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REVIEW ARTICLE

Curcumin and Gastric Cancer: a Review on Mechanisms of Action

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Abstract

Background and Aim Gastric cancer, as the fourth cause of death in women and third in men with malignant tumors, is now threatening people's lives worldwide. Natural anti-tumor products are potential anti-cancer agents with fewer by-effects. Curcumin, an herbal product, has been used as a cosmetic and food additive and as a traditional herbal medicine for thousands of years in Asian countries. Several studies revealed that curcumin can inhibit the invasion and proliferation of gastric cancer cells. This paper analyzes existing data from animal and in vitro studies in order to highlight the mechanisms of therapeutic effects of curcumin in gastric cancer.
Methods Science Direct and Pub Med databases were searched by using "curcumin" and "gastric cancer" for searching the studies aiming the application of curcumin and the beneficial effects of curcumin in gastric cancer control and treatment.
Results These results suggested that curcumin can suppress multiple signaling pathways and inhibit cancer cell proliferation, invasion, metastasis, and angiogenesis. According to the studies, curcumin can inhibit gastric cancer by several mechanisms including decreasing proliferation, inducing apoptosis, and reducing chemo-resistance in gastric cancer cells.
Conclusions The findings of present paper provided novel perceptions about the mechanisms of curcumin action in gastric cancer cell growth inhibition and its therapeutic strategies for gastric cancer control. So, curcumin could be considered as a novel therapeutic strategy to control gastric cancer cell growth.

Keywords Curcumin · Gastric cancer · Mechanisms

Introduction

Gastric cancer is one of the leading causes of high mortality rates and unfavorable prognosis [1]. Despite recent developments in diagnosis and therapy, treatment progress of gastric cancer remains limited. Most of the patients with gastric cancer are incurable and the survival rate is low [2]. Natural products, for example, green tea, resveratrol, vitamins, and functional foods such as probiotics and prebiotics, have probable benefits because of their chemo-prevention [3, 4]. Curcumin, a natural anti-cancer agent, has been paid more consideration because of its inhibitory effect on tumor. Studies have shown that curcumin inhibited inflammation and carcinogenesis in animal models, including breast, esophageal, stomach, and colon cancer models [5]. This natural chemo-preventive agent, derived from rhizomes of curcuma species, provides antioxidant, anti-tumor, and anti-proliferative efficacies [6]. The other obvious feature of curcumin is that it has not been shown to cause any toxicity and side effect despite being consumed for centuries in Asian countries [7]. The pharmacological safety, efficacy, and cost-effectiveness of curcumin and no-dose limiting toxicity [8] have also encouraged many investigators to further examine this molecule.

Curcumin could lessen the proliferation of human gastric cancer cells through numerous biological pathways such as apoptosis [9, 10], mutagenicity [11], cell cycle regulation [12, 13], angiogenesis [14], invasion [15], and tumorigenesis [16]. Moreover, through downregulating the NF-κB (nuclear transcription factor κB) in human gastric carcinoma cells SGC-7901 and AGS, curcumin has exhibited potent chemosensitization [17, 18]. The synergic effect of curcumin with 5-fluorouracil, a chemotherapy drug, has been also confirmed in several investigations [18]. According to Koo et al., long-lasting consumption of a generally recommended dose (8 g/day) of curcumin would be beneficial for the treatment of gastric carcinoma, particularly in conjunction with 5-FU [18]. Although most of the mechanisms of the compound have been studied, more

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studies are needed to investigate its role in gastric cancer control and/or treatment.

We are going to summarize some of the potential mechanisms by which curcumin inhibits, control or destroying formation and invasion of cancer cells and improve cancer cells sensitivity to chemo-therapeutic drugs.

Curcumin and Gastric Cancer

Considering the results of previous researches, curcumin and its analog have been reported to play an anti-cancer role in gastric tumor models (Table 1) [11–13, 16, 19, 20]. Various mechanisms of curcumin anti-carcinogenic properties have been studied in previous investigations (Fig. 1) that are going to be illustrated below [21].

Decrease of Proliferation

Cancer Stem Cells Theory

Cancer stem cells (CSCs), as cancer cells, can result in tumor cell proliferation by the ability to reproduce identical and fraternal cells [22]. CSCs have been isolated from the cancer mass of breast cancer [23], melanoma [24], prostate cancer [25], osteosarcoma [26], brain tumor [27], and many other tumors. Most tumors consist of a heterogeneous population of cells with varying degrees of differentiation matches. According to CSC theory, there are a few tumor cells with an unlimited proliferative capacity to cause tumor growth [28]. CSCs cannot be destroyed by current treatments. That is why current treatments targeting the tumor mass and reducing them cannot prevent tumor regrowth [29]. The genes that are involved in the control of stem cell renewal have been

Table 1 Inhibitory effect of curcumin on tumor

Intervention	Study samples	Mechanism of action	Result
AqTE*, CFAqTE†, and curcumin [11]	Female Swiss mice	Direct reaction between curcumin and the mutagens.	Curcumin inhibited the development of fore-stomach tumors.
Diphenyl Difluoroketone (a curcumin derivative) [12]	HCT-116 and HT-29 colon and AGS gastric adenocarcinoma cells	Cancer cells showed increased levels of activated caspase-3 and increased Bax‡ to Bcl-2 and Bax to Bcl-xL ratios, suggesting that the cells were undergoing apoptosis.	Diphenyl Difluoroketone induced caspase-mediated apoptosis during mitosis and inhibited proliferation
Curcumin [13]	Gastric (KATO-III) and colon (HCT-116) cancer cells	Curcumin caused induction of apoptosis as evidenced by cleavage of PARP§, caspase-3, and reduction in Bcl-XL‖ levels. Curcumin also stimulated the activity of caspase-8, which initiates Fas signaling pathway of apoptosis.	Curcumin exerted anti-carcinogenic properties by inhibiting proliferation and inducing apoptosis in certain gastric and colon cancer cells
Curcumin [19]	Gastric carcinoma BGC-823 cells	Curcumin activated Caspase-3 signal channel by activating Bax protein expression and inhibiting Bcl-2 protein	Curcumin could inhibit human gastric carcinoma BGC-823 cell proliferation
Curcumin [20]	Gastric cancer cell lines (BGC-823, MKN-45, and SCG-7901)	Significant changes of 75 proteins in curcumin-treated cells and protein-protein interacting affected by curcumin in gastric cancer cells	Curcumin-induced cell growth inhibition and apoptosis in gastric cancer cells
Curcumin [16]	Human gastric cancer cell line MKN-45	Curcumin inhibited the accumulation of MDSCs and their interaction with cancer cells and induced the differentiation of MDSCs, so inhibited tumor growth.	Curcumin treatment significantly inhibited cell proliferation and colony formation of cancer cells.
Curcumin [20]	Gastric cancer cells	Curcumin downregulated the mRNA and the protein expression of cyclin D1 and suppressed transition of the cells from G(1) to S phase	Curcumin inhibited the proliferation and invasion of gastric cancer cells

*Aqueous turmeric extract

† Curcumin-free aqueous turmeric extract

‡ A member of the Bcl-2 gene family

§ Poly ADP-ribose polymerase

‖ B cell lymphoma-extra large

¶ Myeloid-derived suppressor cells

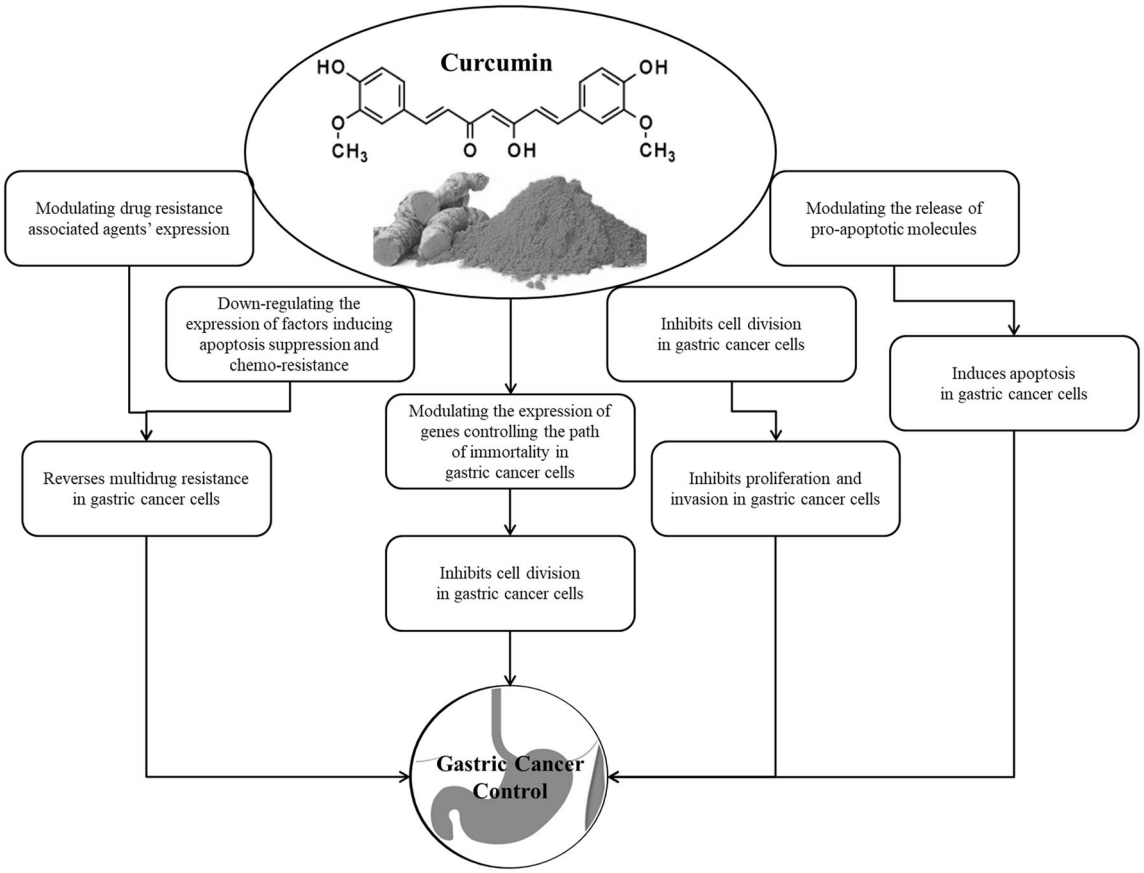

Fig. 1 A summary of curcumin mechanisms of action in gastric cancer control

known as new classes of molecular markers that their uncontrolled expression is important in tumor regrowth [30]. The most important of these genes includes OCT4, NANOG, SOX2, and KLF4 [28]. OCT4, a transcription factor that is expressed by all totipotent cells during embryogenesis of mouse, is also expressed in embryonic stem cells of mice and numerous undifferentiated embryonic and cancer cell lines [28]. This gene produces three different variants (OCT4A, OCT4B, and OCT4B1) with similar gene organizing but different protein structures and different functions [31]. Nanog is a transcription factor that motivates the stem cells' reproducibility. Nanog is one of several factors that are expressed in the pluripotent cells and its expression becomes suppressed in the onset of differentiation [32]. Nucleostemin gene belongs to the GTP-binding protein family that the single subunit protein synthesized by this gene is mainly found in the nucleus and in cell core. This gene plays an important role in regulating the protein P53—a tumor suppressor that triggers apoptosis via multiple pathways—and cell cycle [33]. According to the available evidence about the role of curcumin in the treatment and prevention of cancer and the role of OCT4, NANOG, and Nucleostemin genes in tumor cells growth, several studies have been conducted to investigate the effect of curcumin on the genes controlling the path of immortality in gastric cancer cells. Mirzaei et al. [28] found that expression rate of OCT4A, OCT4B, NANOG, and Nucleostemin (GLN3) at concentrations less than 20 μg/ml curcumin was reduced but OCT4B1 expression showed increased by hours respectively. The results showed that curcumin inhibited cell division [28]. The effect of curcumin on the downregulation of Nanog and Nucleostemin genes' expression is proportional to the time of impact and curcumin extract concentration. In other words, the higher the time and the concentration are, the greater the impact will be [28]. Results showed that curcumin can inhibit cell division and tumor regrowth by reducing the expression of the genes involved in CSC proliferation.

Inhibition of PAK1 Activity

It has been revealed that p21-activated kinase1 (PAK1) is implicated in tumorigenesis and metastasis [34], so, PAK1 inhibitors could become as a novel oncologic therapy [34, 35]. PAK family members can be inhibited by compounds known for their ability to target kinases [35–37]. The p21-activated kinases (PAKs) are the Rho GTPase signaling mediators and are associated with biological routes ranging from cytoskeletal dynamics and motility to tumorigenesis [38, 39].

Irregular PAK1 activation and then high cyclin D1 expression have a major role in tumorigenesis [40]. Transcription of cyclin D1 is regulated by PAK1 through an NF-κB-dependent pathway [40]. Cai et al. [15] revealed that curcumin targets PAK1 in gastric cancer cells, providing a new-known mechanism of curcumin action on inhibiting proliferation and/or invasion of human gastric cancer. Through downregulation of the cyclin D1 expression, curcumin could inhibit the proliferation of gastric cancer cells (Fig. 2) [41].

Cyclin D1 is needed to mediate the G1 to S transition during the DNA synthesis and cell cycle development [42]. It has been shown that curcumin can increase G1 cells and decrease S-cells, so it is clear that the anti-proliferative effects of curcumin are related to the downregulation of cyclin D1 expression [15]. However, there is a time gap between the inhibition of transition of the cells from G1-S and the downregulation of Cyclin D1 expression. Recent evidences recommend that transcription of cyclin D1 might be upregulated by multiple signaling pathways, such as NF-κB [43]. Since PAK1 signaling modulates NF-κB activation [44], and it has been revealed that curcumin can inhibit PAK1 activity [15], it can be determined that curcumin downregulates the expression of cyclin D1 through PAK1 signaling pathway, too. So, the PAK1 inhibition can lead to the decrease of proliferation and/or invasion in gastric cancer cells.

Mechanisms of Curcumin-Induced Apoptosis

Activation of the Caspases-3

Apoptosis, as one of the main targets of many treatment strategies, plays a vital role in cancer control [45–48]. Several investigations have revealed that targeting apoptosis in cancer therapy is possible. Apoptosis, an ordered and arranged cellular process, happens in both physiological and pathological conditions [49]. Apoptosis program disruption can cause the overgrowth of malignant cells [50]. Death receptor-mediated extrinsic and mitochondria-mediated intrinsic pathways are the two pathways involved in apoptosis induction [51]. The intrinsic apoptotic pathway is activated by the mitochondria permeability and cytochrome-c release from mitochondria into the cytoplasm, and the extrinsic apoptotic pathway is characterized by death receptors located on the plasma membrane such as TNFR1 (tumor necrosis factor receptor1) and Fas/CD95 [52–55]. Both pathways cause the activation of killer Caspases-3 through different pro-apoptotic signals and eventually cell death [56].

The activity of caspase-3 could be reflected by the hydrolyzation of PARP (poly ADP-ribose polymerase), a particular substrate for caspase-3 [57]. Xia Xue et al. [58] showed that 5–20 μM curcumin significantly increased the caspase-3 and cleaved PARP expression. These findings proposed that curcumin can caused the SGC-7901 cells' apoptosis. The intrinsic apoptotic pathway is mostly triggered by the mitochondria membrane collapse potential [59]. The collapse provokes the release of pro-apoptotic molecules cytochrome-c into the cytoplasm, recommended as a "point of no return" in mitochondrial pathway [60]. This pathway is severely controlled by a collection of proteins of the Bcl-2 family including the pro-apoptotic proteins (e.g., Bak, Bax, Bad, Bcl-Xs, Bik, Bid, Bim, and Hrk) and the anti-apoptotic proteins (e.g., Bcl-XL, Bcl-W, Bcl-2, Bfl-1, and Mcl-1) [61–63]. The cytochrome-c release is linked to the Bcl-2 decrease and Bax increase followed by caspase-9 and caspase-3 activating and PARP hydrolyzation [64]. Xia Xue et al. showed that after curcumin treatment, cytochrome-c in SGC-7901 cells was redistributed [58]. The cytochrome-c level was noticeably decreased in mitochondria and increased in cytosol. Moreover, the Bax protein expression was upregulated and the Bcl-2 protein expression was

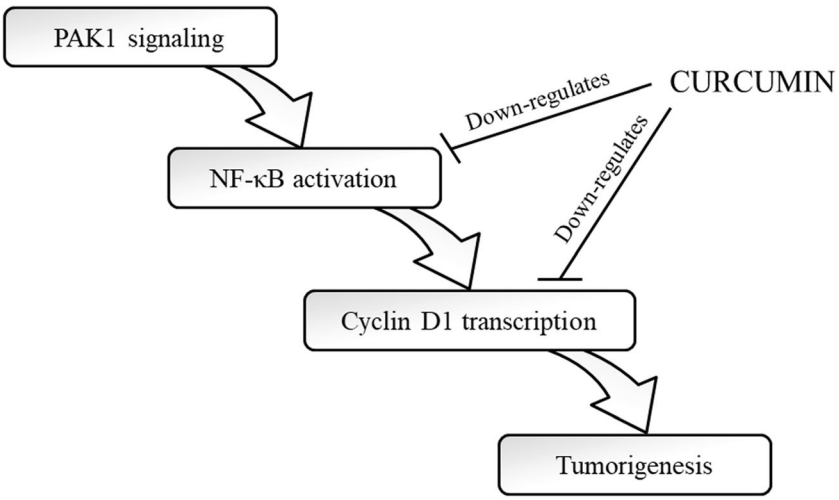

Fig. 2 Curcumin downregulates tumorigenesis through PAK1 signaling pathway

decreased after curcumin treatment. The Bax/Bcl-2 ratio was upregulated intensely and eventually induced the mitochondria-mediated cell apoptosis. They recommended that the curcumin-induction apoptosis in SGC-7901 cells could be as a consequence of the intrinsic apoptosis pathway, mediated by the activation of mitochondria [58]. Luo et al. [65] revealed an increased number of apoptotic cells, decreased ratio of B cell lymphoma 2 (Bcl-2)/Bcl-2-associated X protein, and increased caspase-3 expression after treatment with BDMC (demethoxy derivative of curcumin). The growth of SGC-7901 gastric cancer cells was suppressed and stopped at G1 phase. These results showed that curcumin-induced apoptosis of tumor cells could be mediated via the mitochondria pathway.

Deactivation of ATP-Sensitive Potassium Channels

ATP-sensitive potassium channels (KATP) are distributed throughout the body [66], located on cell and mitochondrial membranes, as well as malignant cells [67]. The mitochondria located KATP is called mito-KATP and its function is adjusting the mitochondrial membrane functions to external stressors through opening the ion channel. Thus, by maintaining mitochondrial membrane potential (MMP), opening of the mito-KATP could reduce cell apoptosis [68]. At the early stage of apoptosis, the opening of mito-KATP could inhibit depolarization of mitochondrial membrane to maintain MMP [69]. So, the mitochondrial membrane was stabilized to stop apoptotic chain reactions, such as cytochrome-c release, transition pore formation, or caspase cascade activation. A recent study has revealed the link between mito-KATP and malignant cancer cells proliferation [70]. This suggestion motivated interests in evaluating whether the anti-cancer effect of curcumin on gastric cancer is related to mito-KATP. Liu et al. [71] revealed the involvement of KATP in the anti-proliferative effects of curcumin in gastric cancer. The in vitro results showed curcumin-induced apoptosis of SGC-7901 cells through enabling the collapse of MMP, which was supposed to initiate the mitochondria-dependent apoptotic pathway. These results showed that curcumin could induce gastric cancer cells apoptosis by deactivating mito-KATP, which could accelerate the collapse of MMP [71]. It has been found that curcumin incubation could induce loss of MMP in SGC-7901 cells in a dose-dependent manner; moreover, the cell apoptotic rate increased after curcumin incubation in a dose-dependent manner. Impaired mito-KATP opening causes MMP loss and is involved in curcumin-induced apoptosis in gastric cancer [71].

Reducing Chemo-resistance

Despite the advancement, made in the gastric cancer treatment, a significant ratio of patients with gastric cancer fails to achieve complete recovery or they relapse because of the multidrug resistance (MDR) [72]. MDR is often associated with the overexpression of ATP-dependent drug efflux proteins belonging to the superfamily of ATP-binding cassette (ABC) transporters: the 170 kDa P-glycoprotein (P-gp) encoded by the MDR1 gene and the 190 kDa MDR-associated protein-1 encoded by the MRP-1 gene [73, 74]. The development of P-gp-associated MDR in tumors is an important barrier for effective chemotherapy [75]. To overcome MDR, a growing investigation on finding new agents that can inhibit the expression and/or function of P-gp has been done. Recent findings have exposed that curcumin can modulate P-gp expression and function, so, it could be a potential new agent for the chemo-sensitization of cancer cells [76]. Considering its extensive range of pharmacological and biological benefits, and lack of toxic effects on animal models, curcumin has been studied to evaluate whether it can overcome MDR. Xiao-qing et al. [72] revealed that curcumin, at different concentrations including 5.0 μmol/L, 10.0 μmol/L, and 20.0 μmol/L, can decrease the IC50 (50% inhibitory concentration) of vincristine (VCR)—a chemotherapy medication—to SGC7901/VCR cells in a dose-dependent manner. These findings show that curcumin can overcome MDR in the SGC7901/VCR—human gastric cancer cells—cell line [72]. Curcumin can improve the VCR-mediated apoptosis of MDR SGC7901/VCR cells, so, it can be suggested that curcumin would reverse the apoptosis-resistance of MDR cells [72]. The research about the effect of curcumin on P-gp expression showed that curcumin could significantly inhibit P-gp expression in SGC7901/VCR cells. Xiao-qing et al. [72] showed that curcumin consistently improved drug-resistant SGC7901/VCR cells sensitivity to VCR with an increase in intracellular drug concentration by decreasing P-gp function and expression. Functional P-gp has a role in modulating cell death by both removing drugs from the cell and inhibiting the activation of proteases involved in apoptotic signaling (caspase-8) [77] and execution (caspase-3) [78]. Xiao-qing et al. [79] showed that SGC7901/VCR cells inhibited VCR-induced caspase-3 activation. However, treatment of the cells with curcumin improved the activation of VCR-induced caspase-3. Moreover, it has been revealed that curcumin reverses P-gp-mediated MDR via induction of caspase-3 activation. The MDR reverse function of curcumin would promote anti-cancer agent-induced caspase-3 activation.

NF-κB is another factor associated with the chemo-resistance of tumor cells. NF-κB has been known as a main mediator in numerous cellular processes from inflammation to cancer [17]. Moreover, inducible chemo-resistance is related to the activation of NF-κB, which stimulates the transcription of anti-apoptotic genes allowing cells to overcome apoptosis induced by chemotherapy [80]. NF-κB, a pleiotropic activator, takes part in the induction of various cellular genes. NF-κB has also been involved in the cellular survival,

transformation, suppression of apoptosis, and oncogenesis [81, 82]. It has been revealed that chemotherapy agents can induce NF-κB, which has been recommended to be associated with chemo-resistance of human tumors [17]. Suppressing the chemotherapy-related activation of NF-κB would enhance the cytotoxic effects of chemo-therapeutics. This connection has been observed in various cancer cell types [17]. It has been revealed that curcumin can inhibit NF-κB activation and modulate the expression of NF-κB-regulated gene products with roles in anti-apoptosis, such as Bcl-xL and Bcl-2 and play a vital role in increasing the effectiveness of chemo-therapeutics [83]. In most un-stimulated cells, NF-κB proteins are sequestered in the cytoplasm and are complex with specific inhibitor proteins called IκB (inhibitor of kappa B) that make the NF-κB proteins inactive [81, 84]. Stimulation of cells causes the phosphorylation and degradation of IκB and allows translocation of NF-κB to the nucleus, leading to expression of target genes. Yu et al. [17] examined the effect of curcumin on reversing the chemo-resistance by downregulating NF-κB in human gastric cancer cells. Etoposide (a cytotoxic anticancer drug) or doxorubicin (a drug used in cancer chemotherapy) suppressed the growth and induced apoptosis of SGC-7901 cells, and activated NF-κB simultaneously. The curative effect of chemotherapy and the induction of apoptosis were promoted when was used combined with curcumin. They showed that curcumin could potentiate the anti-tumor effects of chemo-therapeutics by downregulating the NF-κB activation and NF-κB-regulated gene products [17]. NF-κB activation needs degradation of IκBα to free NF-κB from the heterotrimeric IκB/NF-κB complex and to translocate it into the nucleus. IκBα is the main endogenous inhibitor of NF-κB activation [85]. In order to clarify the mechanism of NF-κB activation in gastric cancer chemotherapy, Yu et al. [17] evaluated the IκBα phosphorylation levels after numerous pharmacological interventions. Chemo-therapeutics has been revealed to induce IκBα phosphorylation, degradation, and then NF-κB activation. Meanwhile, this effect of chemo-therapeutics could be attenuated by curcumin [17]. Moreover, they examined the levels of Bcl-2 and Bcl-xL in their experiments. The results showed that curcumin can reduce the levels of anti-apoptotic genes Bcl-2 and Bcl-xL. In conclusion, evidences demonstrate that curcumin potentiates the anti-tumor effects of chemo-therapeutics by inhibiting anti-apoptosis factors and could be considered as a promising chemo-sensitizer in gastric cancer [86].

Conclusion

Natural products, with fewer side effects and stronger anti-tumor activity, have gained increasing scientific attention in recent years. It has been shown that curcumin can suppress multiple signaling pathways and inhibit cancer cell proliferation, invasion, metastasis, and angiogenesis. This review confirms the potential efficacy of curcumin in cancer prevention and/or control by several mechanisms including decreasing proliferation, inducing apoptosis, and reducing chemo-resistance in gastric cancer cells. Further investigations are needed to illustrate other possible mechanisms of curcumin action in gastric cancer control. Present review could be the basis for more extensive studies on the anti-cancer effect of this traditional herbal compound.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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