Review

Phytochemicals for the Prevention and Treatment of Gastric Cancer: Effects and Mechanisms

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Abstract: Gastric cancer is the fifth most common cancer, and the third most prevalent cause of cancer-related deaths in the world. Voluminous evidence has demonstrated that phytochemicals play a critical role in the prevention and management of gastric cancer. Most epidemiological investigations indicate that the increased intake of phytochemicals could reduce the risk of gastric cancer. Experimental studies have elucidated the mechanisms of action, including inhibiting cancer cell proliferation, inducing apoptosis and autophagy, and suppressing angiogenesis as well as cancer cell metastasis. These mechanisms have also been related to the inhibition of Helicobacter pylori and the modulation of gut microbiota. In addition, the intake of phytochemicals could enhance the efficacy of anticancer chemotherapeutics. Moreover, clinical studies have illustrated that phytochemicals have the potential for the prevention and the management of gastric cancer in humans. To provide an updated understanding of relationships between phytochemicals and gastric cancer, this review summarizes the effects of phytochemicals on gastric cancer, highlighting the underlying mechanisms. This review could be helpful for guiding the public in preventing gastric cancer through phytochemicals, as well as in developing functional food and drugs for the prevention and treatment of gastric cancer.

Keywords: phytochemicals; gastric cancer; anticancer; mechanism of action

1. Introduction

According to the data from the World Health Organization in 2015, cancer has become an important cause of premature death in many countries [1]. Gastric cancer is the fifth most commonly diagnosed cancer in the world, and its mortality ranks third in cancers, with an estimated 783,000 deaths in 2018 [1,2]. Due to the high incidence and mortality rate, gastric cancer is considered a severe public
health problem [3]. According to the anatomy of stomach, gastric cancer can be classified into cardia and noncardia gastric cancer. In histopathology, gastric cancer can be categorized into intestinal-type and diffuse-type [4]. *Helicobacter pylori* infection, high salt intake and smoking are considered to be the main risk factors for gastric cancer worldwide. In Europe, the amplification of HER-2 gene was found to be a risk factor [5]. In Asia, a study revealed that ethnicity plays a role in the onset of gastric cancer, and Chinese race was more susceptible to the cancer [6]. To date, chemotherapy, radiation therapy, and gastrectomy have been recognized as the main therapies for treating gastric cancer [7]. However, these therapies usually cause severe side effects or toxicity, thus restricting their application [8,9]. Additionally, the resistance of anticancer drugs also limits the success rate of chemotherapy [10]. Thus, it is urgent and necessary to find a more effective and less toxic strategy for the prevention and management of gastric cancer.

Diet plays a prominent role in gastric cancer prevention and management [11]. Increasing evidence from epidemiological studies indicated that natural dietary products have anticancer activity, such as fruits, vegetables, spices, soy, cereals, and edible macro-fungi [12–15]. Furthermore, many studies found that the risk of gastric cancer was inversely associated with the intake of natural products [16]. The beneficial effects of these natural products could be attributed to the phytochemicals [17–19], and the chemical structures of several phytochemicals are showed in Figure 1. In addition, experimental studies indicated that phytochemicals exhibited protective effects against gastric cancer through several mechanisms, including inhibition of cell proliferation [20], induction of apoptosis [21] and autophagy [22], anti-angiogenesis [23], suppression of cell metastasis [24], modulation of gut microbiota [25], and inhibition of *Helicobacter pylori* [26]. Moreover, the use of phytochemicals could be a promising adjuvant therapy for gastric cancer. This review aims to summarize the effects of phytochemicals on the prevention and management of gastric cancer, with the mechanisms of action intensively discussed, and it also illustrates the bioavailability and safety of phytochemicals.

![Figure 1. Chemical structures of several phytochemicals against gastric cancer.](image-url)
2. Epidemiological Studies

Numerous epidemiological studies have demonstrated that the consumption of natural dietary products is essential to the prevention and management of gastric cancer [27,28]. A case-control study reported that the consumption of fresh fruits and vegetables could reduce the risk of gastric cancer with an odds ratio (OR) of 0.15 (95% CI, 0.04–0.64) [6]. In addition, the frequent intake of citrus fruits, vegetables, legumes, garlic, and olive oil showed protective effects against gastric cancer [29]. Additionally, the consumption of garlic, onion, and citrus fruits was reported to decrease the risk of gastric cancer with ORs of 0.35 (95% CI, 0.13–0.95), 0.34 (95% CI, 0.19–0.62), and 0.31 (95% CI, 0.17–0.59), respectively [30]. A meta-analysis also found that the high intake of citrus fruits could reduce the risk of gastric cancer (OR, 0.72; 95% CI, 0.64–0.81) [31]. Moreover, the increased intake of mushroom and soybean products was associated with a lower risk of gastric cancer with OR of 0.30 (95% CI, 0.15–0.62) and 0.35 (95% CI, 0.16–0.75), respectively [32].

Several cohort studies also reported that the intake of fresh fruits and vegetables was inversely associated with the risk of gastric cancer [33,34]. The intake of total plant food, including whole grains, vegetables, and citrus fruit, was negatively related to gastric cancer risk in men (RR, 0.79; 95% CI, 0.67–0.93) [35]. Furthermore, higher consumption of brassica vegetables and citrus fruits was correlated with a decreased risk of gastric noncardia cancer with RRs of 0.51 (95% CI, 0.28–0.92) and 0.38 (95% CI, 0.21–0.69), respectively [34]. In addition, a meta-analysis revealed that high intake of allium vegetables could decrease the risk of gastric cancer (OR, 0.54; 95% CI, 0.43–0.65) [36]. Additionally, a decrease in gastric cancer risk was observed with increased intake of yellow vegetable and white vegetable with ORs of 0.64 (95% CI, 0.45–0.92) and 0.48 (95% CI, 0.25–0.89), respectively [33]. High consumption of green and yellow vegetables was associated with lower mortality of gastric cancer (RR, 0.4; 95% CI, 0.2–0.9) [34]. Moreover, soy products also had a protective effect against gastric cancer [18,37]. A prospective study suggested that the intake of total soy products could decrease the risk of gastric cancer death with hazard ratio (HR) of 0.5 (95% CI, 0.26–0.93) [28]. Additionally, the consumption of tofu was inversely associated with distal gastric cancer risk in men (HR, 0.64; 95% CI, 0.42–0.99), and the high intake of dry bean showed a protective effect against gastric cancer in postmenopausal women (HR, 0.63; 95% CI, 0.43–0.91) [38].

The phytochemicals in the dietary natural products played a critical role in reducing the risk of gastric cancer. For example, a case-control study suggested that the intake of total quercetin in foods and beverages was reversely related to the risk of noncardiac gastric adenocarcinoma, with an adjusted OR of 0.57 (95% CI, 0.40–0.83) [19]. Additionally, a nested case-control study revealed that the increased plasma level of β-carotene mainly from fruits and vegetables was associated with the reduced risk of gastric cancer (OR, 0.46; 95% CI, 0.28–0.75) [39]. Another study showed that the concentration of isoflavones in serum was negatively related to gastric cancer risk [37]. Moreover, the increased intake of total dietary flavonoids and lycopene was related to the decreased risk of gastric cancer with ORs of 0.49 (95% CI, 0.31–0.76) and 0.60 (95% CI, 0.42–0.85), respectively [40,41]. Furthermore, a high intake of anthocyanidins presented a reduction in the mortality of gastric cardia cancer (HR, 0.63; 95% CI, 0.42–0.95) [42]. In addition, another study found that isothiocyanates were effective in protecting against gastric cancer, particularly among those who were lack of genes GSTMI (glutathione S-transferase M1) and GSTTI (glutathione S-transferase T1) (OR, 0.44; 95% CI, 0.21–0.93) [43].

However, there are inconsistent results in some epidemiological studies regarding the association between the consumption of fruits and vegetables and gastric cancer risk [44,45]. A cohort study demonstrated that the intake of fruits was not significantly correlated with the risk of gastric cancer, while high consumption of green leafy vegetables and root vegetables significantly reduced the risk of gastric cancer with HRs of 0.64 (95% CI, 0.42–0.99) and 0.43 (95% CI, 0.27–0.69), respectively [46]. Additionally, a pooled analysis of four cohort studies demonstrated that the total vegetable consumption was inversely related to distal gastric cancer risk in men (multivariate HR, 0.78; 95% CI, 0.63–0.97), whereas there was no association between total fruit intake and the risk of gastric cancer [44]. Furthermore, an inverse association was observed between fruit consumption and distal gastric cancer.
risk in men (HR, 0.50; 95% CI, 0.29–0.84), while no relation was found in women [47]. In a prospective study, citrus fruit intake could decrease the risk of gastric cardia cancer, but the intake of vegetables was not related to the risk of gastric cancer [45]. Furthermore, evidence from cohort studies pointed out that the consumption of garlic was not correlated with gastric cancer risk, with a pooled multivariable RR of 1.39 (95% CI, 0.89–2.17) [48]. Additionally, it was inconsistent with the effects of some phytochemicals on the incidence of gastric cancer. The intake of isoflavone or flavonoid showed no relationship with gastric cancer risk [49,50]. Moreover, no association was found between the intake of carotenoids and the risk of gastric cancer [51]. The inconsistent results might be due to the consumed levels of phytochemicals and the differences in regions, dietary, and lifestyles, as well as the data accessing methods [37].

Overall, most epidemiological investigations have suggested that the consumption of natural dietary products is inversely associated with the risk of gastric cancer (Table 1). The protective effects of natural dietary products against gastric cancer could be attributed to the phytochemicals. However, several cohort studies have found that the intake of some vegetables, fruits, and phytochemicals had no effects on gastric cancer. Thus, more epidemiological studies with better design and quality control are needed in the future.

3. Experimental Studies

The effects of phytochemicals against gastric cancer have been extensively investigated, and the mechanisms of action have been also explored. These anti-cancer effects and mechanisms will be intensively discussed below.

3.1. Inhibition of Cell Proliferation

It has been well documented that various phytochemicals can inhibit the proliferation of human gastric cancer cells and the growth of gastric tumors in mice. In several in vitro studies, allitridi [52], mycelia and polysaccharides of a mushroom [20], labdane diterpenes in Curcuma mangga rhizomes [53], poncirin [54], and apigenin [55] were found to inhibit the proliferation of human gastric cancer cell lines. Additionally, the extract of ramson could arrest AGS human gastric cancer cells in G2/M phase via the downregulation of cyclin B, resulting in the inhibition of proliferation [56]. Additionally, diallyl disulfide isolated from garlic could arrest MGC803 human gastric cancer cells at the G2/M phase by activating the expression of checkpoint kinase-1 (Chk1), as well as ataxia telangiectasia and Rad3-related (ATR) protein kinases, and decreasing the expression of cell division cycle 25C (CDC25C) and cyclin B1 [57]. Another study found that the activation of p38 mitogen-activated protein kinase (MAPK) pathway was involved in diallyl disulfide-induced G2/M arrest [58]. It could also induce the differentiation of MGC803 cells by decreasing the phosphorylation of extracellular signal-regulated kinase (ERK1/2) protein [59]. Furthermore, diallyl trisulfide, a garlic organosulfide showed an antiproliferative effect on AGS cells by inducing mitotic arrest with increased expression of cyclin B1 and tumor suppressor p53 [60]. Moreover, latcripin 1 from a mushroom had an antiproliferative effect against SGC-7901 and BGC-823 gastric cancer cells by arresting cells at the S phase [61]. Furthermore, myricetin exhibited an antiproliferative effect against HGC-27 and SGC7901 cells by downregulating the expression of cyclinB1, cyclinD1, CDK1, and CDC25C [62]. An in vivo study pointed out that S-allylmercaptocysteine, one of the garlic derivatives, could suppress the growth of SGC-7901 xenografts in BALB/c nude mice [63]. In addition, 6-shogaol from ginger inhibited the gastric tumor growth in athymic nude mice, and it was also found to inhibit the viability of gastric cancer cells, damage microtubules and induce mitotic arrest [64]. Furthermore, (-)-epigallocatechin gallate (EGCG) inhibited the proliferation of SGC-7901 gastric cancer cells and the growth of gastric tumors in mice by suppressing Wnt/β-catenin signaling [65].
Table 1. The effects of natural dietary products against gastric cancer from epidemiological studies.

| Natural Products | Phytochemicals | Subjects | Study Type | Consumed Levels | Effects | Ref. |
|------------------|----------------|----------|------------|-----------------|---------|------|
| **Fruits**       |                |          |            |                 |         |      |
| Citrus fruits    | NA             | 217 Gastric cancer cases (mean age: 65.4; 151 men) and controls (mean age: 64.3; 265 men) in Iran 120,852 Subjects in Netherlands (58,279 men and 62,573 women), 156 gastric cardia adenocarcinoma cases and 460 gastric noncardia adenocarcinoma cases; aged 55–69 years | Case-control | ≥3 times/week vs. never or infrequently intake of citrus fruits | Reducing gastric cancer risk (OR, 0.31; 95% CI, 0.17–0.59) | [30] |
| Citrus fruits    | NA             | 120,852 Subjects in Netherlands (58,279 men and 62,573 women), 156 gastric cardia adenocarcinoma cases and 460 gastric noncardia adenocarcinoma cases; aged 55–69 years | Cohort study | The highest (median = 156 g/d) vs. the lowest quintile (median = 0 g/d) of citrus fruits | Reducing the risk of gastric noncardia cancer (RR, 0.38; 95% CI, 0.21–0.69) | [34] |
| Total fruits (except watermelon) | NA | 559,247 Chinese men in the cohort and 132 distal gastric cancer cases; aged 40–74 years | Cohort study | ≥104.2 vs. ≤20.1 g/d all fruits (except watermelon) | Reducing distal gastric cancer risk (HR, 0.50; 95% CI, 0.29–0.84) | [47] |
| Total fruits (except watermelon) | NA | 73,064 Chinese women in the cohort and 206 distal gastric cancer cases; aged 40–70 years | Cohort study | >208.0 vs. ≤61.5 g/d all fruits (except watermelon) | No association (HR, 1.02; 95% CI, 0.68–1.54) | [47] |
| Total fruit      | NA             | 191,232 Japanese subjects, (87,771 men and 103,461 women) and 2995 gastric cancer cases (2104 men and 891 women) | Pooled analysis | The highest quintile vs. the lowest quintile of total fruit | No association (HR, 0.9; 95% CI, 0.67–1.22) | [44] |
| **Vegetables**   |                |          |            |                 |         |      |
| Brassica vegetables | NA          | 120,852 Subjects in Netherlands (58,279 men and 62,573 women), 156 gastric cardia adenocarcinoma cases and 460 gastric noncardia adenocarcinoma cases; aged 55–69 years | Cohort study | The highest (median = 59 g/d) vs. the lowest quintile (median = 11 g/d) of Brassica vegetables | Reducing the risk of gastric noncardia cancer (RR, 0.51; 95% CI, 0.28–0.92) | [34] |
| Total vegetables | NA             | 559,247 Chinese men in the cohort and 132 distal gastric cancer cases; aged 40–74 years | Cohort study | >429.3 vs. ≤212.9 g/d total vegetables | No association (HR, 1.00; 95% CI, 0.59–1.68) | [47] |
| Total vegetables | NA             | 73,064 Chinese women in the cohort and 206 distal gastric cancer cases; aged 40–70 years | Cohort study | >373.7 vs. ≤179.5 g/d total vegetables | No association (HR, 0.89; 95% CI, 0.60–1.31) | [47] |
| Natural Products          | Phytochemicals | Subjects                                                                 | Study Type                      | Consumed Levels                                                                 | Effects                                                                                     | Ref. |
|--------------------------|----------------|--------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------|
| Total vegetables         | NA             | 191,232 Japanese subjects, (87,771 men and 103,461 women) and 2995 gastric cancer cases (2104 men and 891 women) | Pooled analysis                 | The highest quintile vs. the lowest quintile of total vegetable                  | Reducing distal gastric cancer risk in men (multivariate HR, 0.78; 95% CI, 0.63–0.97)          | [44] |
| Fruits and vegetables    | β-carotene     | 511 Japanese gastric cancer cases (342 men) and 511 controls (342 men); aged 40–69 years | Nested case-control             | ≥27.0 vs. ≤8.0 ug/dL β-carotene                                                | Reducing gastric cancer risk (OR, 0.46; 95% CI, 0.28–0.75)                                   | [39] |
| Vegetables, citrus fruits, and whole grains | NA | 970,045 American subjects (533,391 women and 436,654 men) and 439 women and 910 men died from gastric cancer | Cohort study                    | The highest vs. the lowest tertile of plant foods                              | Reducing gastric cancer risk in men (RR, 0.79; 95% CI, 0.67–0.93)                             | [35] |
| Fruits, vegetables and beverages | Quercetin | 505 Swedish gastric cancer cases (336 men) and 1116 controls (746 men); aged 40–79 years | Case-control                    | ≥11.9 vs. <4 mg/day quercetin                                                  | Reducing noncardia gastric adenocarcinoma risk (OR, 0.57; 95% CI, 0.40–0.83)                   | [19] |
| Spices                   |                |                                                                          |                                 |                                                                                 |                                                                                              |      |
| Allium vegetables        | NA             | 543,220 Total subjects                                                  | Meta-analysis                   | The highest vs. the lowest consumption category of allium vegetables           | Reducing gastric cancer risk (OR, 0.54; 95% CI, 0.43–0.65)                                   | [36] |
| Garlic                   | NA             | 217 Gastric cancer cases (mean age: 65.4; 151 men) and controls (mean age: 64.3; 265 men) in Iran | Case-control                    | ≥3 times/week vs. never or infrequently intake of garlic                       | Reducing gastric cancer risk (OR, 0.35; 95% CI, 0.13–0.95)                                   | [30] |
| Onion                    | NA             |                                                                          |                                 | ≥ once per day vs. ≤2 times/week onion                                        | Reducing gastric cancer risk (OR, 0.34; 95% CI, 0.19–0.62)                                   |      |
| Soy and soy products     | Isoflavone     | 84,881 Japanese subjects (39,569 men and 45,312 women), 1249 gastric cancer cases; aged 45–74 years | Cohort study                    | The highest vs. the lowest quartile of isoflavone                             | No association (HR, 1.00; 95% CI, 0.81–1.24 for men and HR, 1.07; 0.77–1.50 for women)       | [49] |
| Soy                      | Isoflavone     | 30,792 Japanese subjects (14,219 men and 16,573 women), 678 gastric cancer cases (441 men and 237 women); aged ≥ 35 years | Cohort study                    | >53 vs. ≤28 mg/d isoflavone                                                  | Reducing gastric cancer risk in women (HR, 0.60; 95% CI, 0.37–0.98)                           | [18] |
|                          |                |                                                                          |                                 | >122 vs. ≤62 g/d soy food                                                    | Reducing gastric cancer risk in men (HR, 0.71; 95% CI, 0.53–0.96) and women (HR, 0.58; 95% CI, 0.36–0.94) |
Table 1. Cont.

| Natural Products       | Phytochemicals | Subjects                                                                 | Study Type       | Consumed Levels                                                                 | Effects                                                                                           | Ref. |
|------------------------|----------------|--------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|------|
| Tofu                   | NA             | 128,687 Chinese subjects (70,446 women and 58,241 men), 493 distal gastric cancer cases; aged 40–74 years | Cohort study     | >8.4 vs. <3.1 g/d tofu                                                        | Reducing distal gastric cancer risk in men (HR, 0.64; 95% CI, 0.42–0.99)                              | [38] |
| Dry bean               | NA             |                                                                           |                  | >0.9 vs. 0.0 g/d dry bean                                                     | Reducing gastric cancer risk in postmenopausal women (HR, 0.63; 95% CI, 0.43–0.91)                  |      |
| Total soy product      | NA             | 30,304 Japanese subjects (13,880 men and 16,424 women) and 121 gastric cancer deaths; aged ≥ 35 years | Cohort study     | The highest (median = 49.7 g/d) vs. the lowest tertile (median = 140 g/d) of total soy product | Reducing the risk of gastric cancer death (HR, 0.5; 95% CI, 0.26–0.93)                              | [28] |

| Cereals                | Other          |                                                                           |                  |                                                                                |                                                                                                   |      |
| Flavonoids             | 469,008 American subjects (275,982 men and 193,026 women), 1297 gastric cancer cases; aged 50–71 years | Cohort study     | 438.0–4211.2 vs. 0–84.1 mg/d total flavonoids                                | No association (HR, 1.02; 95% CI, 0.78–1.34) for gastric cardia cancer; (HR, 1.11; 95% CI, 0.86–1.44) for gastric noncardia cancer | [50] |
| Flavonoids             | 334 Korean gastric cancer cases (208 men) and 334 controls (208 men); aged 35–75 years | Case-control study | The highest tertile (median = 152.3 mg/d) vs. the lowest tertile (median = 52.5 mg/d) of flavonoids | Reducing gastric cancer risk (OR, 0.49; 95% CI, 0.31–0.76)                                          | [40] |
| Anthocyanidins         | 248 American gastric cardia cancer cases and 662 controls; aged 30–79 years | Case-control study | ≥18.48 vs. ≤7.21 mg/d anthocyanidins                                         | Reducing the risk of mortality for gastric cardia cancer (HR, 0.63; 95% CI, 0.42–0.95)              | [42] |

NA: not available.
3.2. Induction of Apoptosis

Induction of apoptosis has been found to be a pivotal mechanism of the inhibition on the initiation and the development of cancer [66–68]. It was found that protocatechuic acid could induce the apoptosis of AGS cells through Fas/Fas ligand (FasL) death receptor or mitochondrial pathways accompanied with phosphorylation of c-Jun N-terminal kinase (JNK), p38 mitogen-activating protein kinases (MAPK), and p53 [69]. Additionally, poncirin, rich in citrus fruits, could induce apoptosis in AGS cells via death receptor pathway with increased level of FasL protein, activation of Caspase-8 and Caspase-3, and cleavage of poly (ADP-ribose) polymerase (PARP) [70]. Additionally, the treatment of Citrus reticulata Blanco extract could increase apoptosis in SNU-668 human gastric cancer cells through upregulating the expression of B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and Caspase-3 [71]. Furthermore, an in vitro study demonstrated that α-mangostin isolated from the pericarp of mangosteen induced apoptosis of BGC-823 and SGC-7901 human gastric cancer cell lines via the reduction of the mitochondrial membrane potential, and the suppression of STAT3 signaling pathway with decreased B-cell lymphoma-extralarge (Bcl-xL) and apoptosis regulator Mcl-1 protein levels [72]. In human gastric signet ring carcinoma cells, the extract of dried ripe fruit of Vitex agnus-castus induced apoptosis via intracellular oxidative stress and mitochondrial membrane damage [73]. Moreover, hispolon, a phenolic compound of Phellinus linteus, exhibited cytotoxic activity against human gastric cancer cells but not normal gastric cells via the induction of apoptosis, associated with the mitochondrial pathway [74]. Furthermore, the black soybean extracts induced apoptosis of AGS cells in a dose-dependent manner by increasing the levels of Bax and Caspase-3, as well as the cleavage of PARP [75]. It was found that piperlongumine (isolated from the fruit of long pepper) inhibited the activity of thioredoxin reductase 1 (TrxR1), resulting in the induction of apoptosis in human gastric cancer cells via reactive oxygen species (ROS)-triggered ER-stress and mitochondrial dysfunction [21]. In addition, it was observed that allitridi could lead to apoptosis by decreasing the expression of Bcl-2 and increasing the level and activity of Caspase-3 in BGC823 human gastric cancer cell line [52]. Furthermore, it was found that catechin extract and EGCG of green tea [76], theaflavins of black tea [77], and polyphenol extract of oolong tea [78] could induce apoptosis in KATO III human gastric cancer cells. In murine gastric cancer syngeneic model, bamboo-shaving polysaccharides inhibited tumor growth and prolonged the survival of mice bearing a gastric tumor by inducing tumor cell apoptosis [79]. Accumulating evidence has suggested that phytochemicals can induce apoptosis of gastric cancer cells mainly through death receptors or mitochondrial pathways (Figure 2).

3.3. Autophagy

Autophagy is an important process of intracellular material renewal and recycle. Some damaged proteins or organelles are engulfed by autophagosomes and sent to autolysosomes for degradation [80]. It has been demonstrated that autophagy plays a dual role in the development of cancer [22,81]. On one hand, under most conditions, autophagy can induce autophagic cancer cell death. On the other hand, autophagy can suppress apoptosis, contributing to the survival of cancer cells sometimes. In gastric cancer cells, the treatment of kaempferol, a natural flavonoid, induced autophagic cell death via inositol-requiring-1 (IRE1)/JNK/-CCAAT-enhancer-binding protein homologous protein (CHOP), AMPK/UNC-51-like autophagy activating kinase 1 (ULK1), and histone deacetylase (HDAC)/G9a (a histone lysine 9 dimethylation-specific methyltransferase) pathways [22]. Additionally, pectolinarigenin extracted from Cirsium chanroenicum showed anticancer activity by inducing autophagy in AGS and MKN-28 human gastric cancer cells, mainly through the downregulation of phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway [82]. In addition, 3,3′-diindolylmethane isolated from cruciferous vegetables increased the expression of autophagy-related 5 (ATG5) and microtubule associated protein light chain 3 (LC3) in gastric cancer cells and decreased the level of microRNA-30e, which targets gene ATG5 to inhibit its translation [83]. Moreover, the treatment of latcripin 1 protein present in Lentinula edodes could lead to autophagy in SGC-7901 and BGC-823 gastric cancer cell lines accompanied with the formation of
autophagosomes via the change of LC3I into LC3II [61]. Furthermore, perillaldehyde isolated from *Perilla frutescens* displayed anticancer effects against gastric cancer both in vitro and in vivo. In MFCs mouse and GC9811-P human gastric cancer cells, perillaldehyde increased the phosphorylation of AMPK, leading to autophagy in the cells [84]. In mice bearing gastric tumor, perillaldehyde treatment inhibited the growth of the gastric tumor and upregulated the levels of autophagy-associated proteins, such as beclin-1, LC3-II, and cathepsin. However, it was found that quercetin induced protective autophagy against the apoptosis of AGS and MKN-28 gastric cancer cells, suggesting that autophagy could contribute to the survival of cancer cells in certain circumstances [85].

**Figure 2.** The anticancer mechanisms of phytochemicals on gastric cancer. Diallyl disulfide induced G2/M arrest by activating MAPK pathway. Zerumbone showed anti-angiogenesis activity via the inhibition of Notch1/NF-κB/VEGF pathway. Kaempferol induced autophagic cell death via IRE1/JNK/CHOP and AMPK/ULK1 pathways. Pectolinarigenin induced autophagic cell death via PI3K/Akt/mTOR pathway. Poncirin induced apoptosis via the death receptor pathway. Piperlongumine induced apoptosis via ROS-triggered ER-stress and mitochondrial dysfunction, while protecatechic acid induced apoptosis either through Fas/FasL death receptor or mitochondrial pathways. Tangeretin inhibited migration and invasion by reducing the expressions of Notch-1, Jagged1/2 and Hey-1. Gallic acid could suppress metastasis by downregulating PI3K/Akt pathway.

### 3.4. Inhibition of Tumor Angiogenesis

It has been reported that angiogenesis is critical for tumor growth and survival prognosis of gastric cancer [86]. Vascular endothelial growth factor (VEGF), a cytokine produced by tumor cells, plays an important role in angiogenesis [87]. Luteolin, a dietary flavonoid, was found to inhibit angiogenesis and the formation of vasculogenic mimicry tube in MGC-803 and Hs-746T gastric cancer cells via the suppression of notch receptor 1 (Notch1)/VEGF signaling [88]. Additionally, zerumbone, a bioactive component of ginger, showed anti-angiogenesis activity in AGS cells by decreasing the expression of VEGF via the inhibition of nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) [89]. Moreover, in SGC-7901 and AGS human gastric cancer cell lines, nitidine chloride, generated from *Zanthoxylum nitidum* (Roxb) DC, was found to inhibit signal transducer and activator of transcription 3 (STAT3) signaling, which was associated with tumor angiogenesis. In a xenograft mouse model induced by SGC-7901 cells, the treatment of nitidine chloride reduced the volume of tumors via the inhibition of angiogenesis with decreased levels of STAT3 and VEGF [23].
3.5. Suppression of Cell Metastasis

Invasion and metastasis play a crucial role in the progression of gastric cancer [90]. Several studies found that phytochemicals could inhibit the invasion and metastasis of gastric cancer cells. It was reported that erinacine A present in *Hericium erinaceus* mycelium could inhibit the viability and invasiveness of MKN-28 and TSGH 9201 human gastric cancer cells [91]. In addition, luteolin was effective in suppressing invasion and migration by inhibiting Notch1 signaling and reversing epithelial-mesenchymal transition (EMT) in Hs-746T and MKN-28 gastric cancer cells [92]. Additionally, in SGC7901 cells, tangeretin, a polymethoxylated flavonoid of citrus fruits, inhibited radiation-mediated EMT, migration, and invasion by reducing the expression of Notch-1, two serrate-like ligands (Jagged1/2), two transcription factors (Hey-1 and Hes-1), and increasing the level of miR-410, a tumor-suppressive microRNA [93]. Moreover, gallic acid could suppress the metastasis of AGS cells through decreasing the level of matrix metalloproteinase (MMP)-2, MMP-9, and the activity of NF-κB, and downregulating PI3K/Akt pathway [90]. Gallic acid decreased the expression of RAS, but increased the expression of RhoB. Furthermore, diallyl disulfide inhibited gastric adenocarcinoma cell motility and invasiveness by increasing the tightness of tight junctions and decreasing the levels of MMP-2 and MMP-9 [94].

3.6. Inhibition of Helicobacter Pylori

Accumulating studies have suggested that *Helicobacter pylori* infection can cause various gastric diseases, such as chronic gastritis, peptic ulcers, and atrophic gastritis. The *Helicobacter pylori* infection is highly related to the pathogenesis of gastric cancer, particularly the intestinal type [95–97]. It was reported that infection with cytotoxin-associated gene antigen cagA+ strains of *Helicobacter pylori* might lead to severe gastric inflammation and gastric cancer [98,99]. Moreover, the growth of *Helicobacter pylori* cagA+ strains could be suppressed by curcumin and gingerols in vitro [26,100]. In NCI-N87 gastric carcinoma cells, the expression of CD74 in *Helicobacter pylori*, an adhesion molecule to urease, decreased by bergamottin, a component of citrus fruit, leading to the inhibition of *Helicobacter pylori* adhesion [101]. In addition, the treatment of apigenin, a flavonoid rich in celery, could inhibit *Helicobacter pylori* colonization, and reduce the incidence rate of gastric cancer in *Helicobacter pylori*-infected Mongolian gerbils [102]. Additionally, an in vivo study revealed that curcumin was effective in eliminating *Helicobacter pylori* from infected mice and alleviating *Helicobacter pylori*-induced gastric damage [103].

3.7. Modulation of Gut Microbiota

In recent years, the relationship between gut microbiota and multiple diseases has attracted much attention. The role of gut microbiota on gastric cancer has also been investigated [104,105]. A study revealed that microbiota might be related to gastric cancer, since specific pathogen-free mice were easier to develop atrophic gastritis and gastric cancer than germ-free mice [106]. It was reported that phytochemicals could prevent and manage some cancers via the modulation of gut microbiota, such as colorectal cancer, liver cancer and breast cancer [66]. However, there have been few reports about the anti-gastric cancer of phytochemicals by modulating gut microbiota, which may warrant further elucidation.

3.8. Adjuvant Therapy

Numerous studies have indicated that phytochemicals can enhance the sensitivity of gastric cancer to therapy, and exert a synergistic anticancer effect. A study pointed out that gartanin, a bioactive compound isolated from mangosteen, enhanced the sensitization of AGS human gastric adenocarcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by increasing death receptor 5 [107]. In addition, curcumin was found to enhance the anticancer efficacy of etoposide and doxorubicin, two chemotherapeutic drugs, in SGC-7901 human gastric cancer cells
by inhibiting the activation of NF-κB, and the expression of its related anti-apoptotic gene like Bcl-2 and Bcl-xL [10]. Additionally, the anticancer effects of fluorouracil and cisplatin were potentiated by genistein, an isoflavone present in soy products, which could decrease chemoresistance of MGC-803 cells through reducing the expression of adenosine triphosphate (ATP) binding cassette subfamily G member 2 (ABCG2) and the activity ERK1/2 [108]. Moreover, the combination of paclitaxel and 3,3’-diindolylmethane, a compound of cruciferous vegetables, enhanced the therapeutic efficacy via the inhibition of SNU638 cell proliferation and the induction of apoptosis, which was associated with the downregulation of the Akt/Forkhead box M1 (FOXM1) signaling [109]. Furthermore, combined treatment of diallyl trisulfide and docetaxel showed a synergistic effect against gastric cancer through inducing G2/M cell cycle arrest and apoptosis with increased level of metallothionein 2A (MT2A) and inhibition of NF-κB signaling in BGC823 cells [110]. In another study, diallyl trisulfide enhanced the potency of cisplatin against gastric cancer through the activation of p38 and JNK MAPK signaling pathway, and downregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/Akt pathway in vitro and in vivo [111]. Additionally, 6-gingerol increased the cisplatin sensitivity of HGC-27 cells via the suppression of cell proliferation, migration, and invasion by inactivating PI3K/Akt signaling pathway [112].

Collectively, several phytochemicals exhibit anticancer effects against gastric cancer, such as curcumin, diallyl trisulfide, 3,3’-diindolylmethane and 6-shogaol (Table 2). The mechanisms of action are mainly inhibiting cell proliferation, inducing apoptosis and autophagy, suppressing angiogenesis and metastasis, reducing the Helicobacter pylori infection, and modulating the gut microbiota (Figure 2). Additionally, the combined treatment of phytochemicals and anticancer drugs exhibits synergistic effects against gastric cancer.

4. Clinical Trials

The efficacy of natural products against gastric cancer was also supported in clinical studies. A study reported that daily treatment of 900 mg of Rhus verniciflua Stokes extract decreased the polypoid mass and the flat elevated lesion in an old female patient with gastric adenocarcinoma [123]. Additionally, a randomized intervention trial including 3365 residents revealed that garlic (extract and oil) supplementation could also reduce the mortality of gastric cancer [124]. In a multi-institutional randomized prospective study, combined with clinical medicine tegafur and cisplatin, lentinan could prolong median survival and improve the quality of life in patients with gastric cancer [125]. In addition, a clinical study including 349 subjects with stage II/III gastric cancer revealed that adjuvant treatment of protein-bound polysaccharide K from the mushroom Coriolus versicolor could prolong the survival of major histocompatibility complex (MHC) class I-negative patients [126]. Generally, several natural products exhibited significant synergistic effects with anticancer drugs against gastric cancer. In the future, the anti-gastric cancer effects of more phytochemicals should be confirmed by clinical trials.

5. Bioavailability

Several phytochemicals displayed low bioavailability, such as 3,3’-diindolylmethane and curcumin [127–130]. Some technologies have been applied to increase the bioavailability of phytochemicals, which should improve the anti-gastric cancer action [131,132]. A study showed that 3,3’-diindolylmethane was microencapsulated in starch with d-α-tocopheryl acid succinate, phosphatidylcholine, and silica, which could enhance its bioavailability [127]. In addition, the pterostilbene was encapsulated in nanoemulsions containing carrier oil, which could increase its bioavailability [133]. Moreover, curcumin and genistein showed good solubility and stability after encapsulating within nanostructured lipid carriers [131]. Furthermore, the micellarization could enhance the bioaccessibility of isoflavonoid aglycones [134]. Generally, the bioavailability of phytochemicals can be increased by several methods, such as encapsulation in the nanostructured lipid carriers and micellization.
### Table 2. The effects of phytochemicals against gastric cancer from experimental studies.

| Natural Products | Phytochemicals | Study Type | Models | Mechanisms | Molecular Targets | Ref. |
|------------------|----------------|------------|--------|------------|------------------|-----|
| **Fruits**       |                |            |        |            |                  |     |
| Citrus reticulata| Blanco extract | NA         | In vitro | SNU-668 cells | Induced apoptosis, induced autophagy and apoptosis, inhibited cell growth and proliferation | ↓ Bcl-2, ↑ Bax and caspase-3 | [71] |
| Cirsium chanroenicum| Pectolinarigenin | In vitro | AGS and MKN-28 cells | Inhibited cell growth and proliferation | ↓ p-4EBP1, p-p70S6K, and p-eIF4E, ↑ LC3-II conversion | [82] |
| Citrus fruits    | Poncirin       | In vitro   | AGS cells | Induced apoptosis | ↑ FasL, caspase-8, caspase-3 and PARP cleavage | [70] |
| Black currant    | Phenolic compounds | In vitro | SGC-7901 cells | Inhibited cell proliferation | ↓ p-Rb, cyclin A, cyclin E, Cdk2, Cdk4, and Cdk6, ↑ caspase-2, -3, -8, and -9, PARP cleavage, p53, p2l, p27, and p16 proteins | [113] |
| Blueberries      | Pterostilbene  | In vitro   | AGS cells | Induced apoptosis | ↑ Notch-1, Jagged1/2, Hey-1 and Hes-1, ↑ miR-410 | [93] |
| Citrus fruits    | Tangeretin     | In vitro   | SGC7901 cells | Induced radiation-mediated EMT, migration and invasion | ↓ STAT3, Bcl-xl and Mcl-1, ↑ cytochrome c | [72] |
| Mangosteen       | α-Mangostin    | In vitro   | BGC-823 and SGC-7901 cells | Induced apoptosis, inhibited cell viability | NA | [107] |
| Mangosteen       | Gartanin and TRAIL | In vitro | AGS cells | Enhanced the sensitization of AGS cells to TRAIL | ↑ death receptor 5 | [115] |
| Strawberry       | NA             | In vitro   | SNU-638 cells | Inhibited cell growth | NA | [54] |
| Citrus reticulate cv. Suavissima | Poncirin | In vitro | SGC-7901 cells | Inhibited cell growth | | |
| **Vegetables**   |                |            |        |            |                  |     |
| Cruciferous vegetables | 3,3’-Diindolylmethane | In vitro | BGC-823 and SGC-7901 cells | Inhibited cell proliferation, induced autophagy, inhibited the growth of gastric tumor | ↓ MicroRNA-30e, ↑ ATG5 and LC3 | [83] |
| Cruciferous vegetables | Paclitaxel and 3,3’-diindolylmethane | In vitro | SNU638 cell | Induced apoptosis inhibited proliferation | ↑ PARP, caspase-9, ↓ CDK4, p53, cyclin D1 and p-Akt | [109] |
Table 2. Cont.

| Natural Products | Phytochemicals | Study Type | Models | Mechanisms | Molecular Targets | Ref. |
|------------------|----------------|------------|--------|------------|-------------------|-----|
| Spices | | | | | | |
| Fruit of long pepper | Piperlongumine | In vitro | SGC-7901, BGC-823 and KATO III cells | Induced apoptosis | ↓ TrxR1, ↑ ROS | [21] |
| | | In vivo | Female BALB/cA athymic mice | Reduced tumor cell burden | ↓ TrxR1 | |
| Allitridi | NA | In vitro | BGC823 cells | Induced apoptosis Inhibited cell proliferation | ↑ caspase-3, ↓ Bcl-2 | [52] |
| Allium ursinum L | NA | In vitro | AGS cells | | | |
| Garlic | Diallyl trisulfide | In vitro | HGC, AGS and KATO III cells | Inhibited cell viability Damaged microtubules Suppressed tumor growth | NA | [64] |
| Ginger | 6-Shogaol | In vivo | Athymic nude mice | Anti-angiogenesis | ↓ VEGF and NF-κB | [89] |
| Ginger | Zerumbone | In vitro | AGS cells | | ↑ P21 and P27 | |
| Ginger | 6-Gingerol and cisplatin | In vitro | HGC-27 cells | Inhibited cell proliferation, migration and invasion | ↓ cyclin D1, cyclin A2, MMP-9, p-P3K, Akt, and p-Akt | [112] |
| Curcuma zedoaria rhizomes | Curcuzedoalide | In vitro | AGS cells | Induced apoptosis Inhibited cell viability | ↑ cleavage of caspase-8, caspase-9, caspase-3 and PARP | [116] |
| Curcuma mangga rhizomes | Labdane diterpenes | In vitro | AGS cells | Inhibited cell proliferation | NA | [53] |
| Turmeric | Curcumin, etoposide and doxorubicin | In vitro | SGC-7901 cells | Enhanced the anticancer efficacy of etoposide and doxorubicin | ↓ NF-κB, Bcl-2 and Bcl-xL | [10] |
| Garlic | Diallyl trisulfide and docetaxel | In vitro | BGC823 cells | Induced apoptosis Induced G2/M cell cycle arrest | ↑ MT2A, IκB-α, cyclin B1, activated caspase-3, and Bax, ↓ p-IκB-α, p-P65, cyclin D1, and XIAP | [110] |
| | | In vivo | Female BALB/cA athymic mice | Inhibited tumor growth | ↑ MT2A, IκB-α, CCNB1, and a-CASP3, ↓ CCND1 | |
| Garlic | Diallyl disulfide | In vitro | MGC803 cells | Inhibited cell growth Induced cell differentiation | ↓ CDC25C, cyclin B1, p-ERK1/2, ↑ p-Chkl | [57, 59] |
| Garlic | Diallyl disulfide | In vitro | AGS cells | Inhibited tumor cell motility and invasion | ↓ MMP-2, MMP-9, claudin proteins (claudin-2, -3, and -4), ↑ TIMP-1, TIMP-2 | [94] |
Table 2. Cont.

| Natural Products | Phytochemicals | Study Type | Models | Mechanisms | Molecular Targets | Ref. |
|------------------|----------------|------------|--------|------------|------------------|------|
| Garlic derivatives | S-allylmercaptocysteine | In vivo | Female BALB/c nude mice | Inhibited the growth of gastric tumor | NA | [63] |
| *Zanthoxylum nitidum* (Roxb) DC | Nitidine chloride | In vitro | SGC-7901 and AGS cells | Induced apoptosis Inhibited cell viability and angiogenesis | ↓ p-STAT3, cyclin D1, Bcl-2, Bcl-xL, and VEGF | [23] |
| Mushroom | Blaziin | In vitro | KATO III cells | Induced apoptosis Suppressed cell growth | NA | [118] |
| Liang Jin mushroom | 3’-azido-3’-deoxythymidine (AZT) and RNA-protein complex (FA-2-b-β) | In vitro | MKN-45 cells | Induced apoptosis Inhibited cell proliferation | ↓ tumor cell telomerase and Bcl-2, ↑ caspase-3 | [117] |
| *Agaricus blazei* Murrill | Blazein | In vitro | MKN-45 cells | Induced apoptosis Suppressed cell growth | NA | [118] |
| *Phellinus linteus* | Polyphenol compound hispolon | In vitro | SGC-7901, MGC-803, and MKN-45 cells | Induced apoptosis | ↑ ROS, cytochrome c, caspase-3 and caspase-9 | [74] |
| *Hericium erinaceus* mycelium | Erinacine A | In vitro | TSGH9201 and MKN-28 human gastric cancer cells | Induced apoptosis Inhibited the viability and invasiveness | ↑ ROS, MTUS2, TRAIL, caspase 8, caspase 9, caspase 3, cytochrome c and phosphorylation of FAK/Akt/p70S6K and PAK1, ↓ Bcl-2, MMP-2 and MMP-9, ↓ Bcl-2 and Bcl-XL, ↓ Bcl-xL | [91] |
| *Lentinula edodes* C91-3 | Latcripin 1 protein | In vitro | SGC-7901 and BGC-823 cells | Induced autophagy and apoptosis Inhibit cell growth and proliferation | ↑ Bax, caspase-3, ATG7, ATG5, ATG12, ATG14 and Beclin1 | [61] |
| *Ganoderma lucidum* | NA | In vitro | AGS cells | Induced autophagic cell death Inhibited cell growth | ↑ LC3-II | [119] |
| *Fomes Fomentarius* | Polysaccharide | In vitro | SGC-7901 and MKN-45 cells | Inhibited cell proliferation | ↑ CHOP, ATF4 and GRP78 | [120] |
| *Maitake* (Grifola frondosa) | NA | In vitro | SGC-7901 and MKN-45 and MKN-74 cells | Inhibited cell proliferation | NA | [20] |
### Table 2. Cont.

| Natural Products | Phytochemicals                        | Study Type | Models           | Mechanisms                                      | Molecular Targets                                      | Ref. |
|------------------|---------------------------------------|------------|------------------|-------------------------------------------------|--------------------------------------------------------|------|
| **Soy**          |                                       |            |                  |                                                 |                                                        |      |
| Black soybean    | NA                                    | In vitro   | AGS cells        | Induced apoptosis Inhibited cell proliferation  | ↓ Bcl-2, ↑ Bax, caspase-3, PARP cleavage                 | [75] |
| Soy products     | Genistein, fluorouracil and cisplatin | In vitro   | MGC-803 cells    | Decreased chemo-resistance                      | ↓ ABCG2, ERK1/2                                         | [108]|
| **Traditional medicine** |                             |            |                  |                                                 |                                                        |      |
| Gardenia jasminoides Ellis | Carotenoids           | In vitro   | MKN-28 cells     | Inhibited cell proliferation                    | NA                                                     | [122]|
| Perilla frutescens | Perillaldehyde                         | In vitro   | MFCs and GC9811-P cells | Induced autophagy                              | ↑ p-AMPK                                               | [84] |
| Vitis agnus-castus fruit | NA                                    | In vitro   | KATO-III Cells   | Induced apoptosis                               | ↓ beclin-1, LC3-II, cathepsin, caspase-3 and p53        | [73] |
| Bamboo shavings  | Polysaccharides                        | In vivo    | Syngeneic murine gastric cancer model | Inhibited tumor growth Prolonged the survival | ↑ cleaved caspase 3, Bax and Bik                      | [79] |
| Natural Products | Phytochemicals | Study Type | Models | Mechanisms | Molecular Targets | Ref. |
|----------------|---------------|------------|--------|------------|------------------|-----|
| Protocatechuic acid | In vitro | AGS cells | Induced apoptosis Inhibited cell proliferation | ↓ cyclin B, ↑ JNK and p38 MAPK | [69] |
| Kaempferol | In vitro | AGS, NCI-N87, SNU-638 and MKN-74 cells | Induced autophagic cell death Decreased cell viability | ↑ LC3B, Beclin-1, ATG5, p-IRE1 and p-JNK | [22] |
| Myricetin | In vitro | HGC-27 and SGC7901 cells | Inhibited cell proliferation | ↑ Mad1 | [62] |
| Apigenin | In vitro | SGC-7901 cells | Inhibited cell growth | NA | [55] |
| Luteolin | In vitro | Hs-746T and MKN-28 cells | Induced cell apoptosis Inhibited cell proliferation, invasion, and migration | ↓ Notch1 | [92] |
| Gallic acid | In vitro | AGS cells | Inhibited cell proliferation | ↓ MMP-2, MMP-9, NF-κB, Ras, Cdc42, Rac1, RhoA, RhoB and PI3K | [90] |
| Luteolin | In vitro | MGC-803 and Hs-746T cells | Anti-angiogenesis Inhibited the formation of vascuigenous mimicry tube Reduced the volume of tumors | ↓ VEGF and Notch1 | [88] |
| Quercetin and SN-38 (a metabolite of irinotecan) | In vitro | Female BALB/c nude mice | Anti-angiogenesis and anti-metastasis | ↓ cyclooxygenase-2, Twist1, ITGβ6, VEGF-R2 and VEGF-A | [24] |
| Quercetin and Quercetin glucoside | In vitro | AGS cells | Induced apoptosis | ↓ β-catenin | |
6. Safety

Different from anticancer drugs, phytochemicals commonly have less toxicity, making them safer in the prevention and management of gastric cancer [83,135]. It has been reported that lentinan had low or zero toxicity, even at high doses [135]. In addition, the treatment of hispolon, which was isolated from a traditional medicinal mushroom, showed no adverse effects on human normal gastric cells [74]. In another in vivo study, no observable toxicity was found in rats with long-term exposure to 3,3′-diindolylmethane [136]. Furthermore, the extract of Hericium erinaceus exhibited anticancer activity against the xenograft model of NCI-87 gastric cancer cells without toxicity to the host [137]. However, some spices were found to have adverse effects. A study reported that piperine had reproductive toxicity in mice [133]. Additionally, turmeric and curcumin exhibited hepatotoxicity in mice [138].

Collectively, most experimental studies have suggested a lack or low level of toxicity of most phytochemicals. However, the toxicity and other adverse effects of some phytochemicals, such as allergic reactions, liver or kidney toxicity, have not been tested in humans. Therefore, it is necessary to determine the effective and safe doses of phytochemicals to prevent toxicity in human.

7. Conclusions

The effects of phytochemicals against gastric cancer have been extensively investigated. Numerous epidemiological studies have suggested that the consumption of natural dietary products such as fruits, vegetables, spices, isoflavone and quercetin is inversely related to the risk of gastric cancer. However, inconsistent results have also been reported in some cohort studies. Moreover, both in vitro and in vivo studies have revealed that some phytochemicals showed anti-gastric cancer activity by inhibiting cell proliferation, inducing apoptosis and autophagy, suppressing angiogenesis and metastasis, reducing Helicobacter pylori infection, and modulating the gut microbiota. In addition, phytochemicals enhanced the sensitivity to chemotherapy and had synergistic effects with anticancer drugs against gastric cancer. The clinical trials further verified the anticancer efficacy of several phytochemicals. However, the protective effects of natural products against gastric cancer by regulating gut microbiota have not yet been fully explored and understood. The effects of more natural products against gastric cancer should be evaluated, the phytochemicals should be isolated and identified, and the mechanisms of action should be elucidated. Furthermore, attention should be paid to the safety and bioavailability of phytochemicals. Overall, consumption of phytochemicals is a promising strategy for the prevention and management of gastric cancer, and the public is recommended to consume natural dietary products rich in diverse phytochemicals for the prevention of gastric cancer. These natural products could also be developed into functional foods and pharmaceuticals to prevent and treat gastric cancer.

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Abbreviations

AMPK | AMP-activated protein kinase
ATF4 | activating transcription factor 4
ATG5 | autophagy related 5; ABCG2
ABCG2 | ATP binding cassette subfamily G member 2
Bad | Bcl-2 associated agonist of cell death
Bax | Bcl-2-associated X protein
Bcl-2 | B-cell lymphoma 2
| Abbreviation | Description |
|--------------|-------------|
| Bcl-xL       | B-cell lymphoma-extralarge |
| Bid          | BH3 interacting domain death agonist |
| Bik          | Bcl-2 interacting killer |
| Cdc42        | cell division cycle 42 |
| CDC25C       | cell division cycle 25C |
| CDK4         | cyclin dependent kinase 4 |
| CHOP         | -CCAAT-enhancer-binding protein homologous protein |
| EMT          | epithelial-mesenchymal transition |
| ERK1/2       | extracellular signal-regulated kinase |
| FasL         | Fas Ligand |
| GRP78        | glucose regulated protein 78 |
| GSH          | glutathione |
| Hes-1        | hes family bHLH transcription factor 1 |
| Hey-1        | hes related family bHLH transcription factor with YRPW motif 1 |
| IκB-α        | inhibitor of NF-κB |
| ITGβ6        | integrin subunit beta 6 |
| Jagged1/2    | 2 serrate-like ligands |
| JNK          | c-Jun N-terminal kinase |
| ki-67        | a cell proliferation marker |
| LC3B         | microtubule associated protein 1 light chain 3 beta |
| Mad1         | Mitotic arrest-deficient 1 |
| MAPK         | mitogen-activating protein kinase |
| Mcl-1        | apoptosis regulator belongs to Bcl-2 family member |
| miR-410      | a tumor-suppressive microRNA |
| MMP-2        | matrix metallopeptidase 2 |
| MT2A         | metallothionein 2A |
| MTUS2        | microtubule-associated tumor suppressor candidate 2 |
| NF-κB        | nuclear factor kappa light chain-enhancer of activated B cells |
| Notch1       | notch receptor 1 |
| PARP         | poly (ADP-ribose) polymerase |
| p-ERK1/2     | phosphorylation of extracellular signal-regulated kinase |
| p-Chkl       | phosphorylation of checkpoint kinase-1 |
| p-IRE1       | phosphorylates inositol-requiring-1 |
| p-JNK        | phosphorylates c-Jun N-terminal protein kinase |
| p-4EBP1      | phosphorylated 4E binding protein 1 |
| p-p70S6K     | phosphorylated ribosomal protein S6 kinase |
| p-eIF4E       | phosphorylated eukaryotic translation initiation factor 4E |
| PI3K         | phoshatidylinositol-3-kinase |
| p-IκB-α      | phosphorylation of p-IκB-α |
| Rac1         | Rac family small GTPase 1 |
| RhoA         | ras homolog family member A |
| RhoB         | ras homolog family member B |
| ROS          | reactive oxygen species |
| STAT3        | signal transducer and activator of transcription 3 |
| TIMP         | tissue inhibitor of metalloproteinase |
| TrxR1        | thioredoxin reductase 1 |
| TRAIL        | tumour necrosis factor (TNF)-related apoptosis-inducing ligand |
| Twist1       | twist family bHLH transcription factor 1 |
| VEGF         | vascular endothelial growth factor |
| VEGF-R2      | vascular endothelial growth factor receptor 2 |
| XIAP         | X-linked inhibitor of apoptosis protein |
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