Received: 12 August 2019 | Revised: 16 January 2020 | Accepted: 15 February 2020

DOI: 10.1002/ptr.6663

WILEY

REVIEW

Molecular mechanism of curcumin action in signaling pathways: Review of the latest research

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Funding information
Uniwersytet Łódzki

Recently, many studies have been conducted trying to explain the molecular mechanism of curcumin action in various pathological states of the cell and the organism. Curcumin is considered to play a role in the regulation of T-lymphocytes function in the lymphoid tissue of the large intestine, apoptosis of the human papilloma and the activity of the 26S proteasome, and p53 level. Research works have shown that curcumin in tumor can regulate reactive oxygen species (ROS) and cytosolic calcium ion level as well as affect other signaling molecules [nuclear factor kappa B (NF-KB), cytokines] triggering endoplasmic reticulum and mitochondrial stress, and thus contributing to death of cancer cells. Curcumin can also arrest of the cell cycle in the G2/M phase leading to apoptosis and/or reduction in cancer cells proliferation. Moreover, curcumin is capable of crossing the blood–brain barrier, and thus it may protect the neurons from oxidative stress and inflammation. Finally, curcumin may play a role in cardiological protection and it is possible to use it in the protection of liver and spleen against oxidative and inflammatory injury. Among signaling pathways regulated by curcumin, the most important seem to be those related with regulation of oxidative stress and inhibition of NF-κB activity.

KEYWORDS
apoptosis, calcium ion, cell cycle, curcumin, oxidative stress, reactive oxygen species, signaling pathways

1 | GENERAL CHARACTERISTICS OF TURMERIC AND ITS CURCUMIN INGREDIENTS

1.1 | Structure and function of turmeric

Turmeric (*Curcuma longa* L.), is a perennial plant belonging to the ginger family. Because of its color, it is also called Indian saffron. It grows wild in India and is cultivated in many countries with tropical climates such as India, Pakistan, China and Haiti. This plant produces secondary metabolites, such as: phenolic acids, flavonoids, alkaloids, terpenoids, tannins and saponins, which biological properties have been known for centuries (Dutta, 2015). The rhizome of turmeric is widely used in Asian cuisine to give food a yellow color and characteristic taste and smell (Anand et al., 2008). Turmeric is commonly known for its culinary use as a component of 'Curry' (Kiuchi et al., 1993).

1.2 | Biological properties of turmeric

Biological properties including pleasant aroma of turmeric are associated with the presence of essential oils such as ar-turmeron, following by α- and β-turmeron, while β-caryophyllene, α-eucalyptol and phellandrene are contained in smaller amounts. The most active substances contained in curcumin are polyphenols known as curcuminoids, which content is from 3 to 5% (Palve & Nayak, 2012). Depending on the position of the methoxy group(s) in the aromatic ring, three main natural analogs of curcumin exists, referred to as curcuminoids, of which the highest amount is curcumin (77%)

following by demethoxycurcumin (17%) and bis-demethoxycurcumin (3%) (Anand et al., 2008). In the 1980s of the last century, trace amounts of the fourth natural analog of curcumin such as cyclocurcumin were detected in the curcumin root extracts (Kiuchi et al., 1993) (Figure 1).

Among all turmeric compounds, curcumin also known as diferuloylmethane is the most valuable one, belonging to hydrophobic polyphenols (Kiuchi et al., 1993). Curcumin or 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadieno-3,5-dione, contains two ferulic acid residues joined by a methylene bridge (Figure 1) (Gupta, Kismali, & Aggarwal, 2013. The curcumin plays the most important role in therapeutic properties of turmeric, including its anti-inflammatory and antioxidant activity (Figure 2) (Jurenka, 2009;Gupta et al., 2013; Del Prado-Audelo et al., 2019).

Curcumin can be used to treat various disorders, including chronic diseases, inflammatory disorders, infections and other pathological states (Aggarwal, Sundaram, Malani, & Haruyo, 2007) (Figure 3). The antioxidant properties of curcumin result from the formation of phenoxy radicals or direct hydrogen abstraction. The first mechanism involves the transfer of an electron to the free radical, resulting in a radical cation formation, which produces phenoxy radical by a proton loss. The second mechanism involves direct abstraction of hydrogen, while hydroxyl residue of curcumin is considered to be the most vulnerable to radical attack (Del Prado-Audelo et al., 2019) (Figure 2).

1.3 | Pharmacokinetics and metabolism

The studies have shown that curcumin is rapidly and efficiently metabolized in mammals. In the study on rats, a dietary dose of curcumin (1 g/kg) was metabolized and eliminated (75%) during a few hours, mainly in feces and in negligible amounts in the urine, while after intravenous administration, more than 50% of the dose was excreted in the bile within 5 hr (Wahlstrom and Blennow, 1978). Analytical data have shown that curcumin is mainly metabolized to curcumin glucuronide, and to a lower extent to curcumin sulfate, hexahydrocurcumin, hexahydrocurcuminol and hexahydrocurcumin glucuronide. In humans, curcumin is efficiently eliminated and is also well tolerated. Curcumin orally administrated (dose 0.5–8 g daily for 3 months) to patients with preinvasive malignant or high-risk premalignant conditions of the bladder, skin, cervix, stomach or oral mucosa was well tolerated and its concentrations were found to peak 1–2 hr after intake, and then declined within 12 hr (Cheng et al., 2001). After administration of a dose of 8 g of curcumin daily, its highest concentration determined in blood serum did not exceed 2 μM, which showed that curcumin did not accumulate in the organism. In a clinical study using a standardized oral Curcuma extract containing mainly curcumin, doses up to 180 mg of curcumin per day were given to patients with advanced colorectal cancer for up to 4 months without toxic effects or detectable systemic bioavailability (Sharma et al., 2001).

2 | CURCUMIN INFLUENCES CELL APOPTOSIS AND PROLIFERATION BY ROS LEVEL AND AFFECTS CELL CYCLE REGULATION (IN VITRO AND IN VIVO)

The studies have indicated an important role of curcumin in the regulation of endoplasmatic reticulum (ER) stress, while its role (as it was mentioned above) appears to be highly dependent on the cell type and experimental conditions (in vitro or in vivo). For instance, curcumin can alleviate oxidative stress in normal cells of adipose tissue in vivo (Wang, Zhang, Huang, Liu, & Xie, 2016), while it may enhance this process in vitro in human colon cancer cells (Basile et al., 2013), human papillary thyroid carcinoma cells (BCPAP) (Zhang, Cheng, Xu, Bao, & Yu, 2018), K562 cell line of chronic myeloid leukemia (CML) (Larasati et al. (2018) and in B-precursor lymphoblastic leukemia (ALL) (B-Pre-ALL) cell lines (Kuttikrishnan et al., 2019).

The results have shown that cancer cells are more susceptible to curcumin action than normal cells. Numerous studies have documented that curcumin can trigger apoptosis in normal cells but in much higher concentrations than in cancer cells. For instance, Watson, Hill, Lee, Giacomantonio, and Hoskin (2008) observed that curcumin induced apoptosis in colon cancer cells (HCT116 line) and in normal fibroblasts at the concentrations of 10 and 40 μM, respectively. In another study, Shankar and Srivastava (2007) noticed that

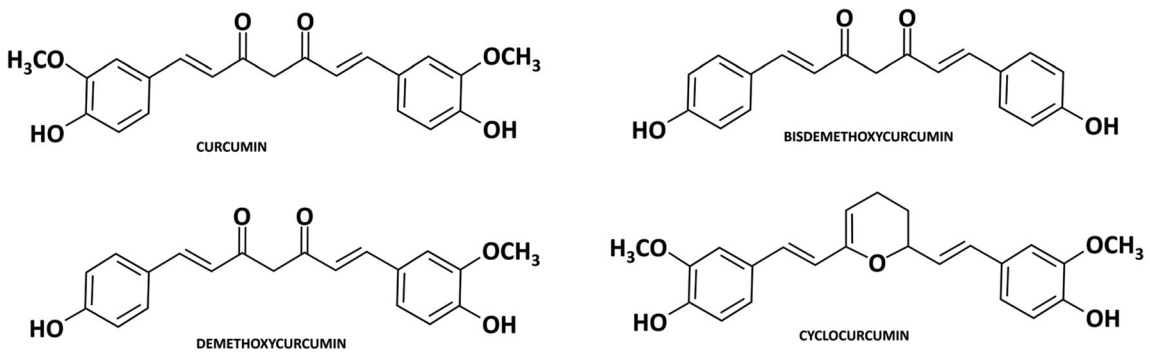

FIGURE 1 Chemical structure of curcumin and its derivatives (based on work Kiuchi et al., 1993)

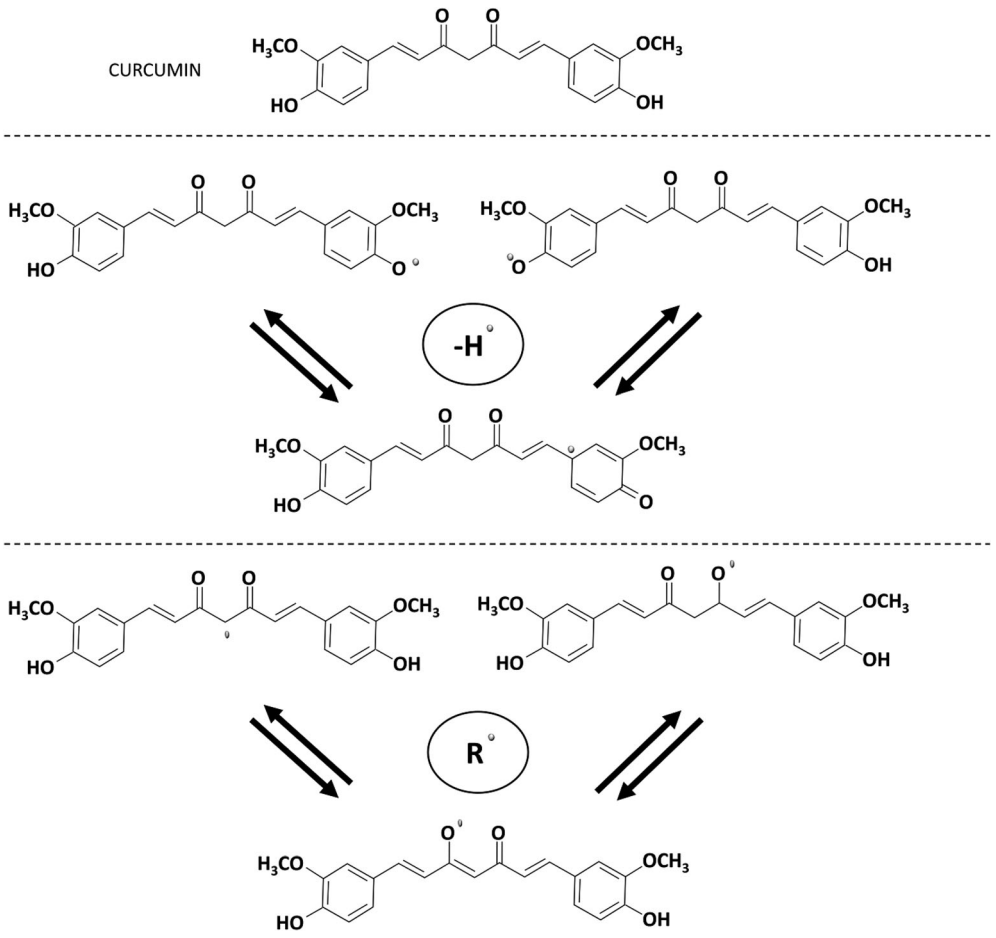

FIGURE 2 Antioxidant mechanism of curcumin action (based on work Del Prado-Audelo et al., 2019)

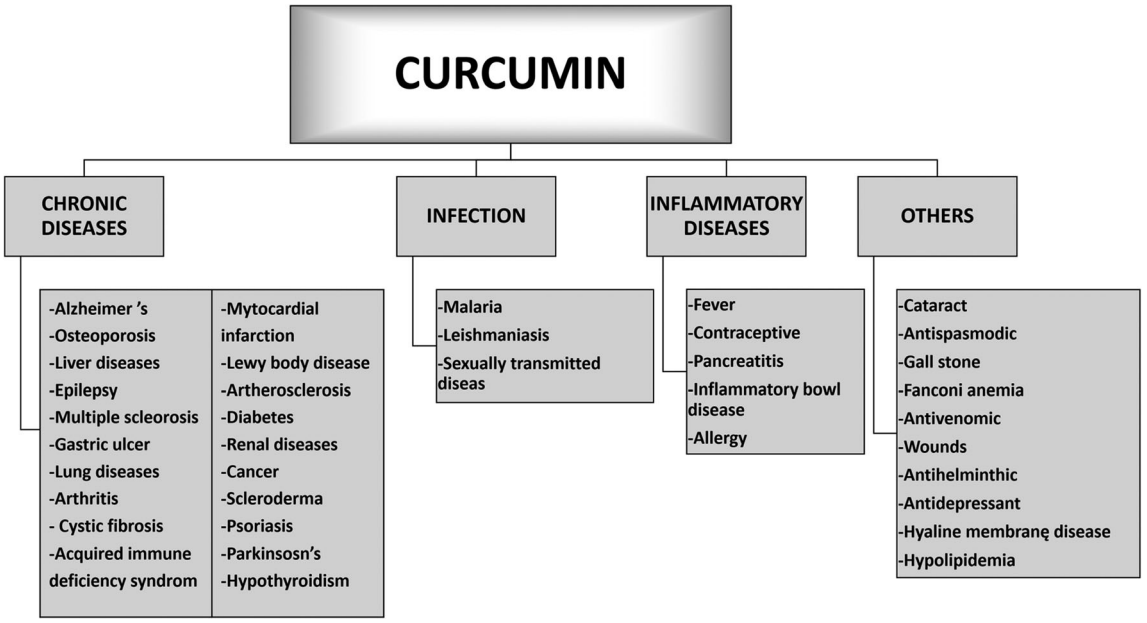

FIGURE 3 Potential applications of curcumin (based on work Gupta, Kismali, & Aggarwal, 2013)

curcumin at 30 μM triggered apoptosis in immortalized mice embryonic fibroblasts, while it did not induce this process in normal lung epithelial cells.

Aggarwal (2004) consider that cancer cells in opposite to most types of normal cells have active nuclear factor kappa B (NF-κB) transcription factor that is the main target of curcumin action, which

mainly explain differences in sensitivity of these cell types. Similarly, Bielak-Zmijewska et al. (2010) observed that mouse oocytes that have inactive form of NF-κB are substantially resistant to curcumin-induced cell death. They have observed that curcumin only from the concentration of 30 μM was capable of inducing apoptosis through action on CDK1 kinase.

2.1 | Curcumin reduces oxidative stress in normal cells (in vivo)

Curcumin exhibits strong antioxidative properties that are comparable to activities of vitamin C or E. It has been documented that curcumin is scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS) including superoxide anion, hydroxyl radical and nitrogen dioxide. Curcumin has also been shown to inhibit oxidative damage including lipid peroxidation in various animal models (Sikora-Polaczek, Bielak-Zmijewska, & Sikora, 2011). Moreover, this substance is capable of activating of enzymatic antioxidant responses through activation of genes coding superoxide dismutase, catalase, glutathione peroxidase and S-glutathione transferase (Menon & Sudheer, 2007).

ROS and RNS that are formed upon normal cellular conditions may be favorable or detrimental for living organism. In low concentrations, they play signaling role in the cell inducing mitogenic effect or participate in a defense against pathogens. Adverse effects of ROS/RNS lead to oxidative stress, which occurs as a result of excessive reactive species production or/and insufficient action of enzymatic and non-enzymatic antioxidants. An excess of ROS may result in lipids, protein and nucleic acids damage, therefore, it is accepted that oxidative stress plays a crucial role in etiology of various diseases and aging. Many chemicals may have both pro- and antioxidative activity, which depends on the concentration/dose of the substance used.

Wang et al. (2016) showed in vivo that curcumin inhibited lipolysis by inhibiting ER stress in normal cells of adipose tissue and prevented hepatic insulin resistance (Wang et al., 2016). The researchers used male C57BL/6 mice, which were fed with HFD (10% lard, 10% yolk, 1% cholesterol, 0.2% cholate, and 78.8% standard diet) for 10 days to build insulin resistance model. The curcumin (50 mg/kg) was administered intragastrically to mouse models. It has been shown that curcumin inhibited ER stress of adipose tissue by dephosphorylation of 1α enzyme requiring inositol and eukaryotic initiator factor 2α, and reduced cAMP accumulation. As a result of cAMP depletion, a release of glycerol and free fatty acid (FFA) proceeded. Additionally, curcumin reduced influx of FFA into the liver, and thus prevented the formation of diacylglycerol deposits in this organ (Wang et al., 2016).

2.2 | Curcumin affects cell cycle in the G1/S and G2/M phase in cancer cells (in vitro)

Lee, Lee, and Kim (2009) showed that curcumin (in concentration 10 μg/mL–27 μM) caused cell cycle arrest followed by antiproliferative effect and induction of apoptosis in human osteosarcoma (HOS) cell line (ATCC CRL-1543) in vitro. Before curcumin induced apoptosis, it had inhibited the cell cycle; the cells were arrested in the G1/S phase, and subsequently in the G2/M phase. Consequently, it was for the first time demonstrated that curcumin is able to arrest cell cycle at its different phases. In order to assess the molecular mechanism of curcumin action, those researchers assessed changes in cell cycle regulatory proteins levels. Cyclin D1 is one of the cyclins required to pass from G1 to the S phase. A decrease of cyclin D1 level is one of the main causes of cell cycle arrest at G1/S phase, which was observed in curcumin-treated HOS cells. On the other side, the cdc2/cyclin B complex is one of the main elements regulating the progression of G2 to M phase. Arresting the cell cycle at the G2/M phase after treatment with curcumin is associated with the reduction of cdc2/cyclin B complex formation, which is necessary step for cells to undergo to mitosis. It may be concluded that curcumin causes death of HOS cells by cell cycle arrest sequentially in the G1/S and G2/M phases (Lee et al., 2009).

In another study, Martínez-Castillo et al. (2018) examined, cellular effects of curcumin (20 μM) on HL-60 and K562 cell lines derived from chronic or acute myeloid leukemia. The K562 cells showed a higher sensitivity to the cytostatic and cytotoxic effects of curcumin in comparison to HL-60. In addition, curcumin induced G1 and G2/M phase arrest in HL-60 cells and K562 cells, respectively.

2.3 | Curcumin influences apoptosis in cancer cells (in vitro)

The anticancer action of curcumin is mainly associated with its antiproliferative and proapoptotic effects, which have been mostly shown in vitro studies in human colon cancer cells (Basile et al., 2013), human papillary thyroid carcinoma cells (BCPAP) (Zhang et al., 2018), K562 cell line of CML (Larasati et al., 2018) and in B-precursor lymphoblastic leukemia (ALL) (B-Pre-ALL) cell lines (Kuttikrishnan et al., 2019). In vivo, curcumin has been shown to prevent cancer cells spread (Kuttan, Kumar, Guruvayoorappan, & Kuttan, 2007) and inhibit angiogenesis (Bhandarkar & Arbiser, 2007).

ER is the main organelle for the synthesis, maturation and formation of spatial structure of proteins. To some extent, the fate of the cell is determined by the balance between survival and apoptotic signaling, while the specific ER stressor, plays a key role in adjusting cell homeostasis (Sano & Reed, 2013). In order to balance extracellular stimulation, the unfolded protein response (UPR) is activated to reduce mis-folded structure of proteins. Increased stress in ER initiates apoptotic cell death, which may be dependent or independent on mitochondrial signaling (Wang, Groenendyk, & Michalak, 2014). UPR is triggered in the cell, when transmembrane protein factors in ER (PERK, IRE, ATF6) detect the accumulation of unfolded proteins. Each component of the UPR plays a crucial role in ER stress-mediated cell death (Sano & Reed, 2013).

Basile et al. (2013) showed that in human colon cancer cells, bis-hydroxy-curcumin (30 μM), a derivative of curcumin, activates ER

stress and induces cell death. The colon cancer cells HCT116 were cultured with bis-hydroxy-curcumin (30 μM) for 16 and 24 hr. The analysis has revealed that the cells treated with bis-hydroxy-curcumin, showed enlargement and extension of the ER, which indicated the activation of oxidative stress in this organelle. Moreover, those scientists have documented that bis-hydroxy-curcumin could influence the activation of caspase-4, which is able to trigger ER stress-induced apoptosis in HCT116 human colon cancer cells. In another study, Lee et al. (2009) observed that curcumin by activation of caspase-3 is capable of inducing apoptosis in human osteosarcoma cells.

Zhang et al. (2018) have shown that curcumin is responsible for the activation of the ATF6 transcription factor in human papillary thyroid carcinoma [BCPAP- (from the German Collection of Microorganisms and Cell Cultures)], and in the consequence activates the ER stress marker such as C/EBP homologous protein 10 (CHOP), referred to as a ER-associated survival or death regulator (Figure 4). CHOP plays a pro-apoptotic role and is the best-known indicator of ER-induced apoptosis. It also suppresses the expression of the anti-apoptotic Bcl-2 protein, which results in the increase of Bax/Bcl-2 ratio leading to the promotion of cellular apoptotic pathway (Rodriguez, Rojas-Rivera, & Hetz, 2011). In addition, Zhang et al. (2018) have found that curcumin induces ER stress in human papillary thyroid carcinoma. BCPAP cells were treated with different concentrations of curcumin (12.5–50 μM) for 24 hr. It has been shown that curcumin sharply decreased Ca^{2+}-ATPase activity, which contributed to a decrease of calcium ion level in ER. ER contains high concentrations of calcium ions. Stress-induced Ca^{2+} efflux is considered to be one of the crucial factors that induce apoptosis (Xu et al., 2016). Excessive accumulation of Ca^{2+} in the mitochondrial matrix causes mitochondrial swelling, changes in transmembrane mitochondrial potential and ROS production, which consequently leads to the rupture of the outer mitochondrial membrane and the release of proapoptotic proteins including cytochrome c into cytoplasm (La Rovere, Roest, Bultynck, & Parys, 2016). In summary, Zhang et al. (2018) observed that curcumin through the effect on ER-induced apoptosis of human thyroid cells (BCPAP line) by activating the ATF6-CHOP pathway and disrupting of intracellular Ca^{2+} homeostasis (Figure 4).

Similarly to the tumor suppressor protein p53, curcumin is able to induce apoptosis and cell aging. In the K562 cell line deprived of functional p53, curcumin influenced control point of the apoptosis pathway below or parallelly to p53 action. Because curcumin strongly regulated redox status, it could act as a prooxidative mediator. Larasati et al. (2018) have shown that in K562 cell line of chronic myeloid leukemia, curcumin (25–75 μM) binds to several enzymes (carbonyl reductase 1 (CBR1), glutathione-S-transferase phi 1 (GSTP1), aldo-keto reductase family 1 member 1 (AKR1C1), glyoxalase I (GLO1), NAD(P)H dehydrogenase [quinone] 1 (NQO1) (Gorrini, Harris, & Mak, 2013; Panieri & Santoro, 2016) that are involved in ROS metabolism. The curcumin inhibits the activity of these enzymes in vitro, causing an increase in cellular ROS level (Cairns, Harris, & Mak, 2011; Larasati et al., 2018). It can therefore be concluded that curcumin exhibits antitumor activity by increasing ROS level due to binding to several enzymes involved in ROS metabolic pathways.

Acute lymphoblastic leukemia (ALL) is a significant cancer of children and development of resistance to chemotherapy has been observed in this disease. Thus, new therapeutic approaches are required to improve patient's prognosis. Kuttikrishnan et al. (2019) tested a panel of B-precursor lymphoblastic leukemia (ALL) (B-Pre-

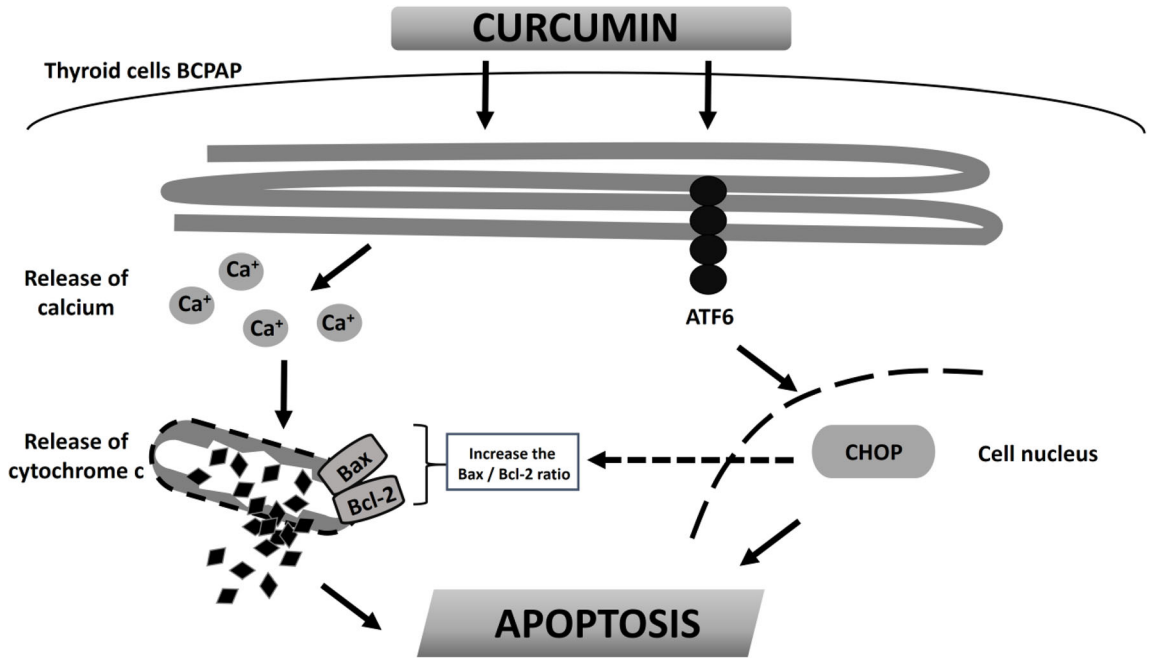

FIGURE 4 The mechanism of apoptosis induction in human papilloma cancer cells by curcumin (based on work Zhang et al., 2018)

ALL) cell lines with various translocations after treatment with different doses of curcumin. Curcumin induced apoptosis in B-Pre-ALL cell lines via ROS formation, activation of caspase-8 and truncation of BID. Moreover, curcumin treatment increased the ratio of Bax/Bcl-2 and resulted in cytochrome c release from the mitochondria into the cytoplasm, caspase 3 activation and poly (ADP-ribose) polymerase (PARP) cleavage. Furthermore, treatment with curcumin of B-Pre-ALL cell lines induced a dephosphorylation of the constitutive phosphorylated AKT/PKB (Protein Kinase B) and a down-regulation of the expression of cIAP1 (also named BIRC2; cellular inhibitor of apoptosis protein-1) and XIAP (X-linked inhibitor of apoptosis protein). It has also been shown that the suboptimal doses (0–80 μM) of curcumin enhanced the anticancer activity of synthetic drug—cisplatin. Altogether, these results have suggested an important therapeutic role of curcumin, acting as a growth suppressor of B-Pre-ALL by apoptosis via inactivation of AKT/PKB and down-regulation of IAPs as well as activation of intrinsic apoptotic pathway via ROS generation. These interesting findings raised the possibility of considering curcumin as a potential therapeutic agent for the treatment of B-Pre-ALL.

Curcumin may also be effective in treatment of multiple cancers including triple-negative breast cancer (TNBC) particularly in combination with electrical pulses (EP). Uma, Aryal, Camarillo, Raman, and Sundararajan (2020) have shown that a combination of curcumin (50 μM) and eight, 1,200 V/cm, 100 μs pulses (the most commonly used electrochemotherapy parameter in clinics) reduced the clonogenic ability in MDA-MB-231 cells, with the induction of apoptosis.

Other studies have also shown that curcumin by induction of apoptosis can kill cancer cells or infected cells, while it does not affect normal cells. Martínez-Castillo et al. (2018) revealed that curcumin (2.5–20 μM) induced caspase 9 and caspase 3-dependent apoptosis of the HL-60 cells and K562 cells, while Araveti et al. (2019) demonstrated that curcumin inhibited the proliferation of Theileria-transformed bovine leucocytes by promoting apoptosis associated with ROS formation, cytochrome c release, caspase 8 and 9 activation and PARP cleavage, having no effect on uninfected bovine cells.

2.4 | Curcumin affects cancer cells proliferation (in vitro)

Cancer cells are formed as a result of multiple mutations in genes encoding essential proteins from different signaling pathways. Modern therapy aims to effect on various mutant proteins to restore their normal functions or to reduce adverse effects (Hanahan & Weinberg, 2011). Imatinib is one of the drugs that inhibits cells proliferation through kinase inhibition (e.g., Bcr-Abl) (Kantarjian et al., 2012; Quintas-Cardama, Cortes, & Kantarjian, 2011). Imatinib is a widely used drug in the treatment of CML. However, despite of the use of imatinib as current first-line drug in CML, its treatment discontinuation results in relapse in more than 60% of patients with this cancer (Mahon et al., 2010). Therefore, new approach to the treatment of CML is recommended by the studies of other substances acting through other pathways, including those related to oxidative stress.

It has been shown that curcumin in vitro affects many pathways and factors associated with tumor cells development, and despite of a wide range of targets, it selectively induces cell death only in cancer cells (Kunwar et al., 2007; Sa & Das, 2008). However, the precise molecular functions of curcumin in tumor suppression remains to be clarified. Larasati et al. (2018) have shown in vitro that curcumin (25–75 μM) and imatinib (synthetic anticancer drug) affected the cell cycle in various CML cell lines including K562, MEG-01, MOLM-7, KCL-22. Imatinib caused cell cycle arrest in the G1 phase and then death of these cells, while treatment with curcumin increased cell population in the G2/M phase and subsequent cell death. These findings have proven that the molecular mechanisms of action of these two substances are different. In addition, cell survival (represented by the subG1 population) induced by curcumin was significantly lower than for imatinib, which indicates an additional antiproliferative mechanism associated with curcumin action. It was also observed that after imatinib removal, the cells were still able to proliferate, while after curcumin elimination, the cells lost their ability to proliferate (Larasati et al., 2018).

Li et al., (2019), Li, Qin, and Li (2019) have investigated the role of curcumin (2.5–10 μM) in regulating PI3K/AKT signaling pathway that plays an important role in tumor development. The study was conducted on human normal lung epithelial BEAS-2B cells and lung cancer A549 cells cultured in vitro. Curcumin downregulated DJ-1 levels and enhanced PTEN expression (the PTEN can negatively regulate the PTEN/AKT signaling pathway, and DJ-1 is the negative regulator of PTEN) in A549 cells in a concentration-dependent manner. Summing up, curcumin has been shown to inhibit lung cancer cells proliferation by downregulating DJ-1 to regulate the activity of PTEN/PI3K/AKT pathway.

In head and neck squamous cell carcinoma (HNSCC), curcumin affected the ATM/Chk2/p53 signaling pathway, leading to cell cycle arrest in the G2/M phase and inhibited angiogenesis both in vitro and in vivo. It has been shown that curcumin by increasing phosphorylation of H2A.X and ATM proteins, which are indicators of DNA damage (ATM plays a key role in repair of DNA damage as it is recruited in places of DNA strand breaks and undergoes autophosphorylation at Ser-1981) was capable of reducing HNSCC proliferation (Hu et al., 2017).

Recently, Chen, Zhan, Wang, You, and Yao (2020) explored the mechanistic insight into the link between curcumin (5–60 μM) and microRNA-21 (miR-21) on diffuse large B-cell lymphoma (DLBCL) and observed that that curcumin repressed the proliferation, migration and invasion abilities and induced apoptosis of SU-DHL-8 cells (DLBCL cell line). The researches have noticed that curcumin inhibited miR-21 expression, and thus exerted anti-proliferative, antimigrative, antinvasive and proapototic effects in SU-DHL-8 cells. Moreover, they have observed that Von Hippel–Lindau (VHL) mRNA was a direct target of miR-21.

3 | MODULATION OF SIGNALING PATHWAYS BY INFLUENCING OXIDATIVE STRESS AND PROTEASOME, NF-KB AND CYTOKINE ACTIVITIES

The curcumin acts by various mechanisms that play a role in tumor progression, that is, strong antioxidant activity by direct scavenging of ROS, induction of programmed cell death and inhibition of various transcription factors like NFκB.

3.1 | Inhibition of oxidative stress by modification of KEAP1-NRF2-ARE system (in vitro)

KEAP1-NRF2-ARE is an antioxidant system, which is activated by ROS (Motohashi & Yamamoto, 2004). During oxidative stress, a conformational alterations in KEAP1 proceeds, which cleave the bond between KEAP1 and factor 2 related to the nuclear factor E2 (NRF2). As a result, a phosphorylated NRF2 is released, which induces an antioxidant response (Itoh, Ye, Matsumiya, Tanji, & Ozaki, 2015; Petri, Korner, & Kiaei, 2012; Satoh, Moriguchi, Takai, Ebina, & Yamamoto, 2013). The induction of antioxidant response affects the antioxidative enzymes levels and the production of detoxification enzymes (Itoh et al., 2015; Sykiotis, Habeos, Samuelson, & Bohmann, 2011). One of these enzymes is glutamate-cysteine ligase (GCLc) (Mani et al., 2013). GCLc limits the rate of reduced glutathione (GSH) synthesis. Glutathione in its native form is a powerful antioxidant that is mainly synthesized in the liver and is the major non-protein thiol tripeptide in the body (Bukowska, 2005). The curcumin is an electrophile that binds to KEAP1 by the sulfhydryl group (–SH) leading to the modification of cysteine (Magesh, Chen, & Hu, 2012; Trujillo et al., 2014).

3.2 | Inhibition of 26S proteasome activity (in vitro)

The curcumin acts as a serine–threonine kinase inhibitor by direct inhibition of IKK (IKB kinase 2) NF-κB pathway (Bharti, Donato, Singh, & Aggarwal, 2003; Singh & Aggarwal, 1995). One of the described mechanisms of curcumin activity is the inhibition of proteasome activity (Bech-Otschir et al., 2001; Dikshit, Goswami, Mishra, Chatterjee, & Jana, 2006; Jana, Dikshit, Goswami, & Nukina, 2004). The curcumin as a proteasome inhibitor, can increase p53 level and induce apoptosis by activation of caspase 3 and 7 (Banerjee et al., 2018; Bech-Otschir et al., 2001; Jana et al., 2004). Mature 26S proteasome complex is composed of 33 different subunits that catalyze the degradation of eukaryotic proteins (Collins & Goldberg, 2017; Coux, Tanaka, & Goldberg, 1996). Proteasome activity, and its abundance in the cell are dynamically regulated during physiological and pathological processes such as cell differentiation, aging as well as neurodegenerative disorders and cancer development (Hoeller & Dikic, 2009; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013; Tai & Schuman, 2008; Vilchez et al., 2012).

The most common way of inhibiting the proteasome activity is the direct action on proteasome regulators (Li et al., 2017; Song et al., 2017). One of the regulators is the dual-specificity tyrosine-regulated kinase 2 (DYRK2). The DYRK2 deficiency, weakens proteasome activity and causes the accumulation of numerous proteins involved in various cellular processes. Cells with depleted DYRK2 exhibit slower proliferation (Guo et al., 2016).

Banerjee et al. (2018) have shown that curcumin inhibited DYRK2 of human embryonic kidney 293 (HEK293T) cells in vitro. The use of curcumin allowed to inhibit the phosphorylation of the proteasome pT25 RPT3 ATPase. In addition, the curcumin 4-hydroxy-3-methoxyphenyl group formed hydrogen bonds with amino acids like Lys251, Glu266 and Asp368 in DYRK2 that anchor curcumin in the ATP binding pocket. The crystal structure of DYRK2-curcumin shows that curcumin inhibits DYRK2 through direct binding to the ATP DYRK2 binding pocket. It is also worth noting that curcumin inhibits DYRK2 in cells even at 1–10 μM. The curcumin is also a highly specific DYRK2 inhibitor with 10 times greater potency for DYRK2 in comparison to other DYRK isoforms. It has also been noted that higher ATP level has little effect on the curcumin interaction with DYRK2, which may indicate that curcumin binds irreversible with this regulator. Impairment of proteasome activity by DYRK2 inhibition is considered to be one of the main mechanisms of potential curcumin activity in the context of treatment of proteasome-dependent cancer (Banerjee et al., 2018).

3.3 | Inhibition of NFκB activity (in vitro)

The curcumin can modulate several signal transcription pathways and acts primarily by inhibiting the activity of NF-κB, a transcription factor associated with inflammation and progression of cancer (Bachmeier et al., 2007; Bachmeier et al., 2008; Killian et al., 2012; Schwertheim et al., 2017). Killian et al. (2012) have demonstrated in vitro that curcumin in concentration 15 μM affects the expression of pro-inflammatory cytokines CXCL1 and CXCL2 in PC-3 human prostate cancer cells. Treatment of the cells with curcumin for 24 hr reduced CXCL1 and CXCL2 transcripts by 50%. In addition, the potency of curcumin was compared with the potency of the inhibitor of kinase IκB SC-514 in a process of phosphorylation inhibition to find out whether curcumin acts as a kinase inhibitor in metastatic prostate cancer cells. Stimulation of the cells with tumor necrosis factor α (TNFα) led to phosphorylation of p65 and IκBα in PC-3 cells. Cells treated for 2 hr with curcumin caused a two- and three-fold reduction of p65 and IκBα phosphorylation, respectively. Furthermore, curcumin impaired translocation of p65 into the nucleus and stopped NF-κB in the cytoplasm (Killian et al., 2012).

Inhibition of the NFκB pathway by curcumin leads to suppression of pro-inflammatory cytokine transcription and expression of pro-metastatic enzymes. Consequently, curcumin disturbs the processes associated with cancer development (Bachmeier et al., 2007; Bachmeier et al., 2008). The curcumin prevents the activation of NFκB by inhibition of phosphorylation and degradation of IκBα, which is the inhibitor of κBα. In this way, NF-κB subunit is not phosphorylated and translocates into the nucleus (Bachmeier et al., 2008; Killian et al., 2012), which leads to inhibition of the expression of genes and gene products associated with cancer. Inhibition of NF-κB leads to reduced proliferation and

growth of tumor cells and induction of apoptosis. The joint action of all effects described above, prevents cancer cells invasion and metastasis (Killian et al., 2012). Inhibition of the NFκB transcription factor is the main goal of preventing of the formation and progression of cancer (Figure 5). Li, Liu, et al. (2019) explored the molecular mechanism of curcumol and curcumin action (2.5–10 μM) in the treatment of chronic obstructive pulmonary disease (COPD). In this experiment, macrophage Raw246.7 cells were stimulated by CSE (cigarette smoke extract) and the damage model of COPD was simulated in vitro to observe potential protective effects of curcumin. They have observed that curcumin reduced ROS production by macrophages, inhibited NF-κB and TGF-β1/Smads signaling pathways and downregulated pro-inflammatory pathways. In conclusion, they have stated that curcumin exhibits anti-inflammatory effects by inhibiting of NF-κB signaling pathway.

3.4 | Regulation of the level of Treg lymphocytes in lymphoid tissue (in vivo)

In the light of recent studies, the role of Treg cells in controlling the immune response is very significant. The imbalance between the activation and suppression of these cells in the immune system, seems to be implicated in the pathogenesis of many diseases. Regulatory T-cells (Treg) play a key role in maintaining of the immune homeostasis (Jani, Chi, & Wan, 2009; Sakaguchi, Sakaguchi, Asano, Itoh, & Toda, 1995) as their insufficient amount or dysfunction leads to inflammatory diseases, autoimmune diseases or lymphoproliferative syndrome, including inflammatory bowel disease (IBD) (Sakaguchi, 2004, 2005; Shevach, 2000, 2002). The suppressive function of Treg cells is based on inhibition of inflammatory response, and thus protection of the mucosa against chronic inflammatory and cancer (Belkaid, 2007; Rouse, Sarangi, & Suvas, 2006; Zou, 2006). Treg cells maintain homeostasis and mucosal tolerance, thereby preventing and treating colitis by direct inhibition of the expression of signaling molecules such as CD40, CD154, CD134 and CD134L or reduction of dendritic cells (DCs) activation (Liu et al., 2000; Veltkamp et al., 2011). The interactions of DCs molecules and Treg cells are closely related to the pathogenesis of IBD and become targeted cells in the treatment of this disorder. Regulatory T-cells (Tregs) are identified as immunosuppressive subset of CD4+ T-cells (Wang et al., 2018). Treg cells are involved in maintaining peripheral tolerance as well as control of the immune response, initiating suppressive action on activated immune cells (Tang & Bluestone, 2008; Valencia & Lipsky, 2007). Zhao et al. (2016) conducted studies in vivo in which they induced colitis inflammation in male C57BL/6 mice (9–-12-week-old) with 2,4,6-trinitrobenzenesulfonic acid (TNBS). TNBS (100 mg/kg) was injected into the colon of male mice. Control mice received saline solution. After induction of colitis, curcumin was given intragastrically at a dose of 200 mg/kg for 7 days. Administration of TNBS caused damage to the colonic mucosa and increased colon mass. Moreover, TNBS caused damage to the mucous membrane with its ulceration and inflammation. The extent of colon mucosa damage was alleviated after administration of curcumin to tested mice. In addition, after treatment with curcumin, interleukin (IL)-17 level decreased, while the number of Treg cells increased, showing that the protective effect of curcumin against colitis is closely associated with a decrease of IL-17 expression and an increase in Treg cells level. Moreover, curcumin decreased the production of related pro-inflammatory cytokines (TNF-α, IL-2, IL-6, IL-12 p40, IL-21) and suppressed the expression of co-stimulatory molecules. Cytokines are secreted by DCs, hence the action of curcumin in colitis is closely related to the suppressive function of Treg cells and the activation of DC cells (Zhao et al., 2016).

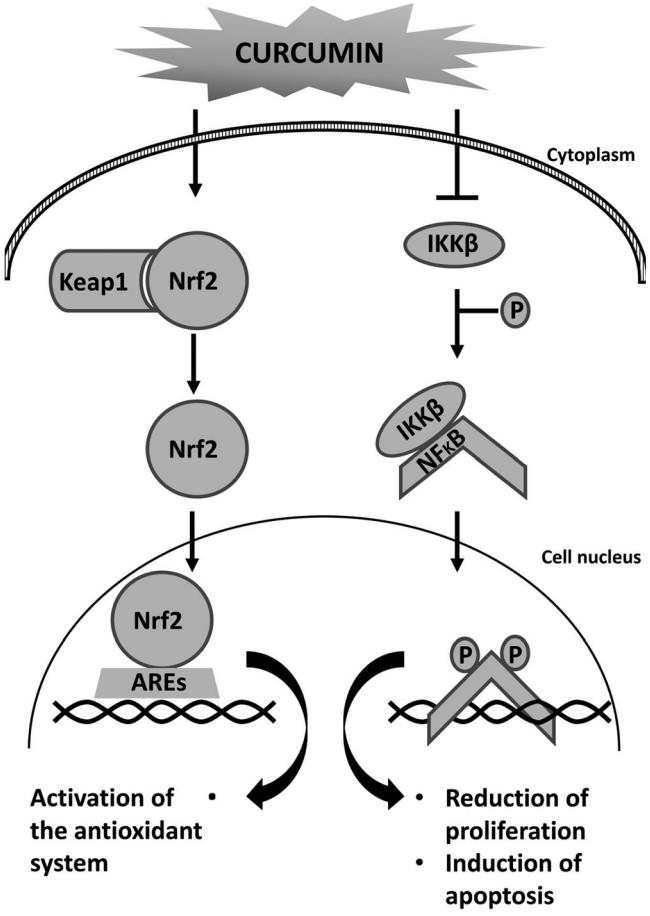

FIGURE 5 Curcumin modulating the antioxidant pathway, proliferation and apoptosis (based on work Killian et al., 2012, Bachmeier et al., 2007; Bachmeier et al., 2008)

4 | SIGNALING IN OTHER PATHOLOGICAL STATES

4.1 | Neurological protection (in vitro and in vivo)

Curcumin due to its ability to cross the blood–brain barrier (BBB), may become promising drug in neurological protection. This property gives a chance to combat oxidative stress and inflammation within neurons, the processes, which are associated with aging of the brain or/and its injuries (Polazzi & Monti, 2010). The BBB is one of the most important protective mechanisms in the central nervous system. It selectively allows individual substances, such as small lipid-soluble molecules, to

cross the capillary endothelial membrane, while limiting the transport of various pathogens or toxins.

Tsai, Chien, Lin, and Tsai (2011) have shown that curcumin and C-NPs [curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles] can pass through the BBB into the brain tissue. Anesthetized male Sprague–Dawley rats were administered with curcumin and C-NPs (25 mg/kg) by the femoral vein. The curcumin and C-NPs have been shown to pass through the BBB reaching the brain tissue, and hippocampus in particular. It has been proven that only drugs with low molecular weight and highly lipophylic can penetrate the BBB. The curcumin and PLGA nanoparticles are insoluble in water, while they have high lipid solubility. Therefore, the ability of curcumin and PLGA to cross the BBB is closely associated with their hydrophobic nature. The study of Tsai and co-workers have observed accumulation of curcumin in various regions of the brain. Half-life time ($T_{1/2}$) of curcumin in the cerebral cortex was estimated to be from 2.32 to 19.9 min and in hippocampus from 7.56 to 16.7 min.

Wu et al. (2013) have shown that curcumin has a protective effect on cortical neurons obtained from the brains of 1-day old Sprague–Dawley rats. The use of oxygen–glucose deprivation/reoxygenation (OGD/R) allowed to mimic an ischemic injury. This resulted in a rapid increase in the expression of NAD(P)H:quinone oxidoreductase 1 (NQO1) and the weakening of Akt phosphorylation. Treatment of the cells with curcumin (300 mg/kg), which was administered by intraperitoneal injection, resulted in the restoration of Akt phosphorylation and increased expression of NQO1. As a consequence, this process increased the binding activity of factor 2 associated with the nuclear factor-erythroid 2 (Nrf2) to the antioxidant response element (ARE).

Neurogenesis is negatively regulated by age, stress and lack of sleep, while it is increased by caloric restriction and physical exercise. Animal studies and clinical trials have suggested that curcumin affects neurogenesis in neurodegenerative disorders, including Alzheimer's disease (AD). Tiwari et al. (2014) investigated the effect of curcumin and PLGA nanoparticles surrounded by curcumin (Cur-PLGA-NPs) in the concentrations from 0.001 to 50 μM on neurogenesis of endogenous neural stem cells (NSCs). Cur-PLGA-NPs strongly induced NSCs proliferation and neuronal differentiation (in vitro) in the hippocampus and sub-ventricular zone of adult rats. Cur-PLGA-NPs significantly increased the expression of genes involved in cell proliferation (reelin, nestine and Pax6) and neuronal differentiation (neurogenin, neuroD1, neuregulin, neuroligin and Stat3). The curcumin-containing nanoparticles increased neuronal differentiation by activating the Wnt/β-catenin pathway involved in the regulation of neurogenesis. They also increased nuclear translocation of β-catenin and increased GSK-3β phosphorylation, leading to increased TCF/LEF and cyclin-D1 promoter activity and increased neurogenesis. Treatment with curcumin coated nanoparticles reversed also the learning and memory disorders in the rat AD model by stimulation of neurogenesis. Curcumin activated NSCs proliferation only at 0.5 μM, while curcumin-encapsulated nanoparticles significantly increased cells proliferation even from a dose of 0.001 μM. These results suggested that curcumin coated nanoparticles induce neurogenesis by stimulation of the canonical Wnt/β-catenin pathway, and thus may be taken into consideration as a therapeutic approach for the treatment of neurodegenerative diseases such as AD by strengthening of the brain repair mechanisms (Tiwari et al., 2014).

In another study, Chandra et al. (2017) studied the effect of curcumin (4 mM) in various domains of β-amyloid (Aβ) peptide. Changes in three specific region sequences of Aβ (the N-terminus, the central salt bridge, and the C-terminus) are considered to be implicated in increased toxicity of this peptide in Alzheimer's disease. It has been shown that curcumin treatment contributed to the appearance of structures similar to fibers containing salt bridges in mature Aβ40 aggregates, but not in Aβ42 aggregates. It has also been observed that curcumin interacts with intermediates of Aβ40 aggregation and changes their toxicity but it does not interact strongly with final mature product of aggregation. Summing up, curcumin has potential to be a modulator of the aggregation pathway involved in toxicity of Aβ peptide in Alzheimer's disease.

In another study, Yuan et al. (2017) have shown that curcumin (100 mg/kg) inhibited microglial activation and matrix metallopeptidase-9 expression, thereby reducing brain edema and attenuating post-subarachnoid hemorrhage (SAH) BBB disruption in mice. SAH was induced in mice via endovascular perforation, and curcumin was administered 15 min after surgery. The researches have shown that curcumin significantly improved neurologic scores and depleted brain water content in exposed mice compared with SAH mice. Moreover, curcumin decreased Evans blue extravasation, matrix metallopeptidase-9 expression and the number of Iba-1-positive microglia in exposed mice compared with SAH mice. Finally, curcumin treatment rised the expression of the tight junction proteins zonula occludens-1 and occluding in treated mice compared with SAH mice.

4.2 | Cardiological protection (in vitro and in vivo)

Cardioprotective activity of curcumin has been reported for heart disease, but the basic mechanisms have not been fully elucidated (Parada et al., 2015). Cao et al. (2018) investigated the effect of curcumin and underlying mechanism of action on chronic heart failure (CHF). The CHF rabbit model was successfully prepared by a 10-week volume overload and 8 weeks of pressure overload. The effect of curcumin in a dose of 100 mg/day/kg in capsules on cardiac function and on the structure of left ventricular (LV) has been assessed. In addition, the effect of curcumin on Dickkopf-related protein 3 (DKK-3), p38 mitogen-activated protein kinase (p38), c-Jun N-terminal kinase (JNK) and apoptosis-1 signaling kinase (ASK1) has been evaluated. It has been observed that 10-week treatment of rabbits with curcumin improved heart efficiency. Pathological changes of the heart such as cardiac hypertrophy, fibrosis, apoptosis and ultrastructure disorganization were alleviated by administration of curcumin to these animals with CHF. Moreover, curcumin upregulated expression of DKK-3 leading to inhibition of p38 and JNK signaling pathways, which may be a potential mechanism by which curcumin exerts a protective effect on the heart.

The curcumin can also be used in neutralization of substances exhibiting cardiotoxic potential. Naserzadeh et al. (2018) examined the protective role of curcumin (10 μM) on cardiotoxic action of *Hemiscorpius lepturus* venom in rats, using isolated cardiac mitochondria and cardiomyocytes. The venom caused an increase in ROS formation in mitochondria of heart tissue. The venom also depleted ATP level and induced a reduction in transmembrane mitochondrial potential (MMP) and mitochondrial edema, responsible for apoptosis showing devastating effect on the mitochondrial respiratory chain. Administration of curcumin effectively reduced venome-induced cytotoxicity, ROS formation, mitochondrial swelling and rupture of the mitochondrial outer membrane of the cells of rat heart. One of the possible mechanisms of curcumin action is scavenging free radicals, and thus acting as an antioxidant, which may explain the usefulness of curcumin in alleviating of cardiotoxicity induced by *H. lepturus* venom (Naserzadeh et al., 2018).

4.3 | Protection against hepatotoxicity and spleen toxicity (in vivo)

Abd-Allah, Alahmadi, Waly, and Alahmadi (2020) conducted the study to verify the protective effects of curcumin against toxicant—carbon tetrachloride (CCl_4), which is known to stimulate liver and spleen injury. Curcumin (200 mg/kg) was given (3 times/weekly) intragastrically to mice and the experiment was continued for 8 weeks. It has been shown that curcumin supplementation of CCl_4 treated group decreased expression of inflammatory markers such as TNF-α, IL-1 IL-6 and COX-2 and improved antioxidant status measured by catalase (CAT), superoxie dismutase (SOD) and glutathione peroxidase (GPx) activities and reduced glutathione (GSH) content. Moreover, mice co-administrated with curcumin had improved histoarchitecture of liver and spleen. The researchers suggested that curcumin protected the liver and spleen from acute CCl_4 induced injury in a rodent model by suppressing hepatic and splenic oxidative stress expression levels of inflammatory markers, and thus it may be recognized as a potential therapeutic antioxidant agent against acute hepatotoxicity and spleen toxicity.

4.4 | Antiviral and antiparasitic potency of curcumin (in vitro and in vivo)

The EV71 is a single-stranded RNA virus from the *Picornaviridae* family. It is known to be highly infectious, susceptible to mutations and capable of causing serious diseases. There are currently no effective drugs or available vaccines against EV71 infection. (Shimizu et al., 2004).

This virus replicates in the digestive tract and then spreads to other organs or tissues. It has been shown that several phytochemicals including curcumin may act against EV71 infection (Li et al., 2015; Tsai et al., 2011; Wang et al., 2016; Zhang et al., 2014). EV71 infection induces phosphorylation of Y311 PKCδ (protein kinase C delta), the process, which is reduced in curcumin-treated cells. Biological functions of PKCδ are regulated by phosphorylation of specific sites of serine and threonine (Shirai & Saito, 2002). Phosphorylation of Y311 leads to conformational changes, and thus reduction of the expression of total PKCδ or PKCδ-pY311, and consequently to inhibition of the expression of the viral protein (Rybin, Guo, Gertsberg, Elouardighi, & Steinberg, 2007). The curcumin exhibits anti-EV71 activity in intestinal epithelial cells. The curcumin activity has been tested by Huang, Chio, and Lin (2018) in the study on C2BBe1 cells derived from Caco-2 human colon carcinoma cells. The C2BBe1 cells were infected with EV71, and then treated with curcumin. They observed that curcumin reduced viral proteins expression. In addition, curcumin could act as a PKCδ inhibitor by reducing the phosphorylation of a specific tyrosine residues. Gene knockout cells responsible for the expression of PKCδ were characterized by a decrease in the expression of the viral protein. This showed the participation of PKCδ in EV71 infection. The expression levels of phosphorylated PKCδ was also tested in human intestinal epithelial cells line HT29 infected with EV71. It has been found that PKCδ phosphorylation was reduced in infected curcumin-treated cells. Dysregulation of PKCδ inhibits the replication of EV71, and thus, the ability of curcumin to inhibit PKCδ activation may contribute to its anti-EV71 activity (Huang et al., 2018).

Dende et al. (2017) showed that curcumin and PLGA-curcumin exhibited better therapeutic effect than curcumin in preventing the onset of neurological symptoms and delaying the death of mice in experimental cerebral malaria. PLGA-curcumin orally administrated was as effective as native curcumin at a 15-fold lower concentration in preventing the breakdown of BBB and inhibition of brain mRNAs for inflammatory cytokines, chemokine receptor CXCR3 and its ligand

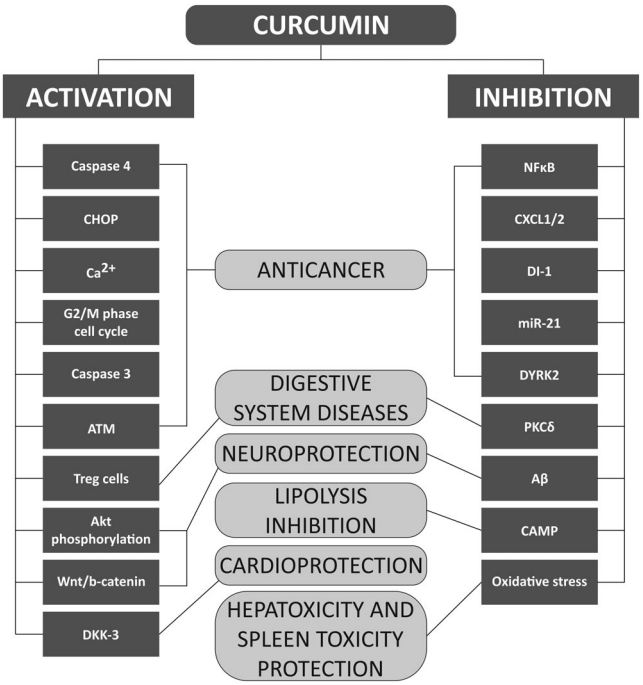

FIGURE 6 Selected molecular and cellular targets of curcumin and its pro-health activity

CXCL10, with an increase in the anti-inflammatory cytokine IL-10. This effect was also shown in serum cytokine and chemokine levels. At equivalent concentrations, a single oral dose of PLGA-curcumin was more effective in decreasing of serum IFNγ levels and increasing of IL-10 levels in comparison to curcumin. It has also been shown that PLGA-curcumin was more effective than native curcumin in inhibiting the sequestration of parasitized-RBCs and CD8+T cells in the brain. Interestingly, a single oral dose of 5 mg PLGA-curcumin (containing 350 μg of curcumin) resulted in 3–4 fold higher concentration and prolonged presence of curcumin in the brain than that achieved with 5 mg of native curcumin, showing better bioavailability of PLGA-curcumin. The researchers concluded that PLGA-curcumin has potential as an adjunct drug to treat human cerebral malaria.

5 | CONCLUSIONS

In this review, beneficial action of curcumin against various processes underlying various diseases development has been presented. It can be concluded that curcumin may play a role in the protection of various disorders mainly through anti-inflammatory and antioxidant action. Curcumin has potential to be used in cancer as well as neurological, cardiovascular and gastrointestinal diseases treatment. Similarly, several specific mechanisms of curcumin action have been taken into consideration to understand its beneficial effects and its role as the nutraceutical substance. The curcumin has anticancer activity through the effects on caspase-3 and -4 activities, CHOP, intracellular calcium ion and ATM levels and cell cycle arrest in G2/M phase. The curcumin also protects the nervous system through the effect on the phosphorylation of Akt, Wnt/β catenin and Aβ peptide and it is active against gastrointestinal diseases through the effect on Treg cells and PKCδ. Finally, the curcumin supports cardioprotection through the effect on DKK-3, and it is involved in the inhibition of lipolysis through the effect on cAMP (Figure 6).

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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How to cite this article: Liczbiński P, Michałowicz J, Bukowska B. Molecular mechanism of curcumin action in signaling pathways: Review of the latest research. *Phytotherapy Research*. 2020;1–14. https://doi.org/10.1002/ptr.6663