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

Review

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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

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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 unremovable toxins, trauma, or infection can occur mutagenic chronic inflammatory response, leading to dyplasia [12]. Considering gastric cancer, *Helicobactor 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*

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(Diks.) 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 rutaecarpa* 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.

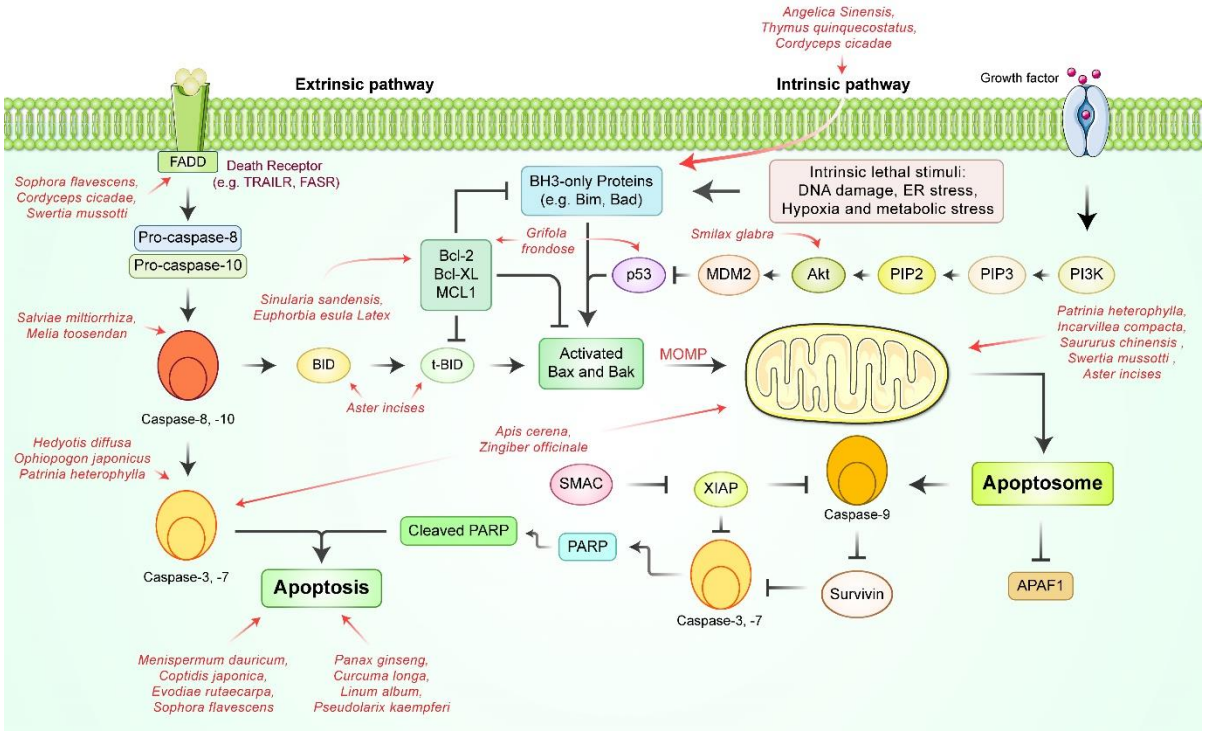

Figure 1. Schematic diagram of natural product-mediated apoptosis signaling pathways. FADD, Fas-associated proteins with death domain; TRAILR, TNF-related apoptosis-including ligand receptor; FASR, Fas receptor; tBid, truncated Bid; PARP, Poly ADP-ribose polymerase; APAF1, Apoptotic Protase Activating 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

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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-methylanthraquinone (DDMN), a flavone isolated from *Hedyotis diffusa* Willd. *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 peroxisome 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 kurarinone against gastric cancer cell line SGC-7901 [52]. Kurarinone is a substance originated from *Sophora flavescens* Aiton *Radix (Fabaceae).* Kurarinone (5 μM) for 24 h significantly enhanced TRAIL-induced apoptosis compared to single treatment by stimulating inhibition of Mcl-1 expressions, 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]. Podophyllotoxin, extracted from *Linum album* Kotschy *(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-acetylsinumaximol B (7-AB), discovered from *Sinularia sandensis (Alcyoniidae)*, 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 lukemia-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. Crosolic acid, isolated from *Actinidia valvata* Dunn. *Radix (Actinidiaceae),* was reported to inhibit proliferation of BGC-823 cells by downregulating the NF-κB pathway [58]. Crosolic acid inhibited phosphorylation of nuclear factor kappa B-alpha (IκBα), expression of p65, and nuclear translocation and DNA-binding activity of NF-κB. Upregulation of Bax and downregulation of Bcl-2 were also observed. Jung *et al.* found that curcuzedoalide, sesquiterpene components of *Curcuma zedoaria* Roscoe *Rhizoma (Zingiberaceae)* induced mitochondrial apoptosis of AGS cells [59]. AGS cells were treated with curcuzedoalide at the concentration of 100 μM and 200 μM for 24 h. Exposure to curcuzedoalide induced cleavage of PARP as well as caspase-8, caspase-9, and caspase-3, in a dose-dependent manner. Deacetylisovaltratum, extracted from *Patrinia heterophylla* Bunge. *(Caprifoliaceae,* was treated to AGS and HGC-27 human gastric cancer cell lines for 24 h at

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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 (*Albatrellaceae)*, 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 *Cynachum 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 oncogenic 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-

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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].

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Table 1. Apoptosis-inducing natural compounds *in vitro*.

Classification	Compound/ Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	References
Alkaloids	Berberine	*(family: Ranunculaceae)* *Coptidis japonica* Makino *Rhizoma*	SGC-7901	5, 10, 20 μM; 24, 48 h	Induction of apoptosis		[38]
Alkaloids	Cyclovirobuxine D	*(family: Buxaceae)* *Buxus microphylla* Richardii *Radix*	MGC-803, MKN-28	30, 60, 120 μM/L; 48 h	Induction of apoptosis	↑c-caspase-3, Bax ↓Bcl-2	[39]
Alkaloids	GFG-3a	*(family: Meripilaceae)* *Grifola frondose* (Diks.) Gray *Mycelia*	SGC-7901	100, 200 μg/mL; 24, 48 h	Induction of apoptosis	↑RBBP4, caspase-3, -8, p53, Bax, Bad ↓RUVBL, NPM, Bcl-2, Bcl-xL, PI3K, Akt1	[40]
Alkaloids	Melittin	*(family: Apidae)* *Apis cerena* Fabricius *venom*	SGC-7901	4 μg/mL; 1, 2, 4 h	Induction of apoptosis	↑caspase-3, cyt c, Endo G, AIF, Smac/Diablo, ROS ↓ΔΨm	[41]
Alkaloids	Phenolic alkaloids	*(family: Menispermaceae)* *Menispermum dauricum* DC. *Rhizoma*	SGC-7901	5, 10, 20 μM; 24h	Induction of apoptosis	↑Bax, caspase-3 ↓K-RAS	[42]
Alkaloids, Terpenoids	Berberine, d-Limonene	(1) *(family: Ranunculaceae)* *Coptidis japonica* Makino *Rhizoma* (2) *(family: Rutaceae)* *Evodiae rutaecarpa* Bentham.	MGC-803	(1) 20 μM; 24, 36, 48 h (2) 80 μM; 24, 36, 48 h	Induction of apoptosis	↑ROS, caspase-3 ↑ΔΨm, Bcl-2	[43]

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		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 sepium* 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	↑TNF-α, Fas, p-p38, p-JNK, p53, p21, caspase-8, -3 ↓p-ERK, CDC2, cyclin A, cyclin B1	[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-methylanthraquinone (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 ↓Bcl-xL, Bcl-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]

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Polyphenols	Esculetin	*(family: Asteraceae) Artemesia scoparia* Waldst. et Kit, *Artemesia capillaris* Thunb., *(family: Plumbaginaceae) Ceratostigma willmottianum* Stapf, *(family: Rutaceae) Citrus limon* Osbeck *Folium*	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	[73]
Polyphenols	Hydroxysafflor Yellow A	*(family: Asteraceae) Carthamus tinctorius* L.	BGC-823	100 μM; 48 h	Induction of apoptosis	↑caspase-3, PPARγ	[51]
Polyphenols	Kurarinone (combined with TRAIL)	*(family: Fabaceae) Sophora flavescens* Aiton *Radix*	SGC-7901	5 μM; 24 h	Enhancement of TRAIL-induced apoptosis	↓Mcl-1, c-FLIP, p-STAT3	[52]
Polyphenols	Licochalcone A	*(family: Fabaceae) Glycyrrhiza glabra* L. *Root*	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	[53]
Polyphenols	Ophiopogonin B	*(family: Asparagaceae) Ophiopogon japonicus* Thunb *Root*	SGC-7901	5, 10, 20 μM	Induction of apoptosis	↑ROS, Bax, caspase-3 ↓p-ERK 1/2, p-JNK 1/2, ΔΨm, Bcl-2	[54]
Polyphenols	Phloretin		AGS	4. 8, 16μM; 24 h	Induction of apoptosis Inhibition of invasion	↑Bax ↓Bcl-2	[55]
Polyphenols	Podophyllotoxin	*(family: Linaceae) Linum album* Kotschy	AGS	200, 400, 600, 800, 1000 μg/mL; 24 h	Induction of apoptosis	↓ZNF703	[56]
Terpenoids	7-Acetylsinumaximol B	*(family: Alcyoniidae) Sinularia sandensis*	NCI-N87	4, 8, 16 μM; 24 h	Induction of apoptosis	↑Bad, Bim, Bax, cyt c ↓p-Bad, Mcl-1, Bcl-	[57]

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						xL, Bcl-2	
Terpenoids	Crosolic Acid	*(family: Actinidiaceae)* *Actinidia valvata* Dunn *Radix*	BGC-823	20, 40, 80 μg/mL; 72 h	Induction of apoptosis	↑Bax, smac, IκBα ↓Fas, Bcl-2, p65, p-IκBα, NF-κB	[58]
Terpenoids	Curcuzedoalide / Methanol extract	*(family: Zingiberaceae)* *Curcuma zedoaria* Roscoe *Rhizoma*	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, pro-caspase-9, ΔΨm	[60]
Terpenoids	Elemene	*(family: Zingiberaceae)* *Curcuma zedoaria* Roscoe *Rhizoma*	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-butylidenephthalide	*(family: Apiaceae) Angelica Sinensis* Diels *Radix*	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 *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, -9	[64]

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Terpenoids	Pseudolaric acid B	*(family: Pinaceae) Pseudolarix 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	[65]
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	[66]
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	[67]
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	[68]
	Arsenic sulfide	*Realgar*	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	[69]
	Pectic oligosaccharide	*(family: Solanaceae)* *Solanum lycopersicum* L.	AGS	10, 20, 30 μg/mL; 48 h	Induction of apoptosis	↓Galectin-3	[70]

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; cyt 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, fasciclin; 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; CypD, Cyclophilin D; PPARγ, Peroxisome proliferator-activated receptor gamma; c-FLIP, Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; p-STAT3, phospho-Signal transducer and activator of transcription 3; HK2, hexokinase 2; p-S6, phosphorylated S6; p-GSK3β, phosphorylated glycogen synthase kinase 3 beta; ZNF703, Zinc Finger Protein 703; Bim, 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;

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MEK5, mitogen activated protein kinase 5; Bak, Bcl-2 antagonist/killer 1; REDD1, regulated in development and DNA damage responses 1; mTOR, mammalian target of rapamycin; MMP, matrix metallopeptidase; P-gp, P-glycoprotein; COX-2, cyclooxygenase 2; EMT, epithelial-mesenchymal transition; miR-200a, MicroRNA 200a; MDM2, murine double minute 2

Table 2. Apoptosis-inducing natural compounds *in vivo*.

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]

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		Schwein.) Kotl. & Pouzar	7901				
	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.

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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 endolichenic fungus EL002332 isolated from *Ribes nigrum* L. *(Saxifragaceae)* showed selective cytotoxicity against AGS human gastric cancer cells [74]. Liu *et al.* reported that the polyphenol-rich extract of *Ribes nigrum* L. *(Saxifragaceae)*, or black currant, induced apoptosis of MKN-45 cells via MAPK- and PI3K/Akt-mediated mitochondrial pathways [75]. *Euphorbia lunulata* 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 ethanolic extract of *Cordyceps cicadae* (Miq.) Massee. (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 *Astragulus 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 *Sophorae flavescentis* 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. *Swertia mussotti* Franch. *(Gentianaceae)* extract showed anti-proliferative effect and induced mitochondria-dependent apoptosis via depolymerization of cytoskeletal filaments, distrupted 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)* hydroalchoholic 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. Ngabire *et al.* reported that *Aster incises* Fisch. *(Asteraceae)* induced mitochondria-related apoptosis in AGS cells [85]. 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 membranceus* 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.

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Table 3. Apoptosis-inducing natural product extracts *in vitro*.

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: Smilacaceae*) *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*) *Astragulus 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) Sophorae flavescentis* 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]

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Ethanol, water extract	*(family: Cornaceae) Cornus mas* L. *Bulbus*	AGS	IC_{50} 5.44 mg/mL; 48 h IC_{50} 2.44 mg/mL; 72 h	Induction of apoptosis and necrosis		[34]
Hydroalchoholic extract	*(family: Urticaceae) Urtia dioica radix*	MKN-45	32, 125, 500 µg/mL; 24 h	Induction of apoptosis	↑ROS	[35]
Methanol extract	*(family: Asteraceae) Aster incises* Fisch. *	AGS	80, 100, 140 µg/mL; 24 h	Induction of apoptosis	↑Bid, Bad, Bak, cyt c, c-caspase-3, -8, -9, AIF, ADP-ribose, PARP ↓Bcl-2, Bcl-xL	[87]
Methanol extract	Propolis produced by *Trigona incisa*	KATO-III	IC_{50} 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	↑ROS, Bax, caspase-3, -9 ↓Bcl-2	[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	↑Bax ↓Bcl-2	[85]
Water extract	*(family: Euphorbiaceae) Euphorbia esula Latex*	SGC-7901	5, 10, 20, 40, 80, 160 mg/L; 24, 48 h	induction of apoptosis	↑Bax, caspase-3, caspase-8 ↓Bcl-2	[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.

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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 membranceus* 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

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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 membranceus* Fisch. *Radix* (*Leguminosae*/*Fabaceae*), *Scutellariae barbata* D. Don *Herba (Lamiaceae), Arisaematis preparatum Preparatum, Citri sarcodactylis Fructus* Swingle. *(Rutaceae), Cremastrae 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)*, *Schisandra 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 (Aistolochiaceae), 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).

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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]
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) Cinnamonun 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	Induction of apoptosis	↑Bax, c-caspase-3, IκB ↓Bcl-2, p65, NF-κB	[90]
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) Cinnamonun cassia* J.Presl *twig, (family: Polygonaceae) Rhubarb*, (family: Paeoniaceae) Paeonia lactiflora* Pallas., *(family: Leguminosae/Fabaceae)Glycyrrhizae uralensis* Fischer.	Wistar rats	3.4 mL/kg; 2 weeks	Inhibition of metastasis	↑Bax, c-caspase-3, IκB ↓Bcl-2, p65, NF-κB	[90]
Yangzhen San-jie decoction	(*family: Leguminosae/Fabaceae*) *Astragalus membranceus* Fisch. *Radix, (family: Lamiaceae) Scutellariae barbata* D.Don *Herba, Arisaematis preparatum Citri sarcodactylis Fructus, Cremastrae Tuber*, (family: Zingiberaceae) Curcuma longa* L. *Rhizoma*	(1) AGS (2) HS-746T	10% serum; 48 h	Induction of apoptosis	↑let-7a ↓c-Myc	[91]
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: Aistolochiaceae) Asiasarum heterotropoides Rhizoma, (family: Fabaceae) Glycyrrhiza glabra* Fisch. *Radix*	AGS, NUGC-3	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]

c-PARP, cleaved poly ADP ribose polymerase; p-p38, phosphorylated p38; p-Erk, phosphorylated extracellular-signal-regulated kinase; p-JNK, phosphorylated Jun N-terminal protein kinase; Bax, Bcl-2 like protein 4; Bcl-2, B-cell lymphoma 2; ΔΨm, mitochondria membrane potential; c-Myc, cellular MYC proto-oncogene protein; IκB, inhibitor of nuclear factor kappa. **Taraxaci Herba* includes *Taraxacum platycarpum* H. Dahlstedt, *Taraxacum officinale* Weber, *Taraxacum mongolicum* Handel-Mazzetti, and *Taraxacum coreanum* 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. *Chremastrae Tuber includes *Cremastra appendiculata* (D.Don) Makino, *Pleione bulbocodioides* Rolfe, and *Pleione yunnanensis* Rolfe. The species used in the study was not indicated.

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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: Aistolochiaceae) 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]

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2.2. Emergeing 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).

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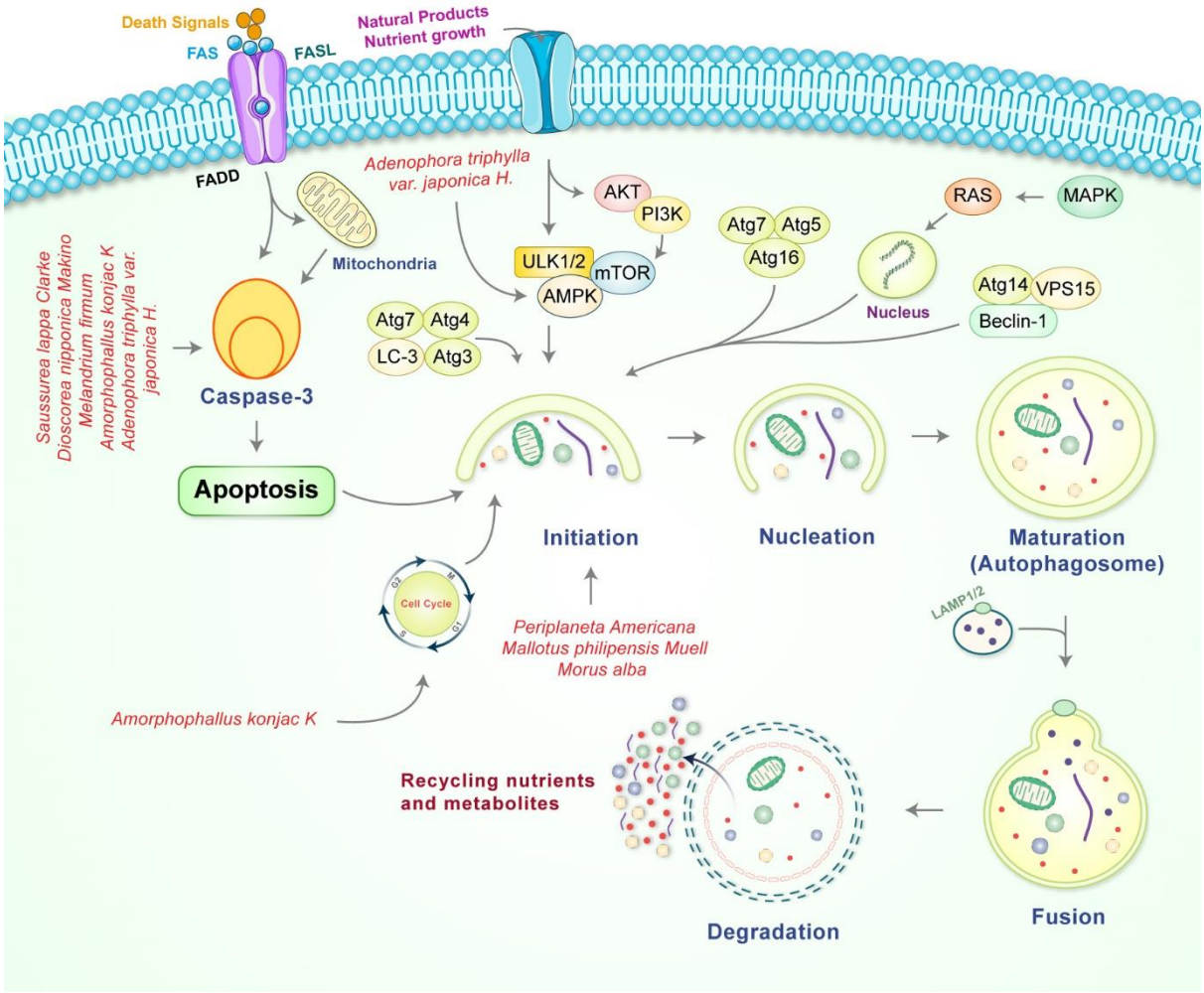

Figure 2. Natural products regulates molecular mechanism of autophagy. Natural products initiate autophagy by the formation of a pre-autophagosomal structure via association of PI3K-AMPK, mammalian target of rapamycin (mTOR), ULK1, Vps34, and the Beclin-1 complex which contribute to the formation of 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 (IC_{50} 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*

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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.

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Table 7. Autophagy-Inducing Natural Products *in vitro.*

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 D_1, 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 (kangfuxin)	*(family: Blattidae)* *Periplaneta americana* Linnaeus.	SGC-7901	0.1, 1 μg/mL; 48 h	↑GRP78, CHOP, caspase-12, LC3-II/LC3-I, Bax ↓Bcl-2	[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.

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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].

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Table 8. Cell Cycle Arrest-Inducing Natural Products.

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+ /Mg^{2+} 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 confluens* (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]

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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) Cinnamonun 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-κB	[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, Mcl-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]

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S		Ethanol extract	*(family: Gentianaceae) Swertia mussotti* Franch.	MGC-803, BGC-823	300, 600, 900 μg/mL; 24 h	↑ROS ↓ΔΨm	[82]
G2/M	Flavonoids	Trifolirhizin	*(family: Fabaceae)* *Sophora flavescens* Aiton. *Radix*	MKN-45	20, 30, 40 μg/mL; 48 h	↑caspase-9, -3, c-PARP, p53, p38 ↓EGFR, CDC2, cyclin B, ΔΨm	[44]
G2/M	Phytosterols	Phloretin		AGS	4. 8, 16μM; 24 h	↑Bax ↓Bcl-2	[55]
G2/M	Phytosterols	Tanshinone IIA	*(family: Lamiaceae) Salviae miltiorrhiza* Bunge. *Radix*	AGS	2.0, 3.7, 5.5 μg/mL; 24, 48 h	↑TNF-α, Fas, p-p38, p-JNK, p53, p21, caspase-8, -3 ↓p-ERK, CDC2, cyclin A, cyclin B1	[46]
G2/M	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	↑p21, caspase-3, c-PARP ↓p-STAT3, pro-caspase-9, ΔΨm	[60]
G2/M		Ethanol and n-hexane extract	*(family: Euphorbiaceae) Euphorbia lunulata* Bunge.	SGC-7901, ADR	10, 20, 40 μg/mL; 24 h	↑Bax, caspase-3, -8, -9 ↓Bcl-2	[76]

Bax, Bcl-2 like protein 4; Bcl-2, B-cell lymphoma 2; Fas, fasciclin; p-IκBα, phospho-inhibitor of nuclear factor kappa B-α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; mTOR, mammalian target of rapamycin; Skp2, S-phase kinase-associated protein 2; CDKN2, cyclin-dependent kinase inhibitor 2; MEK1, mitogen activated protein kinase 1; MEKK3, mitogen activated protein kinase kinase 3; MEK5, mitogen activated protein kinase 5; Bid, BH3 interacting-domain death agonist; Bad, Bcl-2 associated agonist of cell; Bak, Bcl-2 antagonist/killer 1; cyt c, cytochrome c; c-caspase-3, cleaved caspase 3; c-caspase-8, cleaved caspase 8; c-caspase-9, cleaved caspase 9; AIF, apoptosis inducing factor; PARP, poly ADP ribose polymerase; Bcl-xL, B cell lymphoma-extra large ; IκB, inhibitor of nuclear factor kappa B-α; c-PARP, c-PARP, cleaved poly ADP ribose polymerase; Mcl-1, Myeloid cell leukemia-1; XIAP, X-linked inhibitor of apoptosis protein; RBBP4, retinoblastoma-binding protein 4; RUVBL1, RubA like AAA ATPase 1; NPM, Nucleophosmin 1; PI3K, Phosphoinositide 3-kinase; Akt1, protein kinase B 1; ROS, reactive oxygen species; ΔΨm, mitochondrial membrane potential; p-STAT3, phospho-Signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-alpha; p-p38, phosphorylated p38; p-JNK, phosphorylated Jun N-terminal protein kinase; p-ERK, phosphorylated extracellular-signal-regulated kinase; EGFR, epidermal growth factor receptor; CDC2, cell division control protein 2. *The part of the plant used in this was not mentioned in the study.

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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-angiogenesis 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), Poria cocos* (Peck) Ginns *(Polyporaceae), Aurantii immaturus fructus (Rutaceae), Citri reticulatae 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.

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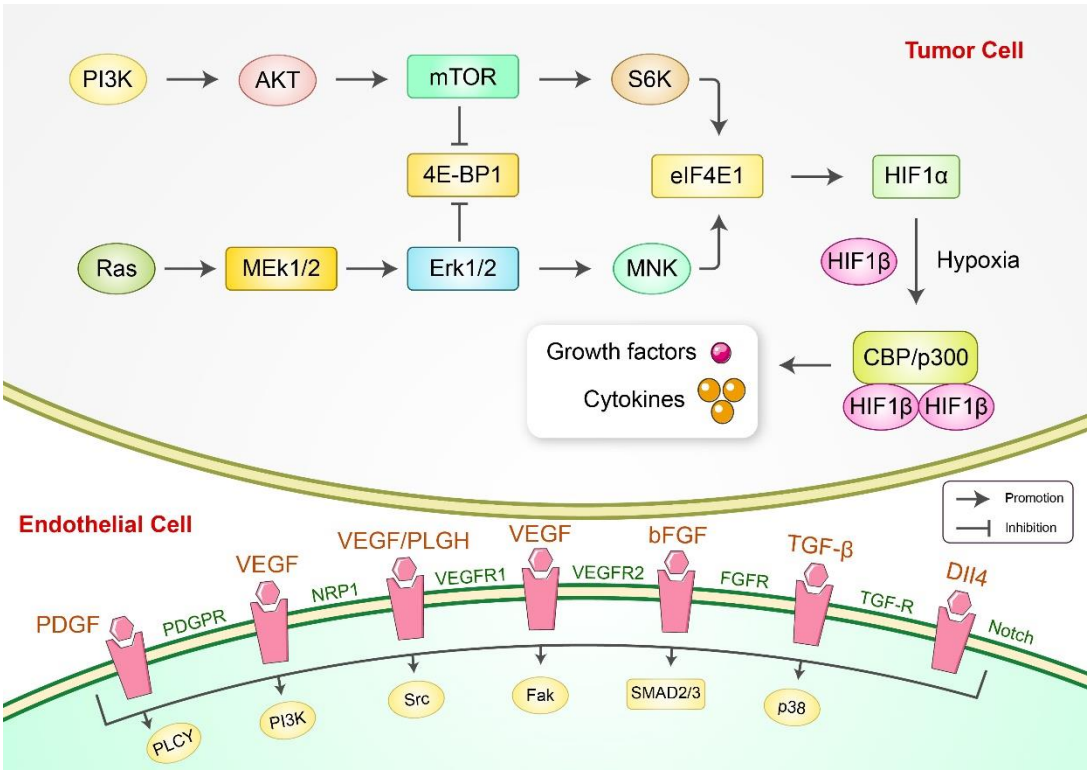

Figure 3. Schematic diagram of angiogenesis signaling pathways. PI3K, Phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; S6K, S6 kinase; MEK1/2, mitogen activated protein kinase kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2; MNK, Mitogen-activated protein kinase-interacting kinase; 4E-BP1, eIF4E-binding protein 1; elF4E1, 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.

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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) Ginns*, (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) Ginns*, (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

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Table 10. Angiogenesis-Inhibiting Natural Products *in vivo*

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: Polyporaceae) Poria cocos* (Peck) Ginns*, (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.	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

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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 *Evoida rutaecarpa (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* Plenk (*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 homobox 1 (CDX1), caudal type homobox 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. Paenol, the water extract of *Paeonia 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 (*Meiliaceae*) 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, galectin-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

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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 paeonol 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 demusticus* Brisson *Endothelium corneum (Phasianidae)*, *Fritillariae cirrhosae Bulbus* (*Liliaceae)*, *Semen brassicae* and *Glycyrrhiza uralensis* Fisch (*Febaceae)* [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 extracts of 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/Fabacea)* [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 fibronectin (FN). Apoptosis and cell cycle arrest was also observed as described above.

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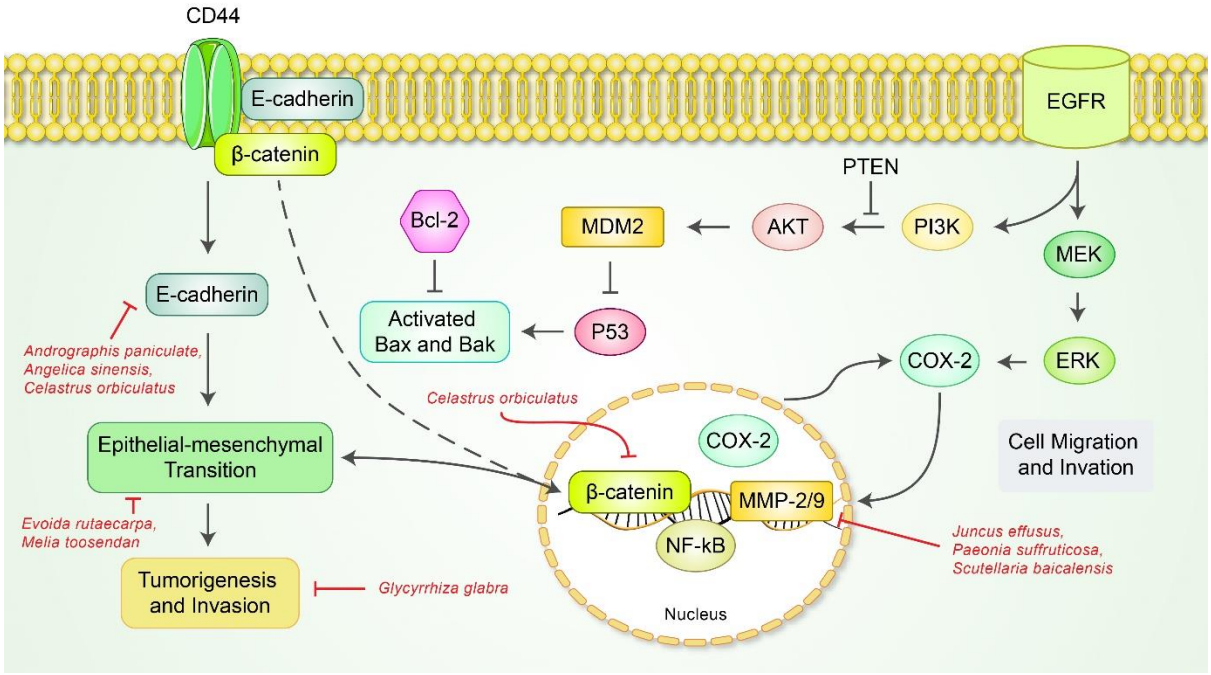

Figure 4. Schematic diagram of metastasis signaling pathways. Akt, protein kinase B; Bak, Bcl-2 antagonist/killer 1; Bax, Bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; CD44, homing cell adhesion molecule; COX-2, cyclooxygenase 2; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MDM2, murine double minute 2; MEK, miTable 2. matrix metalloproteinase-2/9; NF-κB, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog.

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Table 11. Metastasis-inhibiting natural products *in vitro*.

Classification	Compound/ Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Alkaloids	Evodiamine	*(family: Rutaceae) Tetradium rutidcarpum*	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, Bcl-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 ↓Bcl-2, CD147, MMP-2, MMP-9, survivin	[127]

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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 Induction of apoptosis and cell cycle arrest	↑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-Butylideneph-thalide	*(family: Apiaceae) Angelica sinensis* (Oliv.) Diels *Radix*	(1) AGS (2) NCI-N87 (3) TSGH-9201	(1) 50 μg/mL; 24, 48 h (2) 75 μg/mL; 24, 48 h (3) 0, 25, 50, 75 μg/mL; 48 h	Inhibition of migration, invasion and EMT	↑E-cadherin ↓N-cadherin, vimentin slug	[63]
	Ethyl acetate extract	*(family: Celastraceae) Celastrus orbiculatus* Thunb. *Rhizoma*	SGC-7901	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 bellerica (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]

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	Xiaotan Sanjie decoction	*(family: Araceae) Pinellia ternata* Breitenbach *Rhizoma, (family: Araceae) Arisaema erubescens* Schott *Rhizoma, (family: Polyporaceae) Poria cocos* (Peck) Ginns*, (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	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) Cinnamonun 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	Induction of apoptosis and cell cycle arrest	↑Bax, c-caspase-3, IkB ↓Bcl-2, p65, NF-κB	[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, epithelia 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

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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: Polyporaceae) Poria cocos Wolf., (family: Ranunculaceae) Coptis chinensis* Franch., *(family: Rubiaceae) Oldenlandia diffusa* (Willd.) Roxb. *Herba, (family: Compositae) Taraxaci Herba*, (family: Lauraceae) Cinnamonun cassia* J. Presl *twig, (family: Polygonaceae) Rhubarb*, (family: Paeoniaceae) Paeonia lactiflora* Pallas., *(family: Leguminosae/Fabaceae) Glycyrrhizae uralensis* Fischer.	Wistar rats	3.4 mL/kg; 2 weeks	Induction of cell cycle arrest	↑Bax, c-caspase-3, IκB ↓Bcl-2, p65, NF-κB	[90]
Jianpi Bushen decoction	*(family: Campanulaceae) Codonopsis pilosula* Nannfeldt *Radix , (family:Solanaceae) Lycium chinense* Miller *Fructus, (family: compositae) Atractylodis macrocephalae* Koidzumi *Rhizoma, (family: Oleaceae) Ligustri 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; Cdc42, cell division control protein 42 homolog; SDF-1, stromal cell-derived factor 1; FN, fibronectin.

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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 SGC-7901, 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 cotreatment were reported to enhance apoptosis compared to apatinib monotherapy [140]. The efficacy of astragalus polysaccharide, an active component extracted from *Astragalus mambranaceus* 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 *ana*-quinonoid 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.

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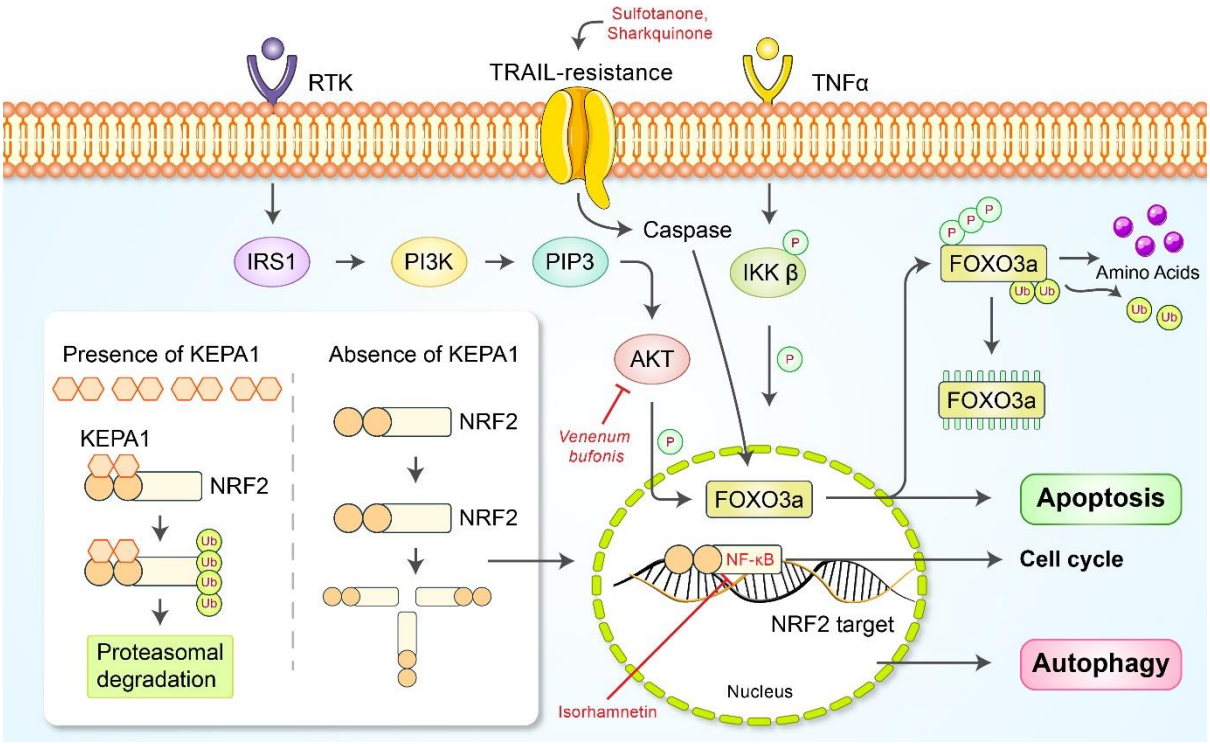

Figure 5. Schematic diagram of resistance signaling pathway. RTK, Receptor tyrosine kinase; IRS1, Insulin receptor substrate 1; PI3K, Phosphoinositide 3-kinases; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; AKT, Protein kinase B (PKB); FOXO3a, Forkhead box O 3; IKK-β, Inhibitor of nuclear factor κB kinase subunit beta; TNF-α, Tumor necrosis factor α; Ub, Ubiquitin; KEAP1, Kelch-like ECH-associated protein 1; NRF2, Nuclear factor erythroid 2-related factor 2.

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. Liquirtin 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 is this review. Curcumin, black currant extract, oligosaccharide isolated from tomato, sulforaphane derived from broccoli, citrus pectin originated from tangerine, grapefruit,

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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.

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Table 13. Drug resistance-overcoming natural products *in vitro.*

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]
Flavonoid	Liquiritin	*(family: Leguminosae/Fabaceae/Fabaceae) Glycyrrhiza 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]
Phytosterol	Bufalin	*Venenum bufonis*	SGC7091, MKN45, BGC823	50, 100, 200 nM; 48 h	Inhibition of acquired cisplatin resistance and proliferation Induction of apoptosis	↓Akt	[139]
Polyphenol	Astragalus polysaccharide	(*family: Leguminosae/Fabaceae/Fabaceae*) *Astragalus mambranaceus* Bunge*Radix*	AGS	20 μg/mL; 24 h	Synergistic effect of inhibitory effects on cell proliferation, migration, invasion and apoptosis with apatinib	↓Akt, MMP-9	[140]

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				10 μM; 24 h			
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 rutaecarpa* 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.

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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. Decoctions 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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