated to human gastric carcinoma AGS and HS-746T cells for 48 h. The treatment enhanced Let-7a miRNA expression, which leads to the downregulation of c-Myc and consequent promotion of apoptosis in both cell lines. Expression of other microRNAs of the let-7 family were altered as well. So-Cheung-Ryong-Tang consists of 8 herbs: Ephedra sinica Stapf. Radix (Ephedraceae), Schisandrae chinensis Fructus (Turcz.) Baill. (Schisandraceae), Paeonia lactiflora pall. Radix (Paeoniaceae), Pinellia ternate (Thunb.) Breit rhizome (Araceae), Cinnamomum cassia Presl radix (Lauraceae), Zingiber officinale Rosc radix (Zingiberaceae), Asiasarum heterotropoides rhizome (Aristolochiaceae), Glycyrrhiza glabra Fisch. Radix (Fabaceae) Yim et al. reported that So-Cheung-Ryong-Tang showed greater apoptotic ability against AGS and NUGC-3 cells when fermented [92]. In an in vivo approach, tumor weight of the athymic nu/nu mice were subcutaneously injected HCT116 cells was smallest in the group treated with the fermented decoction (Table 6).
Table 5. Apoptosis-inducing mixtures in vitro.

| Compound/Extract            | Source                                                                 | Experimental Model | Dose; Duration | Efficacy                        | Mechanism                                      | References |
|-----------------------------|------------------------------------------------------------------------|--------------------|----------------|---------------------------------|------------------------------------------------|------------|
| Jinlong Capsule             | Bungarus, Agkistrodon, Gecko                                           | MGC-803, BGC-823   | 0.1 0.2, 0.4, 0.8 mg/mL; 24 h | Induction of apoptosis           | ↑Bax, caspase-3 \[Bcl-2, survivin\]              | [89]       |
|                            | *(family: Umbelliferae) Bupleurum falcatum Linne. Radix, (family: Araceae) Pinellia ternata (Thunb.) Makino Rhizoma, (family: Polygonaceae) Poria cocos Wolf., (family: Ranunculaceae) Coptis chinensis Franch., (family: Rubiaceae) Oldenlandia diffusa (Willd.) Roxb. Herba, (family: Compositeae) Taraxaci Herba*, (family: Lauraceae) Cinnamonum cassia J.Presl twig, (family: Polygonaceae) Rhubarb*, (family: Paeoniaceae) Paeonia lactiflora Pall., (family: Leguminosae/Fabaceae) Glycyrrhiza uralensis Fischer.* |                    |                |                                 |                                                 |            |
|                            | **Xiao Tan He Wei decoction**                                          | GES-1              | 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 2.56 g/L; 24, 48, 72, 96 h | Induction of apoptosis            | ↑Bax, c-caspase-3, IkB \[Bcl-2, p65, NF-kB\]     | [90]       |
|                            | *(family: Umbelliferae) Bupleurum falcatum Linne. Radix, (family: Araceae) Pinellia ternata (Thunb.) Makino Rhizoma, (family: Polygonaceae) Poria cocos Wolf., (family: Ranunculaceae) Coptis chinensis Franch., (family: Rubiaceae) Oldenlandia diffusa (Willd.) Roxb. Herba, (family: Compositeae) Taraxaci Herba*, (family: Lauraceae) Cinnamonum cassia J.Presl twig, (family: Polygonaceae) Rhubarb*, (family: Paeoniaceae) Paeonia lactiflora Pall., (family: Leguminosae/Fabaceae) Glycyrrhiza uralensis Fischer.* |                    |                |                                 |                                                 |            |
|                            | **Xiao Tan He Wei decoction**                                          | Wistar rats        | 3.4 mL/kg; 2 weeks | Inhibition of metastasis        | ↑Bax, c-caspase-3, IkB \[Bcl-2, p65, NF-kB\]     | [90]       |
|                            | *(family: Leguminosae/Fabaceae) Astragalus membranaceus Fisch. Radix, (family: Lamiaceae) Scutellariae barbata D.Don Herba, Arisaematis preparatum Citri sarcodactylis Fructus, Cremastreae Tuber*, (family: Zingiberaeae) Curcuma longa L. Rhizoma |                    |                |                                 |                                                 |            |
|                            | **Yangzhen Sanjie decoction**                                          | (1) AGS            | 10% serum; 48 h | Induction of apoptosis          | ↑let-7a ↓c-Myc                                 | [91]       |
|                            | *(family: Ephedraceae) Ephedra sinica Stapf. Radix, (family: Schisandraeae) Schisandra chinensis Fructus (Turcz.) Bail., (family: Paeoniaceae) Paeonia lactiflora pall. Radix, (family: Araceae) Pinellia ternata (Thunb.) Breit Rhizoma, (family: Lauraceae) Cinnamonum cassia Presl radix, (family: Zingiberaeae) Zingiber officinalae Rosc radix, (family: Aistolochiaceae) Astilasarum heterotropoides Rhizoma, (family: Fabaceae) Glycyrhriza glabra Fisch. Radix | |                |                                 |                                                 |            |
|                            | **Fermented So-Cheong-Ryong-Tang**                                     | (2) HS-746T        | 500 μg/mL; 0.5, 1, 3, 6 h | Induction of apoptosis          | ↑caspase-3, -8, -9, c-PARP, cyclin D1, cyclin E1, cyclin B1, p21 \[p-p38, p-ERK, p-JNK\] | [92]       |
|                            | *(family: Ephedraceae) Ephedra sinica Stapf. Radix, (family: Schisandraeae) Schisandra chinensis Fructus (Turcz.) Bail., (family: Paeoniaceae) Paeonia lactiflora pall. Radix, (family: Araceae) Pinellia ternata (Thunb.) Breit Rhizoma, (family: Lauraceae) Cinnamonum cassia Presl radix, (family: Zingiberaeae) Zingiber officinalae Rosc radix, (family: Aistolochiaceae) Astilasarum heterotropoides Rhizoma, (family: Fabaceae) Glycyrhriza glabra Fisch. Radix | |                |                                 |                                                 |            |

* Bax, Bcl-2 like protein 4; Bcl-2, B-cell lymphoma 2; ΔΨm, mitochondria membrane potential; c-Myc, cellular MYC proto-oncogene protein; IkB, inhibitor of nuclear factor kappa. *Taraxaci Herba includes Taraxacum platycarpum H. Dahlstedt, Taraxacum officinalae Weber, Taraxacum mongolicum Handel-Mazzetti, and Taraxacum coreum Nakai. Which species was used was not indicated in the study. *Rhubarb includes Rheum palmatum Linné Radix et Rhizoma, Rheum tanguticum Maximowicz ex Balf. And Rheum officinale Baillon. Which species was used was not indicated in the study. *Chremastreae Tuber includes Cremastrea appendiculata (D.Don) Makino, Pleione bulbocodioides Rolfe, and Pleione yunnanensis Rolfe. The species used in the study was not indicated.
Table 6. Apoptosis-inducing mixtures *in vivo*

| Compound/ Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | Reference |
|-------------------|--------|-------------------|---------------|----------|-----------|-----------|
| Fermented So-Cheong-Ryong-Tang | (family: Ephedraceae) Ephedra sinica Stapf. Radix, (family: Schisandraceae) Schisandra chinensis Fructus (Turcz.) Baill., (family: Paeoniaceae) Paeonia lactiflora pall. Radix, (family: Araceae) Pinellia ternate (Thunb.) Breit rhizoma, (family: Lauraceae) Cinnamomum cassia Presl radix, (family: Zingiberaceae) Zingiber officinale Rosc radix, (family: Aristolochiaceae) Asiasarum heterotropoides rhizoma, (family: Fabaceae) Glycyrrhiza glabra Fisch. Radix | athymic nu/nu mice / HCT116 | 157.5 mg/kg; 14 days | Inhibition of tumor growth | [92] |
2.2. Emerging role of autophagy in gastric cancer treatment mediated by natural products

Autophagy is a cellular process in which cytoplasmic contents are degraded within the lysosome/vacuole, and the resulting constituents are recycled [93, 94]. Autophagy can be classified into macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [95]. Among these, macroautophagy, which has been studied the most, is the process of forming autophagosomes that surround organelles and fuses with lysosomes and natural products modulate autophagy [96]. In addition, autophagy can also be categorized into selective and nonselective autophagy. Based on the isolation target, separate kinds of selective autophagy such as mitophagy, pexophagy, and xenophagy can be distinguished [97]. Macroautophagy consists of several sequential steps: initiation, nucleation, elongation, maturation and fusion with the lysosome [98]. Phagosome originates from omegasome, a subdomain of ER, and associates with other organelles such as mitochondria, golgi complex, plasma membrane, recycling endosome, etc. during its development. Four molecules, Unc-51-like kinase 1/2 (ULK1/2), autophagy-related gene 13 (ATG13), family 200-kD interacting protein (FIP200) and AtG101 form the ULK1/2 complex and initiates the process. The mechanistic target of rapamycin complex 1 (mTORC1) is a major inhibitor of the ULK1/2 complex [93]. AMP-activated protein kinase (AMPK) inhibits mTORC1 and leads to the activation of ULK1/2 complex [98]. The ULK1/2 complex phosphorylates the class III phosphatidylinositol-3-kinase (PI3K) vacuole protein sorting 34 (VPS34) complex consisting of VPS15, Beclin-1 and AtG14 complex, which promotes the formation of phosphatidylinositol-3-phosphate (PI3P), which is an essential lipid molecule required for the nucleation step of the phagophore [99]. PI3P recruits PI3P-binding proteins such as WIPI2B, a protein known to facilitate LC3-lipidation [100]. Formation and expansion of the phagophore is related to the generation of Atg12-5-16L1 complex. Atg12 binds with Atg5 and composes a complex with Atg16L. The Atg12-5-16L1 complex lipidates LC3-I into LC3-II [101, 102]. LC3-II, considered a marker of autophagy, is essential for phagosome elongation and fusion [103, 104]. When the phagosome encloses and becomes a mature autophagosome, it fuses with a lysosome and degradation and recycling process follows (Figure 2).
Figure 2. Natural products regulate molecular mechanism of autophagy. Natural products initiate autophagy by the formation of a pre-autophagosomal structure via association of PI3K-AMPK, mammalian target of rapamycin (mTOR), ULK1, Vps34, and the Beclin-1 complex which contribute to the formation of the pre-autophagosomal structure in addition to activate phagophore formation. Fusion of mature autophagosome as well as lysosome causes autolysosome formation. Lastly, elimination of molecule is happened by acid hydrolases which has been produced nutrients as well as recycling metabolites.

Two single compounds and two plant extracts were reported to induce autophagy along with apoptosis against gastric cancer cells (Table 7). Rottlerin, extracted from Mallotus philipensis Muell (Euphorbiaceae), induced autophagy and caspase independent apoptosis against SGC-7901 and MGC-803 cells [105]. Autophagy is induced by down-regulating mTOR and S-phase kinase-associated protein 2 (Skp2). 3-O-β-D-galactopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyl-28-O-[α-L-arabinopyranosyl-(1→4)-α-L-arabinopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranosyl] quillaic acid is an oleanane-type triterpenoid saponin extracted from Adenophora triphylla var. japonica H. (Campanulaceae) [106]. Morus alba root extract, contain oxyresveratrol, has been found to accumulate ROS production and initiated autophagic and apoptotic cell death via FOXO-caspase-3 pathway [107, 108]. It has been demonstrated that cytotoxic activity on AGS, MKN-45 and KATO-III human gastric cancer cells via induction of caspases activation and autophagy via Akt/NF-κB pathway in AGS cells. Chen et al. demonstrated the anti-cancer activity of the ethanol and ligarine based extract of the tuber of Amorphophallus konjac K. Koch Tuber (Araceae) against SGC-7901 and AGS cells (IC₅₀ of 35-45 μg/mL) [109]. Flux analysis of autophagy and increase of the level of LC3-II revealed induction of autophagy by the tuber of A. konjac. G0/G1 phase cell cycle arrest has detected by flow cytometry. Chen et al. determined apoptosis- and autophagy-inducing effects of kangfuxin, an organic extract of Periplaneta
americana Linnaeus. (Blattidae), against SGC-7901 cell line [110]. Proteins that mediate ER stress mediated apoptosis including glucose-regulated protein 78 (GRP78), C/EBP-homologous protein (CHOP) and caspase-12 has been greatly upregulated in the group treated kangfuxin. Transmission electron microscopy (TEM) image results has been shown much more autophagosomes compared with the control. In addition, the LC3-I/LC3-II ratio and expression levels of Beclin-1 were also higher in the kanfuxin group. Additionally, Natural plant extracts of Saussurea lappa Clarke, Dioscorea nipponica Makino, and Melandrium firmum has been found to induce anti-proliferative as well as apoptotic function [111-113]. Therefore, autophagy induction by natural products might possibly be targeted as a potential therapeutic approach to control gastric cancer.
| Classification     | Compound/Extract                      | Source                                      | Experimental Model | Dose; Duration | Mechanism          | References |
|--------------------|---------------------------------------|---------------------------------------------|--------------------|----------------|--------------------|------------|
| Polyphenol         | Rottlerin                             | *(family: Euphorbiaceae)* Mallotus philipensis Muell. | SGC-7901, MGC-803 | 2, 4, 8 µM; 24 h | ↑LC3-II, ↓mTOR, Skp2 | [105]      |
|                    |                                       |                                             |                    |                |                    |            |
| Terpenoid          | 3-O-β-D-galactopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyl-28-O-[α-L-arabinopyranosyl-(1→4)]-α-L-arabinopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranosyl] quillaic acid | *(family: Campanulaceae)* Adenophora triphylla var. japonica H. | AGS, MKN-45, KATO III | 10, 20, 30 µM; 24 h | ↑p-JNK, p-p38, p-AMPK, Bax, cyt c, caspase-3, c-PARP1, LC3-II, ↓p-ERK, p-Akt, p-mTOR, NF-κB, COX-2, Cyclin D1, VEGF, Bcl-2, Bid | [106] |
| Organic extract    |                                       | *(family: Araceae)* Amorphophallus konjac K. Koch Tuber | SGC-7901, AGS      | 50 µg/mL; 24 h | ↑Bax, c-caspase-9, LC3-II, ↓survivin, Bcl-2 | [109] |
| Organic extract    |                                       | *(family: Blattidae)* Periplaneta americana Linneaus. | SGC-7901           | 0.1, 1 µg/mL; 48 h | ↑GRP78, CHOP, caspase-12, LC3-II/LC3-I, Bax | [110] |

p-JNK, phosphorylated Jun N-terminal protein kinase; p-p38, phosphorylated p38; p-AMPK, phosphorylated 5’ AMP-activated protein kinase; Bax, Bcl-2 like protein 4; p-ERK, phosphorylated extracellular signal-regulated kinase; p-Akt, phosphorylated protein kinase B; p-mTOR, phosphorylated mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; COX-2, cyclooxygenase 2; VEGF, vascular endothelial growth factor; Bcl-2, B-cell lymphoma 2; Skp2, S-phase kinase-associated protein 2; GRP78, glucose-regulated protein 78; CHOP, C/EBP-homologous protein.
2.3. Role of natural products to arrest cell cycle in gastric cancer

The cell cycle is regulated through a series of control systems that in turn promote or inhibit cell division. Programmed cell death and cell cycle regulation occur together in many cancerous cells since the tumor suppressor gene p53 and downstream proteins regulate both events [114]. A variety of natural substances were described as causing cell death and inhibited cell proliferation by seizing the cell cycle according to the phase of cell cycle arrest (Table 8). The studies performed cell cycle analysis through flow cytometry to observe cell cycle distribution, albeit the proteins responsible for the event were not confirmed in a large portion of the investigations. Berberine, TTF, ginsenoside-Rh2, crosolic acid, rottlerin, grifolin, methanol extract of aster incises (Asteraceae), organic extract of Amorphophallus konjac K.Koch Tuber (Araceae), and xiao tan he wei decoction induced G0/G1 phase cell cycle arrest [38, 45, 49, 58, 62, 87, 90, 105, 109]. Toosendanin increased the proportion of cells in the G1 and S phase [67, 68]. cyclovirobuxine D, GFG-3a, ethanol extract of Cordyceps cicadae Massee. (Ascomycota) and Swertia mussotti Franch. (Gentianaceae) induced S phase cell cycle arrest [39, 40, 77, 82]. Deacetylisovaltratum, Euphorbia lunulate (Euphorbiaceae) extract, phloretin, trifolirhizin, and tanshinone IIA triggered G2/M phase cell cycle arrest [44, 46, 55, 60, 76]. Jinlong Capsule halted the cell cycle in S and G2/M phase [89]. C. cicadae extract was reported to decrease concentrations of cyclin E/CDK2 complex and cyclin A/CDK2 complex [77]. Tanshinone-IIA inhibited the expressions of CDC2, cyclin A and cyclin B1 [46].
| Phase of cell cycle arrest | Classification | Compound/Extract | Source | Experimental Model | Dose; Duration | Mechanism | References |
|---------------------------|----------------|-----------------|--------|--------------------|----------------|-----------|------------|
| G0/G1                     | Alkaloids      | Berberine       | (family: Ranunculaceae) *Coptidis japonica* Makino Rhizoma | SGC-7901 | 5, 10, 20 µM; 24, 48 h | [38] |
| G0/G1                     | Polyphenols    | 6, 7, 30-trimethoxy-3, 5, 40-trihydroxy flavone (TTF) | (family: Saxifragaceae) *Chrysosplenium nudicaule* Ledeb Herba | SGC-7901 | 2, 4, 8, 16, 32 µg/mL; 24, 48, 72 h | ↑endogenous Ca²⁺/Mg²⁺ dependent endonuclease | [49] |
| G0/G1                     | Phytosterols   | Ginsenoside – rh2 | (family: Araliaceae) *Panax ginseng* C.A. Mey Radix | SGC-7901 | 5, 10, 20 µg/mL; 24, 48 h | ↑Bax ↓Bcl-2 | [45] |
| G0/G1                     | Terpenoids     | Crosolic acid   | (family: Actinidiaceae) *Actinidia valvata* Dunn Radix | BGC-823 | 20, 40, 80 µg/mL; 72 h | ↑Bax, smac, IκBα ↓Fas, Bcl-2, p65, p- IκBα, NF-κB | [58] |
| G1                        | Polyphenols    | Rottlerin       | (family: Euphorbiaceae) *Mallotus philipensis* Muell. | SGC-7901, MGC-803 | 2, 4, 8 µM; 24 h | ↑LC3-II ↓mTOR, Skp2 | [105] |
| G1                        | Terpenoids     | Grifolin        | (family: Albatrellaceae) *Albatrellus conflaus* (Alb. & Schwein.) Kotl. & Pouzar | BGC-823, SGC-7901 | 10, 50 µM; 48 h | ↑caspase-9, -3, CDKN2 ↓MEK1, MEKK3 MEK5 | [62] |
| G1                        | Methanol extract | (family: Asteraceae) *Aster incises* Fisch. * | AGS | 80, 100, 140 µg/mL; 24 h | ↑Bid, Bad, Bak, cyt c, c-caspase-3, -8, -9, AIF, ADP-ribose, PARP ↓Bcl-2, Bcl-xL | [87] |
|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| G1 | Organic extract | (family: Araceae) | Amorphophallus konjac K. Koch Tuber | SGC-7901, AGS | 50 μg/mL; 24 h | ↑ Bax, c-caspase-9, LC3-II | ↓ survivin, Bcl-2 | [109] |
|   |   |   |   |   |   |   |   |   |
|   | G1 | Xiao Tan He Wei decoction | (family: Umbelliferae) Bupleurum falcatum Linne. Radix, (family: Araceae) Pinellia ternata (Thunb.) Makino Rhizoma, (family: Polyporaceae) Poria cocos Wolf., (family: Ranunculaceae) Coptis chinensis Franch., (family: Rubiaceae) Oldenlandia diffusa (Willd.) Roxb. Herba, (family: Compositae) Taraxaci Herba*, (family: Lauraceae) Cinnamomun cassia J. Presl twig, (family: Polygonaceae) Rhubarb*, (family: Paeoniaceae) Paeonia lactiflora Pallas., (family: Leguminosae/Fabaceae) Glycyrrhizae uralensis Fischer. | GES-1 | 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 2.56 g/L; 24, 48, 72, 96 h | ↑ Bax, c-caspase-3, IkB | ↓ Bcl-2, p65, NF-kB | [90] |
|   |   |   |   |   |   |   |   |   |
| G1/S | Terpenoids | Toosendanin | (family: Meliaceae) Melia toosendan Sieb et Zucc Cortex et Fructus | (1) AGS (2) HGC-27 | (1) 0.5, 1, 2 μM; 48 h (2) 0.5, 1, 2 μM; 36 h | ↑ c-caspase-3, -8, -9, c-PARP, Bax, p-p38 | ↓ Bcl-2, Bcl-xl, Mel-1, survivin, XIAP | [68] |
|   |   |   |   |   |   |   |   |   |
| S | Alkaloids | Cyclovirobuxine D | (family: Buxaceae) Buxus microphylla Richardii Radix | MGC-803, MKN-28 | 30, 60, 120 μM/L; 48 h | ↑ c-caspase-3, Bax | ↓ Bcl-2 | [39] |
|   |   |   |   |   |   |   |   |   |
| S | Alkaloids | GFG-3a | (family: Meripilaceae) Grifola frondose (Diks.) Gray Mycelia | SGC-7901 | 100, 200 μg/mL; 24, 48 h | ↑ RBBP4, caspase-3, -8, p53, Bax, Bad | ↓ RUVBL, NPM, Bcl-2, Bcl-xl, PI3K, Akt1 | [40] |
|   |   |   |   |   |   |   |   |   |
| S | Ethanol extract | (family: Ascomycota) Cordyceps cicadae (Miq.) Massee. | SGC-7901 | 200, 400, 800 μg/mL; 48 h | ↑ Bax, caspase-3, -6, -8, AIF, p53, Fas | ↓ Bcl-2, PARP | [77] |
| Effect | Plant Family | Plant Name | Concentration | Time | Markers |
|--------|--------------|------------|---------------|------|---------|
| ↑ROS ↓ΔΨm | (Gentianaceae) | Swertia mussotti Franch. | MGC-803, BGC-823 | 30, 60, 900 µg/mL; 24 h | [82] |
| ↑caspase-9, -3, c-PARP, p53, p38 ↓EGFR, CDC2, cyclin B, ΔΨm | (Fabaceae) | Sophora flavescens Aiton. Radix | MKN-45 | 20, 30, 40 µg/mL; 48 h | [44] |
| ↑caspase-9, -3, c-PARP, p53, p38 ↓EGFR, CDC2, cyclin B, ΔΨm | Lamiaceae | Salviae miltiorrhiza Bunge. Radix | AGS | 2.0, 3.7, 5.5 µg/mL; 24, 48 h | [46] |
| ↑p21, caspase-3, c-PARP ↓p-STAT3, pro-caspase-9, ΔΨm | Caprifoliaceae | Patrinia heterophylla Bunge. | (1) AGS (2) HGC-27 | (1) 4, 8, 16 µM; 24 h (2) 10, 20, 30 µM; 24 h | [60] |
| ↑Bax ↓Bcl-2 | Euphorbiaceae | Euphorbia lunulata Bunge. | SGC-7901, ADR | 10, 20, 40 µg/mL; 24 h | [76] |

*The part of the plant used in this study was not mentioned in the study.*
3. Anti-angiogenesis effects of natural products in gastric cancer

Angiogenesis is the most common pathway for new vessel formation in cancer [115]. Anti-angiogenic agents were studied and developed for anti-cancer therapies because angiogenesis can cause tumor growth [116]. Four *in vitro* and *in vivo* studies demonstrated anti-angiogenic property of natural products (Table 9, 10). Zhang *et al.* demonstrated the anti-angiogenic property of arsenic trioxide with *in vitro* and *in vivo* models [117]. MGC-803 and SGC-7901 cells treated with arsenic trioxide solution at doses of 2, 4, 8 μM for 24 h showed increased level of forkhead box O 3a (FOXO3a) and decreased level of phosphorylated protein kinase B (p-Akt), VEGF, and MMP-9. This caused the reduction of gastric cancer cell viability, cell migration and angiogenesis. The anti-angiogenesis efficacy was confirmed in xenograft models inoculated with MGC-803 cells. After 14 days of treatment of 5 mg/kg arsenic trioxide solution every day daily, the experimental group had lighter and smaller tumors and showed lesser microvessel density than the control group rats. Xiaotan sanjie decoction is a Chinese medicine prescription originated from eleven herbs, *Pinellia ternata* Breitenbach Rhizoma (Araceae), *Arisaema erubescens* Schott Rhizoma (Araceae), *Porzia cocos* (Peck) Ginnis (Polyporaceae), *Aurantii immaturas fructus* (Rutaceae), *Citri reticulateae viride pericardium* (Rutaceae), *Buthus martensii* Karsch (Buthidae), Scolopendra subspinipes mutilans Linne. (Scolopendridae), *Gallus gallus domesticus* Brisson endothelium corneum (Phasianidae), *Fritillariae cirrhosae* D. Don bulbus (Liliaceae), *Brassicae*, *Glycyrrhiza uralensis* Fisch. (Febaceae) Yan *et al.* and Shi *et al.* reported that the Xiaotan sanjie decoction may inhibit angiogenesis by lowering expression of VEGF and VEGFR and down-regulating proteins interleukin 8 (IL-8), notch homolog 1 (Notch-1), hairy and enhancer of split-1 (Hes1), Ki-67, etc. in MKN-45 and HUVECs co-cultured with SGC-7901, respectively [118, 119]. In addition, according to Yan *et al.*, MKN-45 xenograft models treated with 4 mL of Xiaotan sanjie decoction for 2 weeks demonstrated reduction of tumor weight and angiogenesis in a dose-dependent manner. Huang *et al.* studied the anti-gastric cancer efficacy of cyperenoic acid extracted from the roots of *Croton crassifolius* Geiseler Radix (Euphorbiaceae) by treating the supercritical fluid extract and steam distillation extract of *Croton crassifolius* Geiseler Radix to zebrafish embryos [120]. Cyperenoic acid reduced vascular endothelial growth factor A (Vegfa or VEGF-A) genes by targeting the Vegfa-Kdr and Angpt-Tie signaling pathways. Notably, supercritical fluid extract showed stronger anti-angiogenic property than that of stream distillation extract, showing lower cytotoxicity toward both cancer and normal cells compared to the available drug, SU5416 (semaxanib). All studies suggest that inhibition of VEGF leads to anti-angiogenesis in various animal and cell line models. VEGFs take an important role in forming new blood vessels, including angiogenesis and vasculogenesis (Figure 3). These studies show some natural products can effectively downregulate certain VEGF subtypes including VEGFA156, VEGFA121, VEGFR1 and VEGFR2. These factors were modulated on mRNA expression levels.
Figure 3. Schematic diagram of angiogenesis signaling pathways. PI3K, Phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; S6K, S6 kinase; MEK1/2, mitogen activated protein kinase kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2; MNK, Mitogen-activated protein kinase-interacting kinase; 4E-BP1, eIF4E-binding protein 1; eIF4E1, Eukaryotic initiation factor 4E 1; HIF-1α, hypoxia-inducible factor-1 alpha; HIF-1β, hypoxia-inducible factor-1 beta; CBP, CREB-binding protein; p300, CBP homolog; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; NRP1, neuropilin-1; PlGF, placental growth factor; VEGFR-1, vascular endothelial growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2; bFGF, basic fibroblast growth factor; FGFR, fibroblast growth factor receptors; TGF-β, transforming growth factor beta; TGF-R, transforming growth factor receptor; Dll4, delta-like ligand 4.
Table 9. Angiogenesis-Inhibiting Natural Products in vitro.

| Compound/Extract | Source | Experimental Model | Dose; Duration | Mechanism | Reference |
|------------------|--------|---------------------|----------------|-----------|-----------|
| Arsenic trioxide | (1) MGC-803, (2) SGC-7901 | 2, 4, 8 μM; 24 h | ↑FOXO3a, ↓p-Akt, VEGF, MMP-9 | [117] |
| Xiaotan sanjie decoction | (family: Araceae) Pinellia ternata Breitenbach Rhizoma, (family: Araceae) Arisaema erubescens Schott Rhizoma, (family: Polyporaceae) Poria cocos (Peck) Ginn, (family: Rutaceae) Aurantii immaturus fructus, (family: Rutaceae) Citri reticulatae viride pericardium, (family: Buthidae) Buthus martensii Karsch, (Scolopendridae) Scolopendra subspinipes mutilans Linne., (family: Phasianidae) Gallus gallus domesticus Brisson endothelium corneum, (family: Liliaceae) Fritillariae cirrhosae D.Don bulbus, Brassicae, (family: Febaceae) Glycyrrhiza uralensis Fisch. | MKN-45 | 1.46, 2.92, 5.84 g/mL; 24, 48, 72 h | ↓IL-8, Notch-1, Hes1, VEGF, VEGF-A, VEGFR-1, VEGFR-2, Ki-67 | [118] |
| Xiaotan sanjie decoction | (family: Araceae) Pinellia ternata Breitenbach Rhizoma, (family: Araceae) Arisaema erubescens Schott Rhizoma, (family: Polyporaceae) Poria cocos (Peck) Ginn, (family: Rutaceae) Aurantii immaturus fructus, (family: Rutaceae) Citri reticulatae viride pericardium, (family: Buthidae) Buthus martensii Karsch, (Scolopendridae) Scolopendra subspinipes mutilans Linne., (family: Phasianidae) Gallus gallus domesticus Brisson endothelium corneum, (family: Liliaceae) Fritillariae cirrhosae D.Don bulbus, Brassicae, (family: Febaceae) Glycyrrhiza uralensis Fisch. | HUVECs co-cultured with SGC-7901 | 10% serum; 24 h | ↓IL-8, NOTCH-1, VEGF-A, VEGFR-1, VEGFR-2 | [119] |

FOXO3a, forkhead box O 3a; p-Akt, phosphorylated protein kinase B; VEGF, vascular endothelial growth factor; Hes1, hairy and enhancer of split-1; MMP-9, matrix metallopeptidase 9; VEGFR, vascular endothelial growth factor receptor; IL-8, interleukin-8; SFE, supercritical fluid extract; SDE, steam distillation extract.
| Classification | Compound/Extract | Source | Experimental Model | Dose; Duration | Mechanism | Reference |
|----------------|------------------|--------|--------------------|----------------|-----------|-----------|
| Terpenoid       | Cyperenoic acid / SFE or SDE | (family: Euphorbiaceae) Croton crassifolius Geiseler Radix | Zebrafish embryos | 3.75, 7.5, 15 μg/mL; 24, 48 h | ↓Vegfa156, Vegfa121, Kdr, Angpt1, Angpt2, Tie1, Tie2 | [120] |
|                | Arsenic trioxide |        | BALB/C-nu/nu nude mice / MGC-803 | 5 mg/kg/day; 14 days | ↑FOXO3a | [117] |
|                | Xiaotan sanjie decoction | (family: Araceae) Pinellia ternata Breitenbach Rhizoma, (family: Araceae) Arisaema erubescens Schott Rhizoma, (family: Polyarpaceae) Poria cocos (Peck) Ginnis, (family: Rutaceae) Aurantii immaturus fructus, (family: Rutaceae) Citri reticulatae viride pericardium, (family: Buthidae) Buthus martensii Karsch, (Scolopendridae) Scolopendra subspinipes mutilans Linne., (family: Phasianidae) Gallus gallus domesticus Brisson endothelium corneum, (family: Liliaceae) Fritillariae cirrhosae D.Don bulb, Brassicae, (family: Fabeaceae) Glycyrrhiza uralensis Fisch. | SD rats, nude mice / MKN-45 | 1.46, 2.92 and 5.84 g/mL, 4 mL daily; 8 weeks | ↓Notch-1, Hes1 | [118] |

Vegfa, vascular endothelial growth factor A; Kdr, vegfa receptor 2; FOXO3a, forkhead box O 3a; Hes1, hairy and enhancer of split-1
4. Anti-metastasis effects of natural products in gastric cancer

Metastasis is a major contributor of death in cancer patients, arising from a growing tumor from which cells escape to distant organs of body [121]. Targeting metastasis is an attractive strategy in cancer treatment. Sixteen studies highlighted the anti-metastatic ability of diverse natural products in vitro and in vivo models. Epithelial-mesenchymal transition (EMT) was inhibited in many cases while cell cycle arrest and other blockages of tumor proliferations were also observed (Table 11, 12). Evodiamine is a chemical compound extracted from *Evoidea rataecarpa* (*Rutaceae*) [122]. The compound suppressed epithelial-mesenchymal transition of AGS and SGC-7901 gastric cancer cells via inhibition of Wnt/β-catenin signaling pathway (Figure 4). Sulforaphane is an organosulfur compound extracted from *Brassica oleracea* var. *italica* Plen (Brassicaceae) [123]. The compound exerted anti-metastatic ability on AGS and MKN-45 cells when treated at dose of 31.25, 62.5, 125, 250 μg/mL for 48 h. It upregulated caudal type homeobox 1 (CDX1), caudal type homeobox 2 (CDX2), miR-326, and miR-9. Isoliquiritigenin, a phenol found in *Glycyrrhiza glabra* (Fabaceae), inhibited tumor migration and metastasis on MKN-28 in vitro when treated at dose of 20 μM for 24, 48, 72 h [124]. The compound suppressed the phosphoinositide-3 kinase (PI3K)/AKT/mTOR signaling pathway. Dehydroeffusol is a benzenoid derived from *Juncus effusus* L. *Radix et Medulla* (*Juncaceae*) [125]. The compound was tested at the dose of 12, 24, 48 μM for 24 on AGS and SGC-7901 cells in vitro, which resulted in inhibition of matrix metalloproteinase 2 (MMP-2) and reduction of cell-to-cell adherent junction. Downregulation of VE-cadherin and MMP-2 expression was observed. Paeonol, the water extract of *Paenonia suffruticosa* Andr. (*Paeoniaceae*) and *Cynanchum paniculatum* K. Schum (*Asclepiadaceae*), was treated on BGC-823 cells at dose of 0.1, 0.2, 0.4 mg/mL for 24, 48 h [64]. The extract downregulated MMP-2 and MMP-9, leading to inhibition of cell proliferation and migration. Baicalein is a well-known flavone found in the roots of *Scutellaria baicalensis* Georgi *Radix* (*Lamiaceae*) [126]. A 2014 study by Chen F. et al. showed the compound restrains motility, migration, and invasion of AGS gastric cancer cells via downregulation of N-cadherin, vimentin, ZEB1, ZEB2 and TGF-β/Smad4. Baicalein was treated in vitro at dose of 25, 50 μM for 24 h. Andrographolide is a labdane diterpenoid from herb *Andrographis paniculata* Nees Herba (*Acanthaceae*) [127]. Dai L et al. demonstrated that the compound inhibits proliferation and metastasis of gastric cancer SGC-7901 via cell cycle arrest, when treated in vitro at dose of 5, 20, 40 μg/mL for 24, 48, 72 h. Upregulation of Bax, Bik, TIMP-1/2 and downregulation of Bcl-2, CD147, MMP-2, MMP-9, survivin were observed. Wang G et al. demonstrated that a triterpenoid extracted from *Melia toosendan* Sieb et Zucc (*Meliaceae*) named toosendanin has anti-metastatic capability on SGC-7901 cells in vitro [67]. The compound inhibited epithelial-mesenchymal transition of gastric cancer by upregulating miR-200a, E-cadherin and suppressing β-catenin when treated at dose of 0.5, 1 μM for 48 h. Tangerines, grapefruits, lemons and oranges contain low-molecular-weight citrus pectin (LCP) [128]. Wang et al. demonstrated that anti-metastatic effect of LCP by treating it on AGS cells in vitro at dose of 0.625, 1.25, 2.5, 5, 10 mg/mL for 24 h. Epithelial-mesenchymal transition was inhibited followed by downregulation of Cyclin B1, galecin-3 (GAL-3) and Bcl-XL. LCP had both apoptotic and anti-metastatic effects. N-butylidenephthalide is a compound extracted from the roots of *Angelica sinensis* (Oliv.) Diels *Radix* (*Apiaceae*) [63]. When treated at dose of 50 μg/mL for 24, 48 h on AGS, 75 μg/mL for 24, 48 h on NCI-N87 and 25, 50, 75 μg/mL for 48 h on TSGH-9201, inhibition of tumor metastasis was observed. The compound promoted E-cadherin expression while down-regulating N-cadherin and vimentin slug. It is unclear whether natural products exert anti-metastatic effect in a multi-target manner. Further study is required to distinguish the specific mechanism. The primary mechanism observed was through the inhibition of cadherin-catenin adhesion. Compounds and extracts including baicalein, *Celastrus orbiculatus* extract, dehydroeffusol, etc., down-regulated N-cadherin, VE-cadherin, β-catenin and other related factors [125, 126, 129, 130]. Activity of E-cadherin was repressed on the other hand, which inhibits EGFR kinase activity. The mechanism leads to downstream regulation of multiple growth factor related activities, which is associated with anti-metastatic activities of such natural products. Notably, Shi J et al. demonstrated the Xiaotan
Sanjie decoction down-regulated VEGF-A, VEGFR-1 and VEGFR-2 [119]. In other aspect, the Bcl-2 family proteins were also found to play role in anti-metastatic effects of natural products. For example, products such as andrographolide and Xian Tan He Wei elevated Bax protein activity while inhibiting Bcl-2 protein [127, 131]. Many other factors including PI3K, Akt, Rac1, CDX1/2 play a role in anti-metastatic activity of natural products, some of which are also related to apoptosis of tumor cells. For example, Lyu et al. reported the paenol extract suppressed the expression of MMP-2 and MMP-9, which lead to inhibition of proliferation and so inhibition of metastasis (Figure 4) [64]. It is unclear whether natural products exert anti-metastatic effect in a multi-target manner. Further study is required to distinguish the specific mechanism.

Two studies by Zhu Y et al. demonstrated ethyl acetate extract of Celastrus orbiculatus Thunb. Rhizoma (Celastraceae) inhibits TGF-β1 induced epithelial-mesenchymal transition of gastric cancer SGC-7901 [129, 130]. In both studies, the cells were treated with 5, 10, 20 μg/mL dose of the extract for 24 h. Promotion of E-cadherin and downregulation of N-cadherin, vimentin, NF-κB and HSP27 were observed. Triphala is a decoction derived from Terminalia chebula Retz. Fructus (Combretaceae), Terminalia bellerica (Gaertn.) Roxb Fructus (Combretaceae) and Phyllanthus emblica Linn. Fructus (Phyllanthaceae) [132]. The decoction downregulated EGFR, Akt and ERK thus inhibiting tumor proliferation and suppressing cell migration both in vivo and in vitro. Triphala was treated on MGC-803 at dose of 50, 100, 150 μg/mL for 48 h, and tested on Danio rerio at dose of 50, 100, 150 μg/mL. Xiaotan Sanjie is a traditional Chinese decoction composing Pinelliae rhizome (Araceae), Arisaema erubescens Schott Rhizoma (Araceae), Poria cocos (Peck) Ginns (Polyporaceae), Aurantii immaturus Fructus (Rutaceae), Citri reticulatae viride pericarpium (Rutaceae), Scolopendra subspinipes mutilans Linne. (Scolopendridae), Scolopendra (Scolopendridae), Gallus gallus domesticus Brisson Endothelium corneum (Phasianidae), Fritillariae cirrhosae Bulbus (Liliaceae), Semen brassicaceae and Glycyrrhiza uralensis Fisch (Fabaceae) [119]. 10% xiaotan sanjie decoction serum was treated to SGC-7901 gastric cancer cells for 24 hours. It inhibited cell adhesion, migration, and invasion by downregulating IL-8, NOTCH-1, VEGF-A, VEGFR-1 and VEGFR-2. Xu et al. demonstrated the traditional Chinese decoction Xiao Tan He Wei also possesses anti-metastatic effect on tumor-induced animals [90]. Inhibition of invasion and metastasis was detected when wistar rats bearing precancerous lesions of gastric carcinoma were given the decoction orally. Jianpi Bushen is a traditional Chinese decoction made from species including Codonopsis pilosula Nannfeldt Radix (Campanulaceae), Lycium chinense Miller Fructus (Solanaceae), Atractylodis Macrocephalae Koidzumi Rhizoma (Solanaceae), Ligustri lucidum Aiton Fructus (Oleaceae), Cuscuta chinensis Lamark Semen (Convolvulaceae), Psoralea corylifolia Linn. Semen (Leguminosae/Fabaceae) [133]. The treatment, tested on strain-615 model in vivo at dose of 20 g/kg for 7 days, inhibited cancer cell motility and inhibited metastasis by downregulating Ras-related botulinum toxin substrate 1 (Rac1), cell division control protein 42 homolog (Cdc42), stromal cell-derived factor 1 (SDF-1) and fibronecin (FN). Apoptosis and cell cycle arrest was also observed as described above.
Figure 4. Schematic diagram of metastasis signaling pathways. Akt, protein kinase B; Bak, Bcl-2 antagonist/killer 1; Bax, Bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; CD44, homing cell adhesion molecule; COX-2, cyclooxygenase 2; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MDM2, murine double minute 2; MEK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog.
Table 11. Metastasis-inhibiting natural products *in vitro*.

| Classification  | Compound/Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | Reference |
|-----------------|------------------|--------|--------------------|----------------|----------|-----------|-----------|
| Alkaloids       | Evodiamine       | (family: Rutaceae) Tetradium ruticarpum | AGS, SGC-7901 | 2 µM; 48 h | Inhibition of EMT | ↓β-catenin, cyclin D1, c-Myc | [122] |
| Organosulfur compounds | Sulforaphane | (family: Brassicaceae) Brassica oleracea var. italica Plenk | AGS, MKN-45 | 31.25, 62.5, 125, 250 µg/mL; 48 h | Inhibition of metastasis | ↑CDX1, CDX2, ↑miR-326, miR-9 | [123] |
| Polyphenols     | Isoliquiritigenin | (family: Fabaceae) Glycyrrhiza glabra Radix | MKN-28 | 20 µM; 24, 48, 72 h | Inhibition of migration, invasion | Induction of apoptosis and autophagy | ↓Caspase-3, Bax, Bel-2, PI3K, Akt, mTOR | [124] |
| Polyphenols     | Dehydroeffusol   | (family: Juncaceae) Juncus effusus L. Radix et Medulla | AGS, SGC-7901 | 12, 24, 48 µM; 24 h | Reduction of cell-cell adherent junction | ↓VE-cadherin, MMP-2 | [125] |
| Polyphenols     | Paeonol / extract | (family: Paeoniaceae) Paeonia suffruticosa Andr. Cortex, (family: Asclepiadaceae) Cynanchum paniculatum K. Schum Radix | BGC-823 | 0.1, 0.2, 0.4 mg/mL; 24, 48 h | Inhibition of proliferation, invasion, and migration | Induction of apoptosis | ↓MMP-2, MMP-9 | [64] |
| Polyphenols     | Baicalein        | (Lamiaceae) Scutellaria baicalensis Georgi Radix | AGS | 25, 50 µM; 24 h | Inhibition of motility, migration, invasion | ↓N-cadherin, vimentin, ZEB1, ZEB2, TGF-β/Smad4 | [126] |
| Terpenoids      | Andrographolide  | (family: Acanthaceae) Andrographis paniculata Nees Herba | SGC-7901 | 5, 20, 40 µg/mL; 24, 48, 72 h | Inhibition of proliferation, invasion, metastasis | ↑Bax, Bik, TIMP-1/2, ↓Bel-2, CD147, MMP-2, MMP-9, survivin | [127] |
| Terpenoids     | Toosendanin (family: Meliaceae) Melia toosendan Sieb et Zucc Cortex et Fructus | SGC-7901 | 0.5, 1 µM; 48 h | Inhibition of invasion, migration, EMT | ↑E-cadherin ↓β-catenin ↑miR-200a | [67] |
|---------------|----------------------------------------------------------------------------------|---------|----------------|----------------------------------------|-----------------------------------|-----|
| Terpenoids    | Low-molecular-weight citrus pectin (LCP) *Citri Pericarpium*                     | AGS     | 0.625, 1.25, 2.5, 5, 10 mg/mL; 24 h | Inhibition of EMT | ↓Cyclin B1, GAL-3, Bcl-xL | [128] |
| Terpenoids    | N-Butylidenephthalide (family: Apiaceae) Angelica sinensis (Oliv.) Diels Radix    | AGS     | (1) 50 µg/mL; 24, 48 h | Inhibition of migration, invasion and EMT | ↑E-cadherin ↑N-cadherin, vimentin slug | [63] |
|               |                                                                                  | NCI-N87 | (2) 75 µg/mL; 24, 48 h |                            |                                    |     |
|               |                                                                                  | TSGH-9201 | (3) 0, 25, 50, 75 µg/mL; 48 h |                            |                                    |     |
| Ethyl acetate extract (family: Celastraceae) Celastrus orbiculatus Thunb. Rhizoma | AGS     | 5, 10, 20 µg/mL; 24 h | Inhibition of EMT | ↑E-cadherin ↓N-cadherin, vimentin, NF-κB | [129, 130] |
| Triphala decoction (family: Combretaceae) Terminalia chebula Retz. Fructus, (family: Combretaceae) Terminalia bellirica (Gaertn.) Roxb. Fructus, (family: Phyllanthaceae) Phyllanthus emblica Linn. Fructus | MGC-803 | 50, 100, 150 µg/mL; 48 h | Inhibition of migration | ↓EGFR, Akt, ERK | [132] |
| Decoction | Composition | Treatment | Effect | Reference |
|-----------|-------------|-----------|--------|-----------|
| Xiaotan Sanjie decoction | (family: Araceae) *Pinellia ternata* Breitenbach Rhizoma, (family: Araceae) *Arisaema erubescens* Schot Rhizoma, (family: Polyporaceae) *Poria cocos* (Peck) Ginns, (family: Rutaceae) *Aurantii immaturus* fructus, (family: Buthidae) *Buthus martensii* Karsch, (Scolopendridae) *Scolopendra subspinipes mutilans* Linne., (family: Phasianidae) *Gallus gallus domesticus* B. Risson endothelium corneum, (family: Liliaceae) *Fritillariae cirrhosae* D.Don bulbus, Brassicae, (family: Febaceae) *Glycyrrhiza uralensis* Fisch. | HUVECs co-cultured with SGC-7901 10% serum; 24 h | Inhibition of adhesion, migration and invasion ↓IL-8, NOTCH-1, VEGF-A, VEGFR-1, VEGFR-2 [119] |
| Xiao Tan He Wei Decoction | (family: Umbelliferae) *Bupleurum falcatum* Linne. Radix, (family: Araceae) *Pinellia ternata* (Thunb.) Makino Rhizoma, (family: Polyporaceae) *Poria cocos* Wolf., (family: Ranunculaceae) *Coptis chinensis* Franch., (family: Rubiaceae) *Oldenlandia diffusa* (Willd.) Roxb. Herba, (family: Compositae) *Taraxaci Herba**, (family: Lauraceae) *Cinnamomun cassia* J. Presl twig, (family: Polygonaceae) *Rhubarb*, (family: Paeoniaceae) *Paeonia lactiflora* Pal., (family: Leguminosae/Fabaceae) *Glycyrrhiza uralensis* Fischer. | GES-1 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 2.56 g/L; 24, 48, 72, 96 h | Induction of apoptosis and cell cycle arrest ↑Bax, c-caspase-3, IkB ↓Bcl-2, p65, NF-kB [90] |

β-catenin, catenin beta-1; CDX1, caudal type homeobox 1; CDX2, caudal type homeobox 2; miR-326, microRNA 326; miR-9, microRNA 9; Bax, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; VE-cadherin, vascular endothelial-cadherin; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; N-cadherin, neural cadherin; ZEB1, zinc finger E-box binding homeobox 1; ZEB2, zinc finger E-box binding homeobox 2; TGF-β/Smad4, transforming growth factor beta 1/SMAD family member 4; Bik, Bcl-2 interacting killer; EMT, epithelial-mesenchymal transition; TIMP-1/2, tissue inhibitors of matrix metalloproteinase-1/2; CD147, cluster of differentiation 147; E-cadherin, epithelium cadherin; mir-200a, microRNA 200a; GAL-3, galectin-3; Bcl-xL, B-cell lymphoma-extra large; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; IL-8, interleukin-8; NOTCH-1, Notch homolog 1; VEGF-A, vascular endothelial growth
factor-A; VEGFR-1, vascular endothelial growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2; c-caspase-3, cleaved caspase-3; IκB, Inhibitor of NF-κB; p65, nuclear factor NF-κB p65 subunit; Rac1, Ras-related botulinum toxin substrate 1. *Citri pericarpium is derived from several citrus fruits. The exact species used in the research was not identified.

Table 12. Metastasis-inhibiting natural products in vivo.

| Compound/Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | Reference |
|------------------|--------|--------------------|----------------|----------|-----------|-----------|
| Triphala decoction | (family: Combretaceae) Terminalia chebula Retz. Fructus, (family: Combretaceae) Terminalia bellerica (Gaertn.) Roxb. Fructus, (Phyllanthaceae) Phyllanthus emblica Linn. Fructus | Zebrafish (Danio rerio) / MGC-803 | 50, 100, 150 μg/mL; 48 h | Inhibition of migration | ↓EGFR, Akt, ERK | [132] |
| Xiao Tan He Wei decoction | (family: Umbelliferae) Bupleurum falcatum Linne. Radix, (family: Araceae) Pinellia ternata (Thunb.) Makino Rhizoma, (family: Polygonaceae) Poria cocos Wolf., (family: Lauraceae) Cinnamomum cassia 1. Presl twig, (family: Polygonaecae) Rhus Barb*, (family: Rubiaceae) Saekoa lantii Palla, (family: Compositae) Taraxacum Herba*, (family: Rubiaceae) Cinnamomum cassia 1. Presl twig, (family: Compositae) Taraxacum Herba*, (family: Lauraceae) Cinnamomum cassia 1. Presl twig, (family: Leguminosae/Fabaceae) Glycyrrhiza uralensis | Wistar rats | 3.4 mL/kg; 2 weeks | Induction of cell cycle arrest | ↑Bax, c-caspase-3, IκB | [90] |
| Jianpi Bushen decoction | (family: Campanulaceae) Codonopsis pilosula Nannfeldt Radix, (family: Solanaceae) Lycium chinense Miller Fructus, (family: compositae) Atractylodis macrocephalae Koidzumi Rhizoma, (family: Oleaceae) Ligustrum lucidum Aiton Fructus, (family: Convolvulaceae) Cuscuta chinensis Lamark Semen, (family: Leguminosae/Fabaceae) Psoralea corylifolia Linn. Semen | Strain-615 / MFC | 20 g/kg; 7 days | Inhibition of motility | ↓Rac1, Cdc42, SDF-1, FN | [133] |

EGFR, epidermal growth factor receptor; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; Bax, bcl-2-like protein 4; c-caspase-3, cleaved caspase-3; IκB, Inhibitor of NF-κB; p65, nuclear factor NF-κB p65 subunit; Rac1, Ras-related botulinum toxin substrate 1; SDF-1, stromal cell-derived factor 1; FN, fibronectin.
5. Chemotherapy resistance and natural products in gastric cancer

Drug resistance has been an important issue in cancer treatment. It is known as a primary cause limiting cancer treatment [134]. Several studies have indicated that natural products could be used along with the primary drug to overcome drug resistance and reinforce its efficacy. Previous studies focused on how natural products can support conventional antibiotics by suppressing resistance [135]. This review highlighted natural products’ potential in handling cancer chemotherapy resistance (Table 13, 14). Isorhamnetin, a flavonoid metabolite of quercetin commonly found in onions, minimized the apoptotic effects of capecitabine via inhibition of NF-κB and various NF-κB regulated gene products in tumor cells [136]. Attenuation of capecitabine resistance was also observed in an animal model in which athymic nu/nu female mice grafted with SNU-5 were treated with isorhamnetin (1 mg/kg) three times a week for 4 weeks. According to Wei et al., liquiritin isolated from Glycyrrhiza uralensis Fischer. Radix (Leguminosae/Fabaceae/Fabaceae) could circumvent the resistance of cisplatin-based chemotherapy [137]. SGC7901/DDP cells were treated with DDP (2 µg/mL) or liquiritin (80 µM) or both for 24 h. The combination greatly suppressed cell proliferation and induced apoptosis, autophagy and G0/G1 phase cell cycle arrest against DDP resistant gastric cancer cells compared to DDP single treatment. Cleavage of caspase-8, caspase-9, caspase-3 and PARP were activated and increased expression levels of LC-3B and Beclin 1 were observed. Abdelfattah et al. isolated a new alkyl sulfonic acid derivative from the methanolic extract of mycelium of Streptomyces sp. IFM 11694 and named it sulfotanone [138]. Its bioactivity was evaluated for effects on TRAIL-resistance of AGS cells by comparing cell viability in the presence and absence of TRAIL (100 ng/mL). Sulfotanone showed TRAIL-resistance overcoming activity in AGS cells at concentrations of 40 µM. Bufalin, a traditional Chinese medicine extracted from Venenum bufonis, showed synergetic effects with cisplatin to inhibit proliferation and promote apoptosis of gastric cancer cells SGC7901, MKN-45, and BGC-823 by diminishing the activation of cisplatin-induced Akt and its downstream molecules under normoxic and hypoxic conditions [139]. Astragalus polysaccharide and apatinib co-treatment were reported to enhance apoptosis compared to apatinib monotherapy [140]. The efficacy of astragalus polysaccharide, an active component extracted from Astragalus membranaceus Bunge Radix (Leguminosae/Fabaceae/Fabaceae), arises mainly from its ability to inhibit autophagy of apatinib-resistant cells which serves as a survival mechanism. Abdelfattah et al. isolated a new anhydroquinonoid tetracene metabolite from the ethyl acetate extract of the culture of marine bacteria Streptomyces sp. EGY1 and named it sharkquinone [141]. Sharkquinone sensitized TRAIL-resistant AGS cells and suggested their potential use in combination with TRAIL against AGS cells. Tanshinone IIA is identified as an interesting agent with potential to treat doxorubicin-resistant gastric cancer cells. [142]. 5 µM Tanshinone IIA solution combined with 0.05 µg/mL of doxorubicin showed anticancer effect against doxorubicin-resistant cell lines including SNU-638, SNU-668 and SNU-216 and SNU-620. Apoptosis was mainly induced by inhibition of multidrug resistance-associated protein 1 (MRP1). Zuo Jin Wan Formula is a traditional Chinese medicine pill that consists of Coptidis Rhizoma (Ranunculaceae), and Evodiae rutaecarpa Bentham. Fructus (Rutaceae) in the ratio of 6:1. Sun et al. reported that Zuo Jin Wan Formula induced apoptosis in primary DDP-resistant gastric carcinoma cells by stimulating cofilin-1 mitochondrial translocation [143]. Translocation of cofilin-1 was mediated by Akt. Accumulation of Bax was observed while expression level of Bcl-2 was decreased. Natural protucts and their target signal is presented in figure 5.
Although specific targets vary, most natural products aimed to prevent drug resistance by downregulating Akt and NF-κB and following pathways (Figure 4). Bufalin from *Venenum bufonis* and the Zuo Jin Wan formula effectively down-regulated Akt [139, 143]. Similarly, the mineral isorhamnetin from *Quercetin* inhibited cell viability and prevented drug resistance by downregulating NF-κB [130]. Reduction of drug resistance by natural compounds was demonstrated in other aspects. Pseudolaric acid B from *Pseudolarix kaempferi* inhibited COX-2, PKC-α and P-gp, factors that promote angiogenesis by cancer cells. Liquiritin from the *Glycyrrhiza* genus promoted p53, p21 and caspase cleavages while inhibiting cyclin activities. The compound’s anti-resistant ability may be focused on apoptotic effects. Other factors such as Bax/Bcl-2 in mitochondria, ERK1/2, MMP2, and PARP are broadly affected by many natural products covered in the review. Each compound, extract or decoction had anti-resistant effects over various aspects of cancer cells when tested *in vitro* or on animal models.

6. Limitation and future perspectives of natural products in gastric cancer treatments

Gastric cancer is known to account for the fifth highest incidence and the fourth highest mortality among all cancers worldwide [1]. Chemotherapy is one of the methods typically used in advanced gastric cancer treatment, but it exerts severe side effects that limit the efficacies and decrease quality of life. Development of therapeutic remedies with less adverse effects and lower chemo-resistance is required. Natural products are emerging as alternative resources to combat gastric carcinoma. While few natural products such as aflatoxins may be noxious or even carcinogenic [144], many phytochemicals with beneficial bioactivity can be successfully selected through deliberate investigations. Therefore, several natural resources obtained from dietary fruits and vegetables were discussed in this review. Curcumin, black currant extract, oligosaccharide isolated from tomato, sulforaphane derived from broccoli, citrus pectin originated from tangerine, grapefruit,
lemon and orange are good examples. These medicinal resources are still being extensively used in traditional Korean and Chinese medicine. Many natural substances were shown to exhibit multiple effects. The variety is attributed to the structural diversity and multi-target characteristic of natural compounds [145]. Several decoctions were also reported to suppress cancerous cells and tumors comprehensively. In this light, decoctions have the potential to develop as effective therapeutic agents against gastric cancer based on their multi-efficacy and enhancement of efficacy through various methods of post-processing.
| Classification        | Compound/Extract | Source                                           | Experimental Model         | Dose; Duration          | Efficacy                                               | Mechanism                                                                 | Reference |
|-----------------------|------------------|-------------------------------------------------|----------------------------|-------------------------|-------------------------------------------------------|---------------------------------------------------------------------------|-----------|
| Flavonoid             | Isorhamnetin     | Quercetin                                       | AGS, SNU5, SNU16, MKN45, NUGC3, AZ521 | 50 μM; 6, 12, 24, and 48 h | Inhibition of the cell viability                       | ↓NF-κB, p65, VEGF, COX-2, MMP-9                                           | [136]    |
|                       |                  |                                                 |                            |                         |                                                       |                                                                           |           |
|                       | Liquiritin       | (family: Leguminosae/Fabaceae/Fabaceae) Glycyrhriza uralensis Fischer. Radix | SGC-7901/DDP               | 80 μM; 24 h             | Potentiation of the suppressive effects of DDP, induction of G0/G1 cell cycle arrest, enhancement of apoptosis and autophagy | ↑c-caspase-8, -9, -3, c-PARP, LC-3B, Beclin 1                             | [137]    |
|                       |                  |                                                 |                            |                         |                                                       |                                                                           |           |
| Organosulfur compound | Sulfotanone      | Streptomyces IFM 11694                          | AGS                        | 20, 40, 80 μM; 16 h     | Induction of TRAIL resistance-overcoming activity     |                                                                           | [138]    |
|                       | Bufalin          | (family: Leguminosae/Fabaceae/Fabaceae) Venenum bufonis | SGC7091, MKN45, BGC823    | 50, 100, 200 nM; 48 h  | Inhibition of acquired cisplatin resistance and proliferation | Induction of apoptosis                                                   | [139]    |
|                       |                  |                                                 |                            |                         |                                                       |                                                                           |           |
| Polyphenol            | Astragalus polysaccharide |                                                 | AGS                        | 20 μg/mL; 24 h          | Synergistic effect of inhibitory effects on cell proliferation, migration, invasion and apoptosis with apatinib | ↓Akt, MMP-9                                                              | [140]    |

Table 13. Drug resistance-overcoming natural products *in vitro*.
Polyphenol  | Sharkquinone  | Streptomyces sp. EGY1  | AGC  | Sensitization of TRAIL-resistant AGC cells  | [141]
---|---|---|---|---|---
Terpenoid  | Tanshinone IIA  | (family: Lamiaceae) Salvia miltiorrhiza Bunge Radix  | SNU-638, SNU-668, SNU-216, SNU-620  | 5 μM; 24 h  | Induction of apoptosis, autophagy and cell cycle arrest  | ↓MRP1  | [142]
Zuo Jin Wan Formula  | (family: Ranunculaceae) Coptidis Rhizoma*, (family: Rutaceae) Evodiae rutacearpa Bentham. Fructus  | SGC7901/DDP  | 20, 50, 100 μg/mL; 48 h  | Increase of chemosensitivity  | ↑cofilin-1, Bax  | ↓Akt, Bcl-2  | [143]

NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase 2; MMP-9, matrix metallopeptidase 9; c-caspase-8, cleaved caspase 8; c-PARP; cleaved poly ADP ribose polymerase; LC-3B, microtubule-associated protein 1 light chain-3B; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Akt, Protein kinase B (PKB); MRP1, multidrug resistance protein 1; DDP, cisplatin; Bax, Bcl-2 like protein 4; Bcl-2, B-cell lymphoma 2. * Coptis teeta Wallich, Coptis japonica Makino, Coptis deltoidea C. Y. Cheng et Hsiao, and Coptis chinensis Franchet. Are called Coptidis Rhizoma. The study did not mention which species was used.

**Table 14.** Drug resistance-overcoming natural products *in vivo.*

| Classification | Compound/Extract | Source | Experimental Model | Dose; Duration | Efficacy | Mechanism | Reference |
|---|---|---|---|---|---|---|---|
| Flavonoid  | Isorhamnetin  | Quercetin  | Athymic nu/nu mice / SNU-5  | 1 mg/kg; 4 weeks  | Enhancement of the efficacy of capecitabine  | ↓NF-κB, VEGF, COX-2, MMP-9  | [136]|

NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase 2; MMP-9, matrix metallopeptidase 9.
While there have been similar reviews highlighting the anti-neoplastic efficacies of natural products or phytochemicals, few of them are written with regards to the chemical classification of each bioactive compound [146]. This review is not only a simple compilation of previous in vitro studies testing natural products on gastric cancer but goes as far as to systematically organizing previous works depending on each cancer related pathways, namely, apoptosis, autophagy, metastasis, drug-resistant capability and more. Studies grouped into each pathway were then organized according to the phytochemical classification of the active compounds. As there is currently no golden standard for classifying phytochemicals, we adopted a comprehensive and clear method previously demonstrated in a literature highlighting the efficacies of natural products on gastrointestinal diseases [147]. This will help researchers rule out or select appropriate candidate species of natural products for further studies. One limitation of this review is that it only included studies published from 2014 to 2020. Also, clinical trials were excluded to focus on laboratory experiments highlighting specific biological pathways. Several investigations were insufficient to elucidate anti-cancer mechanisms at molecular levels. They were generally focusing on the cytotoxicity of the chemicals or reporting newly discovered compounds, which makes incisive research burdensome. By and large, more than half of the studies only carried out experiments in vitro. More in vivo studies are recommended to bridge the advance to clinical trials and therapeutic use. Decotions and extracts proven safe for human should go under well designed clinical trials to prove their efficacy in the evidence-based medicine perspective.

Natural products are indeed effective in the single compound to single target mechanistic perspective; however, it is worth highlighting the complex interactions between many compounds. While the importance of studying the interactions between multi-compound natural products and other drugs was previously highlighted in many literatures, it is also important to further investigate the interactions between different natural products, including herbal medicines in a biochemical manner [148]. A systemic approach with focus on structural similarities of several phytochemical compounds and human metabolites is a potential way of clearly highlighting the efficacies of multi compound drugs. Furthermore, the fact that current drug interaction analytical methodology for novel multi-targeted agents closely resembles the Kun-Shin-Choa-Sa in many perspectives makes it more intriguing to apply this principle in modern drug studies [149, 150].

7. Conclusions

In this review, we summed up seventy-six studies considering natural products that have anti-cancer efficacy against gastric cancer. Natural products mainly induced cell death by apoptosis and autophagy, cell cycle arrest, inhibit angiogenesis and metastasis, and circumvent chemo-resistance against stomach cancer cells in vitro or in vivo through various molecular mechanisms. Several compounds, extracts and decoctions showed multiple efficacies, attributed to structural complexity and multiple target pathways and proteins of natural products. Thus, natural substances implicate possibilities of being used in nutrition or medications which may lead to novel discoveries in alternative medicine in cancer treatment. This review would provide data for future research and clinical trials to develop novel drugs from natural products for gastric cancer treatment.
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