Received: 21 November 2018 | Accepted: 21 December 2018

DOI: 10.1002/jcp.28122

REVIEW ARTICLE

WILEY Journal of Cellular Physiology

Mechanisms of apoptosis modulation by curcumin: Implications for cancer therapy

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Abstract

Cancer incidences are growing and cause millions of deaths worldwide. Cancer therapy is one of the most important challenges in medicine. Improving therapeutic outcomes from cancer therapy is necessary for increasing patients' survival and quality of life. Adjuvant therapy using various types of antibodies or immunomodulatory agents has suggested modulating tumor response. Resistance to apoptosis is the main reason for radioresistance and chemoresistance of most of the cancers, and also one of the pivotal targets for improving cancer therapy is the modulation of apoptosis signaling pathways. Apoptosis can be induced by intrinsic or extrinsic pathways via stimulation of several targets, such as membrane receptors of tumor necrosis factor-α and transforming growth factor-β, and also mitochondria. Curcumin is a naturally derived agent that induces apoptosis in a variety of different tumor cell lines. Curcumin also activates redox reactions within cells inducing reactive oxygen species (ROS) production that leads to the upregulation of apoptosis receptors on the tumor cell membrane. Curcumin can also upregulate the expression and activity of p53 that inhibits tumor cell proliferation and increases apoptosis. Furthermore, curcumin has a potent inhibitory effect on the activity of NF-κB and COX-2, which are involved in the overexpression of antiapoptosis genes such as Bcl-2. It can also attenuate the regulation of antiapoptosis PI3K signaling and increase the expression of MAPKs to induce endogenous production of ROS. In this paper, we aimed to review the molecular mechanisms of curcumin-induced apoptosis in cancer cells. This action of curcumin could be applicable for use as an adjuvant in combination with other modalities of cancer therapy including radiotherapy and chemotherapy.

KEYWORDS
apoptosis, cancer, curcumin, JNK, NF-κB, p53

1 | INTRODUCTION

Every year, millions of people are diagnosed with cancer worldwide (Siegel, Miller, & Jemal, 2017). Treatment of cancer is important not only for the preservation of a patient's life but also to relieve pain associated with this disease (Farhood, Najafi, & Mortezaee, 2018). Radiotherapy and chemotherapy are the most known noninvasive modalities for tumor control, while immunotherapy is growing (Farhood, Goradel, Mortezaee, Khanlarkhani, Salehi et al., 2018; Mortezaee et al., 2018). During radiotherapy, patients receive a high total dose of ionizing radiation fractionated over a period of weeks (Yahyapour, Salajegheh et al., 2018). Similarly, chemotherapy drugs are administrated in various treatment cycles depending on the cancer types and specific chemotherapeutic (Afrin & Ergul, 2000; Akaza, 2007). Many patients receive both modalities for a better outcome (Chon et al., 2011; Skinner et al., 2013). However, there are some concerns related to severe toxicities toward normal tissues (Barnett et al., 2009; Yahyapour, Amini et al., 2018). Furthermore, exposure of cancer cells to radiotherapy and chemotherapy leads to adaptation of these cells via regulation of signaling pathways that are involved in cell proliferation and death (Farhood, Goradel, Mortezaee, Khanlarkhani, Najafi et al., 2018; Farhood, Goradel, Mortezaee, Khanlarkhani, Salehi et al., 2018).

Apoptosis is the most obvious type of cell death after radiotherapy or chemotherapy in high sensitive organs, such as bone marrow, tongue, gastrointestinal system, and testis (Panganiban, Snow, & Day, 2013). In normal conditions, apoptosis is needed for homeostasis. Also, a critical role of apoptosis is removing precancerous cells and preventing the development of malignancy (Thompson, Strange, & Schedin, 1992). The high rate of apoptosis in normal tissues after radiotherapy and chemotherapy leads to severe reactions that may limit the therapeutic ratio of these modalities (Najafi, Motevaseli et al., 2018). Apoptosis of parotid gland and intestinal stem cells is responsible for the initiation of xerostomia and mucositis, which is common for patients that undergo chemotherapy or radiotherapy for head and neck and abdomen cancers (Köstler, Hejna, Wenzel, & Zielinski, 2001). On the other hand, apoptosis is the major type of cell death in tumor cells that play a key role in cancer therapy (Bold, Termuhlen, & McConkey, 1997).

Modulation of apoptosis in both normal tissues and tumor cells is an interesting strategy for improving the therapeutic window and decreasing toxicity (Koff, Ramachandiran, & Bernal-Mizrachi, 2015). For example, inhibition of apoptosis in bone marrow and the gastrointestinal system has alleviated toxicity from radiation therapy in these organs (Qiu, Leibowitz, Zhang, & Yu, 2010; X. Wang et al., 2017). Also, the induction of apoptosis in tumor through modulation of different signaling pathways have produced interesting results (Balcer-Kubiczek, 2012; Fulda, 2009). Flavonoids, polyphenols, and some natural agents, such as melatonin and metformin, are low toxic agents that not only decrease toxicity in normal tissues but also potentiate cancer cell death (Amini et al., 2018; Bagheri et al., 2018; Hosseinimehr, 2010; Najafi, Cheki et al., 2018; Najafi, Hashemi Goradel et al., 2018; Yahyapour, Shabeeb et al., 2018). Curcumin is one such natural flavonoid that has shown interesting properties for cancer therapy (Mirzaei et al., 2016; Momtazi et al., 2016; Saha, Adhikary, Bhattacharyya, Das, & Sa, 2012). Besides, this phytochemical has been reported to possess antioxidant (Panahi, Khalili et al., 2017; Sahebkar, Serban, Ursoniu, & Banach, 2015), anti-inflammatory (Ghandadi & Sahebkar, 2017; Karimian, Pirro, Majeed, & Sahebkar, 2017; Panahi et al., 2015; Sahebkar, Cicero, Simental-Mendía, Aggarwal, & Gupta, 2016), hepatoprotective (Panahi, Kianpour et al., 2017; Rahmani et al., 2016; Zabihi, Pirro, Johnston, & Sahebkar, 2017), analgesic and antiarthritic (Panahi et al., 2014; Sahebkar & Henrotin, 2016), pulmonoprotective (Lelli, Sahebkar, Johnston, & Pedone, 2017), lipid-modifying (Cicero et al., 2017; Ganjali et al., 2017), immunomodulatory (Abdollahi, Momtazi, Johnston, & Sahebkar, 2018; Momtazi-Borojeni et al., 2018), and antidiabetic (Panahi et al., 2018; Parsamanesh, Moossavi, Bahrami, Butler, & Sahebkar, 2018) actions. In this review, we focus on apoptosis induction after radiotherapy and chemotherapy in normal tissues and tumors, and the possible modulatory effect of curcumin that could be exploited to improve therapeutic outcomes.

2 | APOPTOSIS

Apoptosis is programmed cell death that is initiated after damage to DNA and other cell organelles, such as mitochondria and endoplasmic reticulum (Elmore, 2007). Usually, apoptosis can be seen after exposure of cells to stress conditions, such as oxidative stress, ionizing radiation, chemotherapy drugs, hypoxia, and high temperature (Kannan & Jain, 2000; Moeller, Richardson, & Dewhirst, 2007). Depending on the stimulator type, apoptosis can occur through intrinsic or extrinsic pathways. Damage to DNA is the main effect of ionizing radiation, which induces upregulation of the Bax to Bcl-2 ratio, leading to the penetration of Bax into the inner layer of mitochondria, which causes release of cytochrome C and the development of the apoptosome complex (Elumalai et al., 2012; Fulda & Debatin, 2006). The extrinsic pathway of apoptosis occurs after stimulation by some cytokines and growth factors or hormones. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL or CD95L) are triggered by TNF-α, and transforming growth factor (TGF)βR1 and TGFβR2, which are activated by TGF-β, are the most known apoptosis ligands that bind cell surface receptors (Almasan & Ashkenazi, 2003; Hu & Kavanagh, 2003; S. Wang & El-Deiry, 2003). TGF-β induces regulation of the Bax

and Smad2/3 pathways, which lead to the release of cytochrome C (Schuster & Krieglstein, 2002). Also, it upregulates caspase-3, caspase-8, and caspase-9 through activation of JNK and ARTS translocation (Moustakas & Heldin, 2005). Approximately 14 caspases are involved in apoptosis. Among these proteins, caspases 2, 8, 9, and 10 are involved in the initiation of apoptosis, while some other caspases such as caspases 3, 6, and 7 directly induce DNA and membrane degradation and nuclear shrinkage (Slee et al., 1999). Caspase-9 is engaged with cytochrome C and Apaf 1, leading to the development of the apoptosome complex that can degrade membranes and DNA (Cain, Bratton, & Cohen, 2002). p53 plays a key role in apoptosis induction in both precancerous and tumor cells. It can attenuate the function of Bcl-2 through activation of Puma and Noxa, leading to the activation of Bax and penetration into the mitochondria (Brown & Wouters, 1999; Mihara et al., 2003; Rödel et al., 2000). Moreover, p53 can induce extrinsic apoptosis via regulation of cell death receptors (Almasan & Ashkenazi, 2003). p53 activates the expression of TRAIL and FasL, thus facilitates apoptosis induction by TNF-α (Sayers, 2011).

Both normal and tumor cells have some mechanisms for inhibition of apoptosis. NF-κB signaling is the most known anti-apoptosis pathway. NF-κB comprises various subfamilies, including RelA (p65), RelB, c-Rel, and also the NF-κB proteins p50 and p62 (Moynagh, 2005). In normal conditions, NF-κB proteins are inhibited by IκBα and AκBβ. However, in stress conditions, such as exposure of cells to radiation or chemotherapy agents, IκBα and AκBβ proteins are phosphorylated by IκB kinase (IKK) and then NF-κB can translocate into the nucleus (Duran et al., 2008; Hayden & Ghosh, 2004). NF-κB suppresses both intrinsic and extrinsic apoptosis pathways via stimulation antiapoptosis proteins, such as Bcl-2 family proteins and the caspase-8 inhibitor FLIP (Micheau, Lens, Gaide, Alevizopoulos, & Tschopp, 2001). Also, the c-Rel subunit of NF-κB is able to inhibit apoptosis through TRAIL (X. Chen, Kandasamy, & Srivastava, 2003). AKT is another antiapoptosis modulator that inactivates caspase-8 and also phosphorylates IκB proteins, leading to the upregulation of NF-κB (Madrid et al., 2000). Upregulation of AKT and NF-κB, as well as inhibition of their inhibitors including PTEN and IκB, is involved in tumor development and resistance to radiotherapy and chemotherapy (Vasudevan, Gurumurthy, & Rangnekar, 2004).

3 | CURCUMIN ATTENUATES RADIATION-INDUCED APOPTOSIS IN NORMAL TISSUES

Apoptosis is responsible for several side effects of radiotherapy in normal tissues such as xerostomia, lymphopenia, and food malabsorption (Eriksson & Stigbrand, 2010). Usually, apoptosis is observable in organs with high mitotic activity, such as bone marrow and gastrointestinal system (Hendry & West, 1997). Curcumin can attenuate radiation toxicity in bone marrow cells via reducing DNA damage and cell death (Bagheri et al., 2018). A study by Dange et al. (2017) evaluated the protective effect of curcumin on radiation-induced apoptosis in mice bone marrow cells and thymic lymphoma. Mice were fed with a normal diet, including 0.05 to 1% curcumin for 3 weeks and then exposed to 3 Gy gamma rays. Results showed a significant reduction of radiation-induced apoptosis, which was associated with amelioration of DNA damage and downregulation of caspase-3.

4 | CURCUMIN ATTENUATES CHEMOTHERAPY-INDUCED APOPTOSIS IN NORMAL TISSUES

The high rate of apoptosis induction in gastrointestinal and bone marrow plays a central role in the development of mucositis and myelosuppression after chemotherapy (Bertolini, Sobue, Thompson, & Dongari-Bagtzoglou, 2017; Y. Kwon, 2016). Attenuation of apoptosis in these organs can preserve stem cells, leading to improving organ tolerance and attenuation of side effects (Zhan et al., 2016). Some studies have been conducted to investigate the protective effect of curcumin on chemotherapy-induced toxicity in normal tissues. The results showed that curcumin attenuated DNA damage after exposure to cisplatin in rat bone marrow cells (Antunes, Araujo, Darin, & Bianchi, 2000). Some in vivo studies have shown that curcumin is able to attenuate oxidative stress, DNA damage, apoptosis, and bone marrow suppression after injection of chemotherapeutic agents, such as cisplatin and carboplatin (X. Chen et al., 2017; Said Salem, Noshy, & Said, 2017). For example, Yao et al. (2013) evaluated the protective effect of curcumin on intestinal apoptosis markers after injection of 5-FU to rats. Rats were injected with 100 mg/kg 5-FU for 3 days, and after 24 hr curcumin was administered at 30 mg/kg for 3 days. The results showed that 5-FU caused damage to normal intestinal morphology, while treatment with curcumin attenuated progression of intestinal injury. Also, immunohistochemical staining showed that 5-FU upregulates Bax and Caspase-3 and reduces Bcl-2. Treatment with curcumin reversed these changes.

5 | MODULATION OF APOPTOSIS PATHWAY BY CURCUMIN IN CANCER

In contrast to normal tissues, curcumin alone and in combination with radiation or chemotherapy is able to potentiate apoptosis in most of cancers. Curcumin can modulate various signaling pathways in cancer cells, leading to the upregulation of proapoptosis genes such as Bax, PUMA, and caspase cascades, whereas it downregulates antiapoptosis genes such as Bcl-2 (Shankar & Srivastava, 2007; Zhu & Bu, 2017). For example, treatment of MCF-7 cells with curcumin potentiates apoptosis induction by radiation through elevation of poly ADP ribose polymerase (PARP) expression (Calaf, Echiburú-Chau, Wen, Balajee, & Roy, 2012; Girdhani, Ahmed, & Mishra, 2009). Furthermore, in contrast to normal cells, curcumin causes disruption of redox reactions in cancer cells, leading to more reactive oxygen species

(ROS) production. Activation of redox activity and ROS production by curcumin in cervical carcinoma cell lines, including HeLa and SiHa potentiates radiation toxicity and apoptosis in these cells (Javvadi, Segan, Tuttle, & Koumenis, 2008). In addition to radiation, curcumin is able to sensitize cancer cells to apoptosis when it is combined with chemotherapy drugs (Yallapu et al., 2010).

5.1 | Inhibition of NF-κB

It is suggested that NF-κB plays a central role in the survival and resistance of cancer cells against radiotherapy and chemotherapy (Baud & Karin, 2009; Karin, 2006). Also, the inhibition of NF-κB can reduce survival of cells, including both normal and cancer cells (Godwin et al., 2013). Upregulation of NF- κB/p65 is associated with resistance to chemotherapy in patients with breast cancer (Montagut et al., 2006). Also, it is suggested that upregulation of NF-κB in patients with breast cancer may be associated with an increased level of Bcl-2 and apoptosis resistance (Buchholz et al., 2005). An association between the upregulation and tumor resistance of NF-κB subfamilies and chemotherapy or radiotherapy has been shown for other cancers, such glioblastoma, multiple myeloma, hematological malignancies, and others (Bours et al., 2000; Braun et al., 2006; Friedmann-Morvinski et al., 2016; Garg, Hortobagyi, Aggarwal, Sahin, & Buchholz, 2003; F. Li & Sethi, 2010; Nakanishi & Toi, 2005; Tornatore et al., 2014). RelA/p65 and c-Rel overexpression is associated with poor survival of patients with B-cell lymphoma (L. Li et al., 2015; M. Zhang et al., 2016). NF-κB is one of the most important targets of curcumin for its effects on both normal and tumor cells. Curcumin suppresses IKK, leading to the prevention of IκB phosphorylation and activation of NF-κB (Olivera et al., 2012). It has been shown that treatment with curcumin can inhibit the nuclear translocation of p65 and reduces c-Rel gene expression (Vageli, Doukas, Spock, & Sasaki, 2018). Also, curcumin via targeting the PI3K p85/Akt pathway attenuates the protein levels of AKT and AKK (Buhrmann et al., 2011).

The treatment of colorectal cancer cells with curcumin enhances cell death and inhibits cell growth by 5-FU. Although 5-FU itself induces NF-κB, curcumin through suppression of NF-κB and antiapoptosis genes including Bcl-xL has a synergic effect via reduction of chemoresistance (Shakibaei et al., 2013; Shakibaei et al., 2015). Similar results have shown a synergistic effect on NF-κB inhibition by curcumin and 5-FU on other cancer cell types such as esophageal squamous cell carcinoma (Tian, Fan, Zhang, Jiang, & Zhang, 2012; Tian, Zhang, Tian, Jiang, & Zhang, 2012; Wei, Yang, Cao, & Zhao, 2018). Curcumin via activation of IκB reduces NF-κB activity in ovarian cancer cell lines, leading to potentiation of apoptosis induction by cisplatin (Fogoros, Choi, & Liu, 2005). It is suggested that curcumin through inhibition of NF-κB sensitizes colorectal cancer cells to capecitabine. This is associated with suppression of angiogenesis and metastasis factors, such as vascular endothelial growth factor (VEGF), intercellular adhesion molecule 1, matrix metallopeptidase 9 (MMP-9), and chemokine receptor type 4 (Kunnumakkara et al., 2009).

In addition to chemotherapy, NF-κB is one of the most important radioresistance mediators in radiotherapy. A large body of studies have confirmed that radiotherapy can upregulate its expression, so inhibition of NF-κB is an interesting strategy for radiosensitization of a wide range of cancers (Tsolou et al., 2017). Kunnumakkara et al. (2008) used HCT116 xenograft in nude mice for evaluating the radiosensitization effect of curcumin. They treated tumor-bearing mice with 1 g/kg curcumin per day and irradiated tumors with 4 Gy twice per week. The treatment and irradiation were continued for 1 month, and mice were killed 2 days after the end of treatment. Results showed a significant delay in tumor regrowth (19 days) and reduction of microvascular density by more than 50%. The western blot and immunohistochemical analysis showed that although the irradiation of tumor cells leads to a significant increase in NF-κB, treatment with curcumin caused potent inhibition in irradiated mice. Similar results were observed for other NF-κB downstream proteins, including COX-2, VEGF, and MMP-9. The results also showed that curcumin alone increases apoptosis, while it could not reverse the inhibition of pro-caspase-3 and 8 following irradiation. In contrast to this study, an in vitro study showed that in addition to suppression of NF-κB by curcumin, it reversed the inhibition of proapoptosis caspases, including caspase-2, caspase-3, and caspase-7 in human neuroblastoma cells. This study showed that curcumin inhibits p50/65 in irradiated cells in a dose-dependent manner (Aravindan, Madhusoodhanan, Ahmad, Johnson, & Herman, 2008). Similar results were observed for rhabdomyosarcoma both in vitro and in xenograft mice (Orr et al., 2013).

5.2 | Inhibition of COX-2

COX-2 is an inflammation mediator that produces prostaglandins and inhibits apoptosis. Furthermore, COX-2 is able to produce ROS that leads to mutations in both normal and malignant cells (Chai et al., 2012; Chai et al., 2013). Moreover, increased COX-2 is a hallmark for inflammatory reactions and diseases. So, COX-2 upregulation is involved in both normal tissue toxicity and tumor resistance in several organs and tumors (Cheki et al., 2018). COX-2 has been targeted in several experimental and clinical studies modifying the responses elicited by radiation and chemotherapy (Gore, 2004; Gore et al., 2011). COX-2 targeting by curcumin suggests that curcumin can act as an anti-inflammation agent, which is another mechanism by which curcumin can modulate the effects of chemo/radiation therapy (Goel, Boland, & Chauhan, 2001). For example, curcumin can inhibit COX-2 and inflammation induced by inflammatory stimulus agents (F. Zhang, Altorki, Mestre, Subbaramaiah, & Dannenberg, 1999). Furthermore, curcumin directly targets COX-2 and the production of PGE2. Koeberle, Northoff, and Werz (2009) showed that curcumin can suppress microsomal PGE2 synthase-1 in A549 cells. They showed that curcumin prevented biosynthesis of PGE2 from PGH-2, while other polyphenols such as resveratrol, eugenol, coniferyl alcohol, and rosmarinic acid were not able to suppress this pathway. Treatment of macrophages and human colon cancer cells (HT-29) with curcumin and related β-diketone analogs showed that

curcumin and its analogs inhibit generation of arachidonic acid in both macrophages and HT-29 cells following stimulation by lipopolysaccharide or A23187 (Hong et al., 2004). Similar results were observed by Goel et al. (2001) as they showed that treatment of HT-29 cells with curcumin (5–75 μM, 6–72 hr) inhibited COX-2 expression and enzymes activity in a dose and time-dependent manner. Interestingly, this study showed that curcumin inhibits COX-2 selectively and does not affect the expression of COX-1. Lev-Ari et al. (2006) proposed that curcumin may have a synergistic inhibitory effect on osteoarthritis synovial adherent cells in combination with celecoxib. They showed that combination of these agents potentiated apoptosis induction that was mediated through the suppression of COX-2. Results showed that treatment with celecoxib at 20 μM led to the suppression of PGE2 by 80%, but when 20 μM curcumin was added to cell medium, PGE2 production reduced by 95%. Similar results were observed for pancreatic adenocarcinoma and colorectal cancer cells. Also, this combination selectively inhibited COX-2 but not COX-1 (Lev-Ari, Strier et al., 2005; Lev-Ari, Zinger et al., 2005). S. H. Lee et al. (2012) showed that curcumin inhibits COX-2 and its downstream genes including vasodilator-stimulated phosphoprotein, leading to apoptosis induction in MCF-7 cells. The authors showed that COX-2 suppression by curcumin was mediated through AMP-activated protein kinase (AMPK). Similar results were observed for HT-29 cells. Curcumin treatment of these cells led to the upregulation of AMPK and suppression of COX-2, which caused apoptosis induction. However, inhibition of AMPK led to attenuation of this pathway and apoptosis (Y. K. Lee, Park, Kim, & Park, 2009).

5.3 | Curcumin and the ceramide pathway

Ceramide is an apoptosis initiator that is generated after the interaction of free radicals with the plasma membrane phospholipid sphingomyelin. Also, ceramide may be produced after the stimulation of sphingomyelin by inflammatory cytokines and environmental stress (Yabu et al., 2014). As several anticancer agents stimulate apoptosis through the ceramide pathway, it is known as a mediator of tumor suppression (Huang, Chen, Lin, Lin, 2011). It was suggested that ceramide through upregulation of other proapoptosis mediators, such as stress-activated protein kinase, JNK, and ERK, initiates an apoptosis signaling cascade (Haimovitz-Friedman, Kolesnick, & Fuks, 1997; Pena, Fuks, & Kolesnick, 1997). Some studies have been conducted to investigate the possible role of the ceramide pathway in curcumin-mediated induction of apoptosis in cancer cells. Moussavi, Assi, Gomez-Munoz, & Salh (2006) proposed that curcumin via accumulation of ceramide induces apoptosis in human colon cancer cells. This study showed that curcumin through modulation of the redox state in colon cancer cells increases ROS production, leading to ceramide production. Then, ceramide through the upregulation of JNK induces apoptosis signaling. They showed that neutralization of ROS by an antioxidant could prevent ceramide accumulation and apoptosis. Abdel Shakor et al. (2014) evaluated ceramide accumulation and apoptosis in multidrug-resistant human leukemia HL60 cells. They showed that curcumin was able to activate sphingomyelinase and inhibit sphingolipid-modifying enzymes activity, leading to ceramide generation. Also, results showed that ceramide generation by curcumin was a biphasic cycle. Activation of sphingomyelinase after treatment with curcumin caused ceramide generation, which mediated more ceramide generation at later time-points. Further study showed that activation of sphingomyelinase by curcumin was followed by depletion of glutathione that is needed for the activation of caspase-8 and inhibition of Bcl-2. It is possible that curcumin through suppression of glutathione increases ROS, leading to ceramide generation and apoptosis (Abdel Shakor, Atia, Alshehri, Sobota, & Kwiatkowska, 2015). Similar results have been reported in PC3 cells. Treatment of PC3 cells with curcumin leads to the inhibition of glutathione that resulted in ceramide accumulation, causing damage to mitochondria and release of cytochrome C and apoptosis-inducing factor (AIF). Interestingly, apoptosis induction in PC3 cells by curcumin was not dependent on caspase or MAPKs, and suppression of these genes does not prevent apoptosis (Hilchie et al., 2010).

5.4 | Modulation of p53

The p53 tumor suppressor regulates various signaling pathways in response to different stress signals. One of the most critical roles of p53 is triggering apoptosis on precancerous and cancer cells (Fridman & Lowe, 2003). Furthermore, p53 mediates inhibition of cell cycle progression and cell senescence in malignant cells (Aubrey, Kelly, Janic, Herold, & Strasser, 2018). In this regard, activation of p53 has been proposed as a mechanism for improving the tumor's response to radiotherapy and chemotherapy (Amaral, Xavier, Steer, & Rodrigues, 2010). Treatment of breast cancer cells with curcumin can induce apoptosis via activation of p53 (Hallman et al., 2017). Moreover, it has been proposed that p53 activation by curcumin lead to the upregulation of Bax and mitochondrial damage, leading to apoptosis (Choudhuri, Pal, Agwarwal, Das, & Sa, 2002). Similar results have been revealed in multiple myeloma cells (W. Li et al., 2015). The combination of curcumin and radiation elicited synergistic apoptosis induction and inhibited cell cycle progression in human leukemic cells, IM-9, K-562, and HELA cells that correlated with p53 activity (Baatout, Derradji, Jacquet, & Mergeay, 2005; Baatout et al., 2004).

In contrast to these studies, a study by Moos, Edes, Mullally, & Fitzpatrick (2004) showed that treatment of colon cancer cells with curcumin disrupted p53 regulation, phosphorylation, and DNA binding. Phosphorylation of p53 was apparent when cells were treated with 60 μM curcumin, whereas lower concentrations of curcumin could not prevent p53 phosphorylation significantly. However, lower concentrations of curcumin reduced p53 activity.

5.5 | Modulation of the PTEN/PI3K/Akt pathway

PTEN is a tumor suppressor gene and its mutation is a hallmark of carcinogenesis (Mutter, 2001). Its activity is crucial for induction of apoptosis, while mutations or other changes which suppress its activity led to the upregulation of antiapoptosis genes including PI3K

and Akt (Kurose et al., 2001; Vazquez & Sellers, 2000). Activation of Akt leads to the upregulation of Bcl-2 and inhibition of apoptosis (Sun et al., 1999). So, inhibition of PI3K/Akt can facilitate apoptosis induction in cancer cells, especially cancers with a mutation in PTEN. Curcumin has induced apoptosis via regulation of PTEN and its downstream signaling. For example, X. Wang et al. (2017) showed that the treatment of MCF-7 cells with curcumin causes a remarkable upregulation of PTEN and downregulation of Akt, leading to apoptosis. Further analyses showed that the inhibition of mir-21 by curcumin was involved in the increased expression of PTEN. Also, the inhibition of mir-21 and Akt, as well as upregulation of PTEN was completely dependent on curcumin concentration. Curcumin attenuated the mir-21 level via increasing exclusion of mir-21 exosome and also suppression of its gene expression (J.Chen, Xu, & Chen, 2015). On the other hand, transfection of mir-21 into A549 cells reduced the toxicity of curcumin via inhibition of PTEN, which indicates the pivotal role of PTEN pathway in the anticancer effect of curcumin (W. Zhang, Bai, & Zhang, 2014). In addition to mir-21, mir-19 is also able to dysregulate PTEN expression, and curcumin can reverse its function (X. Li et al., 2014; Mirzaei et al., 2018). Beside the PTEN pathway, curcumin can inhibit PI3K/Akt signaling directly. Jin, Qiao, Wang, Xu, & Shang (2015) showed that curcumin increases apoptosis via upregulation of miR-192-5p, which directly targets PI3K/Akt regulation. Curcumin also via upregulation of mir-15 induces the downregulation of Akt and Bcl-2, leading to the inhibition of cell proliferation. Inhibition of mir-15 leads to the attenuation of the anticancer effect of curcumin through activation of the PI3K/Akt pathway (Mou, Zhou, He, Liu, & Gong, 2017).

Qiao, Jiang, & Li (2013) evaluated the role of the PI3K/Akt pathway in the radiosensitization effect of curcumin in human Burkitt's lymphoma cell lines (Namalwa, Ramos, and Raji cells). Results showed that the irradiation of these cells without treatment leads to significant phosphorylation and activation of PI3K/Akt. This also led to the upregulation of NF-κB in human Burkitt's lymphoma cells. Treatment of cells with 20 or 50 μM curcumin inhibited PI3K/Akt and NF-κB that was associated with the activation of caspase-3 and PARP, and ultimately induction of apoptosis.

5.6 | Modulation of TRAIL

As mentioned earlier, TRAIL is one of the most important apoptosis receptors, which is activated by TNF-α. Upregulation of this receptor plays a key role in the sensitization of cancer cells to apoptosis. It has suggested that ROS production, activation of p53, and inhibition of NF-κB can upregulate the expression of TRAIL (Farhood, Najafi, Salehi et al., 2018). As curcumin induced the production of ROS via stimulation of redox reactions within cells, it seems that activation of these pathways is crucial for TRAIL overexpression by curcumin (Wu et al., 2010). A study by Sah et al. (2003) in PC3 cells showed that the upregulation of JNK by curcumin was necessary for the upregulation of TRAIL. Also, it has been shown that ROS production by curcumin induces overexpression of dead receptor 5 (DR5) in resistant breast cancer cells (Park, Cho, Andera, Suh, & Kim, 2013). Furthermore, curcumin via inhibition of the antiapoptosis Mcl-1 gene can trigger upregulation of TRAIL, leading to apoptosis (Koohpar, Entezari, Movafagh, & Hashemi, 2015).

Jung et al. (2005) showed that curcumin through the production of ROS in human renal cancer cells upregulates DR5, which led to the overexpression of TRAIL. Neutralization of ROS leads to the downregulation of TRAIL. The expression and activity of DR5 showed a direct relationship with curcumin concentration. Moreover, when cells were treated with both curcumin and TRAIL, the incidence of apoptosis was increased by more than fivefold. Inhibition of DR5 can also attenuate apoptosis induction by curcumin via downregulation of TRAIL (Jung et al., 2006; Table 1)

Deeb et al. (2003) evaluated the modulatory effect of curcumin on the expression of TRAIL in LNCaP prostate cancer cells. They treated cells with 10 μM curcumin and 20 ng/ml TRAIL alone or in combination. Results showed that neither curcumin nor TRAIL was able to induce apoptosis and reduce the viability of LNCaP prostate cancer cells. However, when cells were treated with them in combination, the viability of cells reduced by more than 60%. Curcumin could induce both intrinsic and extrinsic apoptosis when it was combined with TRAIL. Another study showed that inhibiting IκB phosphorylation and NF-κB upregulation was involved in curcumin-induced apoptosis through the TRAIL pathway (Deeb et al., 2004). Curcumin also upregulated TRAIL-R1/DR4 and TRAIL-R2/DR5 in both PC3 and LNCaP cells (Shankar, Chen, Sarva, Siddiqui, & Srivastava, 2007). Similar results have been revealed for HCT116 colon cancer cells (X. Yang et al., 2017). Furthermore, an in vivo study confirmed these results. Mice bearing LNCaP xenografts were treated with 30 mg/kg curcumin and 15 mg/kg TRAIL alone or in combination. The results showed that curcumin alone attenuated tumor growth, reduced COX-2 and VEGF (as markers of angiogenesis) and MMP-2 (as a marker for metastasis). TRAIL alone did not show a significant effect on the expression of these markers. However, in combination with curcumin, apoptosis was increased and also angiogenesis and metastasis markers were suppressed (Shankar, Ganapathy, Chen, & Srivastava, 2008).

D. Kwon, Oh, Park, Lee, & Lee (2014) showed that curcumin induces more apoptosis induction through the TRAIL pathway compared with TRAIL treatment. They also showed that apoptosis occurred in a dose-dependent manner after curcumin alone or in combination with TRAIL. For example, apoptosis was increased by more than 80% when cells treated with 10 or 50 μM curcumin. Furthermore, Wahl, Tan, Griffith, Choi, & Liu (2007) showed that treatment of cisplatin-resistant ovarian cancer cells with the combination of curcumin and TRAIL stimulates apoptosis through activation of both intrinsic and extrinsic apoptosis signaling pathways.

5.7 | Modulation of FasL

FasL is another TNF-dependent pathway of apoptosis that can trigger apoptosis induction independently from p53. FasL is one of several pathways that the immune system can use to induce cancer

TABLE 1 Mechanisms of apoptosis induction in tumor cells by curcumin

Tissues/cells	Concentration	Mechanisms	References
In vitro studies			
Colorectal cancer cells	0–80 μM	Suppression of NF-κB Bcl-xL, sensitization to 5-FU	Shakibaei et al. (2013); Shakibaei et al. (2015)
Human neuroblastoma cells	10–100 nM	Inhibition of NF-κB, activation of caspase-2, caspase-3, and caspase-7 in irradiated cells	Aravindan et al. (2008)
HT-29 cells	5–75 μM	Suppression of COX-2	Goel et al. (2001)
Pancreatic adenocarcinoma, colorectal cancer cells	10–15 μM/L	Suppression of COX-2	Lev-Ari, Strier et al. (2005); Lev-Ari, Zinger et al. (2005)
HT-29 cells	50 μM	Upregulation of AMPK and suppression of COX-2	Y.K. Lee et al. (2009)
Human colon cancer cells	50–100 μM	ROS production via stimulation of redox activity, accumulation of ceramide, upregulation of JNK	Moussavi et al. (2006)
Human leukemia HL60 cells	10–30 μM	Activation of sphingomyelinase, ceramide generation	Abdel Shakor et al. (2014)
Human leukemia HL60 cells	20 μM	Suppression of glutathione, increase of ROS level, ceramide generation	Abdel Shakor et al. (2015)
PC3 cells	25–100 μM	Inhibition of glutathione and ceramide accumulation	Hilchie et al. (2010)
Breast cancer cells	5–60 μM	Activation of p53 and estrogen receptors	Hallman et al. (2017)
MCF-7	0–10 μM	Upregulation of PTEN and downregulation of Akt through inhibition of mir-21	X. Wang et al. (2017)
Laryngeal cancer cells	20 and 40 μM	Inhibition of Akt and Bcl-2 through upregulation of mir-15	Mou et al. (2017)
PC3 cells	25 μM	JNK is involved in TRAIL upregulation by curcumin	Sah et al. (2003)
Resistant breast cancer cells	10 and 20 μM	Overexpression of DR5 following ROS production	Park et al. (2013)
Human renal cancer cells	30 μM	Upregulation of TRAIL following ROS production and activation of DR5	Jung et al. (2005)
LNCaP	10 μM	Synergic effect when it combined with TRAIL	Deeb et al. (2003)
PC3 and LNCaP cells	5–40 μM	Stimulation of TRAIL-R1/DR4 and TRAIL-R2/DR5 pathways	Shankar et al. (2007)
Glioblastoma multiforme (GBM)	10 and 50 μM	Upregulation of TRAIL pathway	Kwon et al. (2014)
Hepatocellular carcinoma Huh7 cells	30 μM	Upregulation of FasL and p38	W. Z. Wang et al. (2013)
Melanoma cells	25 μM	Activation of JNK through upregulation MST1, ROS production	Yu et al. (2013)
Human choriocarcinoma cells	10–50 μM	Activation of JNK and ERK1/2	Lim et al. (2016)
PC3, DU145, and LNCaP	0–100 μM	Activation of JNK and ERK1/2	J. Li et al. (2015)
In vivo studies			
esophageal squamous cell carcinoma (ESCC)	50 μM per mice every 3 days for 21 days	Downregulation of the IκBα phosphorylation	Tian, Fan et al. (2012)
Human ESCC xenograft	50 μM per mice every 3 days for 15 days	Inhibition of p65	Tian, Zhang et al. (2012)
Mice bearing HCT116 cells	1 g/kg	Enhancing the effect of capecitabine via inhibition of NF-κB, VEGF, and COX-2, reduction of microvascular density	Kunnumakkara et al. (2008); Kunnumakkara et al. (2009)
Mice bearing LNCaP xenografts	30 mg/kg	Inhibition of COX-2, VEGF, and MMP-2	Shankar et al. (2008)
U87 xenograft tumor-bearing nude mice	5 or 10 μM	Inhibition of JNK, upregulation of DUSPs	Zhang et al. (2015).

Note. AMPK: AMP-activated protein kinase; DR5: dead receptor 5; DUSPs: dual-specificity phosphatase; MMP-2: matrix metallopeptidase-2; MST1: mammalian sterile 20-like kinase 1; ROS: reactive oxygen species; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; VEGF: vascular endothelial growth factor.

cell killing via apoptosis. However, it is suggested that stimulation of this pathway alone, for example using anti-Fas antibodies may lead to severe side effects (Peter et al., 2015). Moreover, experimental studies have revealed that stimulation of this pathway alone may not be sufficient for apoptosis in most cancers (Ogasawara et al., 1993). Studies investigating apoptosis induction by curcumin through modulation of FasL are very limited. Curcumin has shown that in addition to its actions on the TRAIL pathway, induces upregulation of Fas-associated protein with death domain (FADD) by FasL, leading to the activation of caspase-8 and finally apoptosis (Bush, Cheung, & Li, 2001). W. Z. Wang et al. (2013) showed that FasL is a necessary pathway for apoptosis induction in human hepatocellular carcinoma Huh7 cells. They treated Huh7 cells with curcumin and observed the fast upregulation of FasL and p38, leading to the activation of caspase-3 and apoptosis. Furthermore, inhibition of either FasL or p38 led to the attenuation of apoptosis induction by curcumin.

5.8 | Modulation of the JNK pathway

JNK plays a key role in redox reactions and apoptosis induction. For the first time, Collett and Campbell (2004) showed that curcumin was able to induce apoptosis through activation of JNK. They treated HCT116 human colon cancer cells with curcumin and observed a significant increase of JNK but not other MAPK genes, including ERK and p38. Inhibition of JNK in curcumin-treated cells reduced apoptosis, thus it confirmed the pivotal role of JNK in apoptosis. Another study by C.-W Yang et al. (2012) showed that curcumin induced apoptosis via upregulation of both JNK and ERK in human monocytic leukemia THP-1 cells. However, curcumin did not change the regulation of the PI3K/FOXO pathway (antiapoptosis pathway).

Curcumin can induce mammalian sterile 20-like kinase 1, leading to the activation of JNK and Foxo3 nuclear translocation in melanoma cells. Activation of this pathway leads to ROS production, stimulation of caspase proteins, and induction of apoptosis (Yu, Ji, & Guo, 2013). Activation of JNK by curcumin also has been shown in other cancer cell lines. Curcumin activates JNK in Rh30 and HT-29 cancer cells through the phosphorylation of MKK4 and also c-Jun, which is a substrate for JNK. Moreover, curcumin attenuates the expression of protein phosphatase 5 (PP5) which is an inhibitor of JNK (Huang, Han, & Xu, 2011). Inhibition of PP5 by curcumin can also enhance ROS production by JNK and ERK1/2 pathways and potentiates apoptosis via stimulation of p53 (Han et al., 2012).

Lim, Jeong, Bazer, & Song (2016) evaluated apoptosis induction by curcumin in human choriocarcinoma cells (JAR and JEG3) through MAPKs. They showed that treatment with curcumin induces apoptosis in a concentration-dependent manner. This was associated with the upregulation of JNK and ERK1/2 and their downstream genes. Interestingly, p38 has a negative effect on apoptosis induction and suppression of it by its inhibitor antibody potentiated apoptosis in cancer cells.

The upregulation of JNK and ERK1/2 by curcumin may enhance the therapeutic efficiency of chemotherapy drugs. Combination of curcumin and bicalutamide has a synergistic effect on cell death in human prostate cancer cells, including PC3, DU145, and LNCaP. Also, curcumin has a potent inhibitory effect on p65, whereas bicalutamide may enhance its expression. It seems that further phosphorylation of JNK and ERK1/2 and suppression of antiapoptosis pathways by curcumin has a key role in eliciting significantly more cell death in PC3, DU145, and LNCaP when given in combination with chemotherapy drugs (J. Li et al., 2015).

In contrast to these studies, Somasundaram et al. (2002) showed that curcumin inhibits JNK upregulation and ROS production produced by chemotherapy drugs including camptothecin, mechlorethamine, and doxorubicin. This was associated with the reduction of chemotherapy-induced apoptosis in breast cancer cells including MCF-7, MDA-MB-231, and BT-474. Treatment of U87 xenograft tumor-bearing nude mice with curcumin before irradiation also showed that the expression of JNK was reduced, whereas apoptosis was increased. Treatment of mice with curcumin alone also showed a significant reduction in JNK. This study proposed that curcumin in combination with radiation induces apoptosis in U87 cells through upregulation of dual-specificity phosphatase, which can activate or inactivate several enzymes (L. Zhang et al., 2015).

6 | CONCLUSION

As mentioned in this review, curcumin has several anticancer effects. The antitumorigenesis effect of curcumin can prevent the development of cancer through apoptosis induction in precancerous cells. It seems that modulation of apoptosis signaling pathways is one of the most potent effects of curcumin that can sensitize tumor cells to therapeutic modalities such as chemotherapy and radiotherapy. Apoptosis can be modulated via different signaling pathways that affect extrinsic or intrinsic apoptosis mediators. Extrinsic apoptosis can be induced after ROS production and oxidation of phospholipids in the plasma membrane. Also, the upregulation of cell membrane apoptosis receptors such as TGFβR1 and TGFβR1, TRAIL, and Fas ligand plays a key role in the initiation of extrinsic apoptosis. On the other hand, changes in mitochondria function, as well as upregulation of Bax and PUMA, and downregulation of Bcl-2 are the most crucial changes that are needed to elicit intrinsic apoptosis. Furthermore, some other factors such as hypoxia and inflammatory mediators such as NF-κB, COX-2, mTOR, and PI3K pathway play a key role in preventing apoptosis through downregulation of proapoptosis and upregulation of antiapoptosis genes. Moreover, several cancers show a low activity of tumor suppressor genes such as p53 and PTEN, which are interesting targets for improving tumor control via potentiation of their activity. Curcumin can change the redox activity of cancer cells via attenuation of the antioxidant defense of cells. Then, oxidative stress can upregulate the expression of apoptosis ligands, such as TRAIL and FasL, which trigger activation of caspase-8 through FADD. Also, an increased level of ROS in cancer cells can facilitate the development of ceramide, which initiates apoptosis through JNK.

Curcumin has potent anti-inflammatory properties that have a close relation with apoptosis signaling cascades. It is able to prevent upregulation and activity of NF-κB in different types of cancers. This is associated with attenuation of the expression of antiapoptosis genes such as COX-2 and Bcl-2, and also upregulation of Bax. Curcumin also via an increase in the activity of p53 facilitates cell cycle arrest and apoptosis of precancerous and cancer cells. PTEN is another tumor suppressor gene that is activated by curcumin and induces apoptosis through inhibition of the PI3K/Akt pathway. Taken as a whole, the study proposes that the apoptosis modulatory effect of curcumin can be used to enhance the therapeutic efficiency of other current treatments such as chemotherapy.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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How to cite this article: Mortezaee K, Salehi E, Mirtavoos-mahyari H, et al. Mechanisms of apoptosis modulation by curcumin: Implications for cancer therapy. *J Cell Physiol*. 2019;1–14. https://doi.org/10.1002/jcp.28122