Curcumin Cell Signaling: A Possible Target for Chemotherapy

Shahanas Chathoth, Faisal Thayyullathil and Sehamuddin Galadari*

Cell Signaling Laboratory, Department of Biochemistry, Faculty of Medicine and Health Sciences,
UAE University P.O. Box 17666, Al Ain, UAE
* For Correspondence - sehamuddin@uaeu.ac.ae

Abstract
Many components that are derived from medicinal or dietary plants, known as phytochemicals, posses chemopreventive properties. Curcumin, the active chemical of the spice turmeric, exhibits anticancer activity in several cancer cell lines. Nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1) play a critical role in the transcriptional regulation of genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance and inflammation. A number of studies have shown that curcumin exerts its anti-cancer effects through the suppression of activation of NF-κB and AP-1, and lead to the down-regulation of its target gene products COX-2, cyclin D1, Bcl-2, Bcl-xL, cIAP1, XIAP and survivin. On the other hand, Curcumin also is shown to induce cancer cell growth arrest and apoptosis in several cell models. Curcumin treatment up-regulates the expression of proteins involved in apoptosis and exhibits common apoptotic features like altered expression of Bcl-2 family of proteins, imbalanced mitochondrial trans-membrane permeability (∆ψm), release of cytochrome c, Smac, and AIF from mitochondria. These effects induce apoptosis via caspase-dependent and independent pathways. There are conflicting reports as to the role of curcumin in redox balance. It has been shown to act as potent scavenger of reactive oxygen species (ROS), and at the same time it induces free radical generation and significant cell death through apoptosis in other cancer cell models. Both in vivo and in vitro studies have shown that curcumin inhibit some of the enzyme activities which have important role in cell regulation. Curcumin acts as a potent inhibitor of Phosphorylase kinase (PhK), and Phospholipase D (PLD) under in vitro conditions. In vivo studies have shown that curcumin inhibits LPS induced expression of inducible nitric oxide synthase (iNOS), and also acts as a novel inhibitor of class I histone deacetylase (class I HDACs) such as HDAC1, HDAC3, and HDAC8. Apart from these, it has been shown that curcumin induces apoptosis of cancer cells through the generation of the sphingolipid metabolite ceramide. This review attempts to summarize curcumin cell signaling pathways responsible for cell growth arrest or apoptosis.

Key words
Chemoprevention, curcumin, NF-κB, apoptosis, ROS, ceramide.

Introduction
Cancer cells are characterized by loss of growth control, invasiveness, and metastasis. This can be caused by physical, chemical, and biological agents called carcinogens. Carcinogens damage or alter the DNA and lead to the transformation of genes controlling cell proliferation, differentiation, and apoptosis. In normal tissue the rate of normal cell growth and death are kept in balance. In cancer this balance is disrupted leading to either cellular overgrowth and/or lack of apoptosis of damaged cells that later become malignant. Apoptosis or programmed cell death is the mechanism by which old or damaged cells normally self...
destruct, so induction of apoptosis can be considered as a promising approach towards cancer therapy. Indeed, some chemotherapy relies on apoptosis of tumor cells.

Chemotherapy, one of the methods used in cancer treatment, refers to the approach of treating cancer cells with anticancer drugs that can destroy cancer cells and stop uncontrolled cell growth. Research over the last decade has shown that phytochemicals, chemical agents obtained from some fruits and vegetables, exert their inhibitory effects on carcinogenesis and tumor progression. Extensive research in the last few years have demonstrated that some dietary components such as curcumin, capsaicin, 6-gingerol, and ajoene (phytochemicals), which are present in common spices, have inhibitory effect on human cancers. This suggests that these phytochemicals may serve as chemotherapeutic agents. In vitro and in vivo experimental studies indicate that these phytochemicals interfere with several cell signaling pathways and lead to apoptosis and cell cycle arrest. A population based study of cancer incidence showed a lower percentage of cancer victims in South East Asian countries as they consume large amounts of these phytochemicals through their diet (1). Since these phytochemicals are consumed in daily life as dietary components, they have received much attention among the public and the medical community. Furthermore, as these agents are obtained from natural sources, and have been consumed by people for centuries, they can be considered as “safe” chemotherapeutic agents.

Phytochemicals have been shown to inhibit cancer cell growth through the modulation of genes that are related to the control of cell proliferation, cell cycle, apoptosis, signal transduction, oncogenesis and transcription (2-5). Curcumin, or diferuloyl methane (Figure.1), is one of the major components of Curcuma longa L. (Zingibraceae) and it is used commonly as a spice. It has gotten much attention by virtue of its great variety of pharmacological activities. Curcumin exhibits major biological effects such as having anti-inflammatory, antioxidant, and anti-venom activities. Table 1 summarizes some of the biological effects of curcumin. Importantly, curcumin has been shown to exhibit anti-tumor activities. Several studies support curcumin as a chemotherapeutic agent as it induces cell growth arrest and apoptosis (6-8).

Involvement of curcumin in the down-regulation of anti-apoptotic proteins

Curcumin down-regulates the expression of genes involved in cell growth by inhibiting the activation of transcription factors involved in cell proliferation and survival. It has been shown that the activation of nuclear factor-kappa B (NF-êB), an inducible transcription factor, is critical to the establishment of cancer. Inactive NF-êB in the cytoplasm is a heterotrimer composed of three subunits p50 (NF-êB1), p65 (RelA) and inhibitor êB (IêBá). Upon stimulation, IêBá is phosphorylated by IêB kinase complex (IKK), followed by ubiquitination-dependent degradation of IêBá, leading to nuclear translocation, and binding of NF-êB to a specific DNA sequence. This results in transcription of multiple êB-dependent genes, including TNF-á, IL-6, IL-8 and other chemokines, MHC class II, ICAM-1, inducible nitric oxide synthase (iNOS), Cox-2, as well as, apoptosis suppressing proteins such as Bcl-2 and Bcl-xL which inturn induce cellular transformation, proliferation, differentiation, growth and inflammation.


Table 1. Molecular targets and consequent biological effects of curcumin treatment in different cell model

<table>
<thead>
<tr>
<th>Cell model</th>
<th>Molecular Targets</th>
<th>Biological effects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantle cell lymphoma (MCL)</td>
<td>↓Akt, ↑IKK, ↑IkBα, ↑NF-κB, ↓Cyclin D1, ↓Bcl-2, ↓Bcl-xL, ↓COX-2, ↓cIAP1, ↓xIAP, ↓survivin</td>
<td>G1/S phase cell cycle arrest and Apoptosis</td>
<td>(16)</td>
</tr>
<tr>
<td>Human umbilical vein epithelial cells (ECV304)</td>
<td>↑CDK1, ↑p21^WAF1/CIP1, ↑p27^KIP1, ↑p53, ↓Cyclin B1, ↓cdc2</td>
<td>G0/G1 and G2/M phase cell cycle arrest</td>
<td>(55)</td>
</tr>
<tr>
<td>Ehrlich’s ascites carcinoma (EAS)</td>
<td>↑Bax, ↑cytochrome c, ↑caspase-3</td>
<td>Apoptosis</td>
<td>(56)</td>
</tr>
<tr>
<td>Promyelocytic leukemia cells (HL-60)</td>
<td>↑Bcl-2, ↑ROS</td>
<td>Apoptosis</td>
<td>(57)</td>
</tr>
<tr>
<td>Human myelomonoblastic leukemia cells (ML-1a)</td>
<td>↓NF-κB, ↓AP-1</td>
<td>TNF-α, phorbol ester and hydrogen peroxide mediated activation</td>
<td>(13)</td>
</tr>
<tr>
<td>Human breast cancer cells (MCF-7)</td>
<td>↑p53, ↑Bax</td>
<td>Apoptosis</td>
<td>(29)</td>
</tr>
<tr>
<td>Immature B cell lymphoma (BKS-2)</td>
<td>↓egr-1, ↓c-myc, ↓Bcl-xL, ↓NF-κB</td>
<td>Growth arrest and apoptosis</td>
<td>(2)</td>
</tr>
<tr>
<td>Human lung cancer cells (A549 &amp; H1299)</td>
<td>↑p53, ↑Bcl-2, ↑Bcl-xL, ↑PARP cleavage</td>
<td>Apoptosis</td>
<td>(32)</td>
</tr>
<tr>
<td>Human T-cell lines (CEM, HSB2, Jurkat &amp; Molt-4)</td>
<td>↓Akt, ↓GSKβ, ↓cIAP1, ↓xIAP, ↓survivin, ↓cytochrome c, ↓caspase-3, ↓PARP cleavage</td>
<td>Apoptosis</td>
<td>(32)</td>
</tr>
<tr>
<td>Human colon carcinoma cells (HCT116)</td>
<td>↑Ceramide, ↑ROS, ↑JNK</td>
<td>Apoptosis</td>
<td>(54)</td>
</tr>
</tbody>
</table>
The inhibitory activity of curcumin is not only restricted to the NF-κB pathway, but also, it inhibits the pathway of activator protein-1 (AP-1), another important transcription factor involved in cell proliferation and survival. AP-1 consists of a homodimer of c-Jun, or a heterodimer of c-Jun/c-Fos family members. Like NF-κB, AP-1 regulates the expression of several genes that are involved in cell differentiation and proliferation. Phosphorylation of c-Jun by c-Jun N-terminal kinases (JNKs; also named stress activated protein kinases, SAPKs) is important for c-Jun transcriptional activity. These kinases (JNK1, JNK2, and JNK3) are members of the mitogen activated protein kinase (MAPK) family that is involved in cellular responses to mitogen stimulation, environmental stress, proinflammatory cytokines, and apoptotic stimuli. Besides c-Jun, the JNK pathway also activates the transcription factors ATF-2 (9), Elk-1 (10), and Sap-1a (11), and interacts with the NF-κB pathway (12). Curcumin also has been shown to inhibit JNK activation. Several studies have shown that curcumin inhibits the activation of NF-κB and Ap-1, and down-regulates the expression of their target gene products, finally leading to cell cycle arrest, suppression of proliferation, and induction of apoptosis. These biological effects are summarized in Figure 2.

**Inhibition of NF-κB activation upon curcumin treatment**

The three NF-κB stimuli; TNF-α, Phorbol ester, and Hydrogen peroxide, could not activate NF-κB when a human myelomonoblastic leukemia cell, ML-1a, was pre-treated with curcumin. Curcumin treatment totally suppressed TNF-α induced NF-κB activation, even after treating the cells with reducing agents like dithiothreitol (DTT) or 2,3-dimercaptopropanol (DMP). These reducing agents have been shown to reverse the inhibitory effect of L-1-tosylamido-2-phenylethyl chloromethyl ketone (TPCK) and phenylarsineoxide on NF-κB activation (13). The effect of curcumin regulation of the IκB/NF-κB pathway in nontransformed intestinal epithelial cell line IEC-6, human HT-29 colonic epithelial cells, and Caco-2 epithelial cells, have been examined by inducing cells with IL-1α. In these studies, it was shown that curcumin downregulates IL-1α-mediated ICAM-1 and IL-8 gene expression by inhibiting NF-κB activation, through blocking an upstream signal leading to NIK (NF-κB inducing kinase) activity, that phosphorylates and activates IκB kinase complex (14). The critical anti-apoptotic role of NF-κB in curcumin induced cell regulation is strongly supported by a study conducted with a relA gene, encoding the p65 (RelA) subunit of NF-κB, in transfected L-929 (mouse fibrosarcoma) cells. The transfected cells showed significant resistivity to curcumin induced apoptosis when compared to the parent cell line. On the other hand, resistivity of the transfected cells was totally demolished by co-transfection with a super-repressor form of IκB-α, which is known to inhibit NF-κB (15).
Mantle cell lymphoma (MCL) cell line JeKo-1, Mino, SP-53, and Granta 519 have been used in studying the effect of curcumin in down-regulation of cyclin D1 expression, as these MCL cells are characterized by overexpression of cyclin D1. Upon curcumin treatment, NF-κB is inactivated through the inactivation of IκB kinase (IKK) by inhibiting Akt activation. As a consequence, curcumin treatment attenuated the expression of NF-κB regulated genes such as IκBα, cyclin D1, Bcl-2, Bcl-xL and Cox-2. Curcumin treatment also down-regulated the expression of NF-κB targeted tumor cell survival genes cIAP1, XIAP, TRAF1 and survivin leading to G1/S arrest, suppression of proliferation, and finally apoptosis (16). A study conducted on the effect of curcumin on immature B cell lymphoma cell line (BKS-2) demonstrated curcumin induced apoptosis through repression of NF-κB binding activity, and down-regulation of the survival genes egr-1, which has been shown to be essential for the growth of B lymphoma cells (17), c-myc, Bcl-xL as well as tumor suppressor gene p53 (2). Ku70, a subunit of Ku protein complex, plays a major role in keeping Bax protein in an inactive conformation during apoptosis (18). Overexpression of Ku70 and Bcl-xL proteins in human colon cancer cell line (SW480) inhibited curcumin induced apoptosis. This inhibition is achieved through blocking the release of cytochrome c, apoptosis inducing factor (AIF), and second mitochondria derived factor of caspase (Smac) from mitochondria, therefore, inactivating caspase cascade. This study supported the role that Ku70 plays in the retention of Bax in the cytosol (19).

Inhibition of AP-1 and JNK activation upon curcumin treatment

Activator protein-1 has a central role in controlling the eukaryotic gene expression. Activation of c-Jun/AP-1 plays an important role in signal transduction of phorbol 12-myristate 13-acetate (PMA) induced tumor promotion. It has been reported that curcumin can suppress the PMA induced activation of c-Jun/AP-1 in mouse fibroblast cells NIH 3T3 (20). The transcriptional activity of c-Jun is dependent on JNK activation, and is essential for its gene expression (21). Thus, inhibition of JNK by curcumin would result in inhibition of c-Jun activation, and transcription of the c-Jun gene. In support of the inhibitory action of curcumin on c-Jun/AP-1 activation, curcumin completely blocks JNK activation by various agents such as PMA, ionomycin, α-radiation, UV-C, TNF-α, and sodium orthovanadate in Jurkat cells (22). Suppression of NF-κB and AP-1 activation upon curcumin treatment is well demonstrated in human promyelocytic leukemia (HL-60) cells (23). Phorbol ester induced activation of NF-κB, AP-1 and its DNA binding to its response elements was completely interrupted by curcumin pretreatment. Sustained JNK activity, is found to be pro-apoptotic, whereas, rapid transient JNK activation could be anti-apoptotic (24-26). Unlike the inhibitory effect of curcumin on JNK activation, curcumin induced apoptosis in the human colon cancer cell line HCT116 is accompanied by sustained phosphorylation and activation of JNK and p38 MAPK. Curcumin treatment inhibited NF-κB transcriptional activity, but it showed a significant increase in AP-1 transcriptional activity (27).

Involvement of curcumin in up-regulation of pro-apoptotic agents

Curcumin is shown to induce apoptosis in several cancer cell lines through the downregulation of the expression of anti-apoptotic proteins. However, curcumin treatment upregulates the expression of proteins involved in apoptosis and exhibits common apoptotic features like altered expression of Bcl-2 family of proteins, imbalanced mitochondrial transmembrane permeability (ΔΨm), release of cytochrome c, Smac, and AIF from mitochondria which in turn induce apoptosis via caspase-dependent and independent pathways (Figure 3).
Curcumin also facilitates the rapid generation of ROS that leads to cell death in several cancer cell lines.

**Figure 3.** Schematic representation of curcumin induced apoptotic signaling pathways. Curcumin induces apoptosis through ROS generation, cytochrome c release, activation of caspase cascade, PARP cleavage and DNA fragmentation. Curcumin induces rapid generation of ceramide which also leads to apoptosis. The dotted arrows indicate not well-established pathways.

**Involvement of p53 and caspase cascade in curcumin induced apoptosis**

The inhibitory action of curcumin on colon adenocarcinoma was has been proven by treating the human HT-29 colon adenocarcinoma cell line with curcumin. These undergo apoptosis by activating p53 through phosphorylation at Ser15 residue, and by decreased expression of the anti-apoptotic protein Bcl-2, increased expression of pro-apoptotic protein Bax, and increased caspase-3 and caspase-9 activation (28). Similarly, curcumin induced apoptosis in the human breast cancer cell line MCF-7 by potentiating p53 DNA binding activity which induces Bax expression (29). Another interesting result was obtained when MCF-7 cells and normal mammary epithelial cells (NME) were treated with curcumin. In this case curcumin induced apoptosis at G2 phase of MCF-7 cells, while it blocked NME cell cycle progression without apoptosis. Curcumin induces apoptosis in carcinoma cells through increased expression of p21 Waf-1, a cell cycle inhibitory protein, p53, and cytochrome c release (30). Curcumin has been shown to arrest cell cycle progression, and induce apoptosis in vascular smooth muscle cell line A7r5 through reduced expression of c-myc, and Bcl-2, without altering p53 expression level (31). Curcumin posses chemopreventive potentials against a panel of acute lymphoblastic leukemia cells (T-ALL) including CEM, HSB2, Jurkat and Molt-4 cells by inducing apoptosis. It has been demonstrated that curcumin suppresses targets of PI3'-kinase i.e. Akt, FOXO, and GSK3â, and it induces caspase-dependent apoptosis through cytochrome c release, activation of caspase-3 and PARP cleavage. At the same time, curcumin down regulates the expression of survival proteins such as cIAP, xIAP and survivin (32). Curcumin treatment effectively suppressed the AK-5 (a rat histiocytic tumor) development in an in vivo study. In vitro study with single AK-5 tumor cell BC-8 exhibited apoptosis through ROS generation, caspase-3 activation, but not caspase-1, PARP cleavage, and DNA fragmentation (8). It has been reported that p53 is not necessary for intercellular induction of apoptosis (33), and the relationship between p53 and c-myc in the process of apoptosis is still controversial (34,35). Curcumin has been reported to induce apoptosis in p53 proficient A549 and p53 deficient H1299 human lung cancer cell lines. In both cell lines curcumin induces apoptosis by up-regulation of c-myc, and down regulation of anti-apoptotic genes BclXL and Bcl-2. This result suggests a multiple p53 independent pathways in lung cancer cells where c-myc is possibly playing a major role (36).
Involvement of reactive oxygen species in curcumin induced apoptosis

Several studies have shown that curcumin acts as an anti-oxidant, and as a potent scavenger of free radicals, thereby, usually being considered as protecting cells from oxidative stress. Curcumin acts as a potent scavenger of a variety of reactive oxygen species (ROS) including superoxide anion (37), hydroxyl radical, singlet oxygen (38), and nitric oxide radicals (39). On the other hand, curcumin has been shown to induce free radical generation and significant cell death through apoptosis under certain experimental conditions. There are conflicting reports as to the role of curcumin in redox balance. An investigation aimed at finding out the role of curcumin as an antioxidant against the oxidative stress damage induced by H2O2 on the neuronal cell NG108-15 leads to a contradictory result. Co-treatment of curcumin with H2O2 increased cell viability of NG108-15 cells, but when curcumin was pretreated, not only curcumin was unable to inhibit H2O2 induced cell death, it actually significantly decreased cell viability (40). The role of ROS generation in curcumin induced apoptosis or necrosis is well studied using the human osteoblast cell line HFOb1.19. Low concentration of curcumin treatment leads to increased ROS generation, JNK activation, loss of ΔΨm, caspase-3 activation, PARP cleavage and finally to apoptosis. Whereas, high dose treatment led to less ROS generation, loss of ΔΨm and necrosis, while, JNK and caspase-3 had no effect. Moreover, intracellular ATP levels, important mediators capable of switching the mode of cell death from apoptosis to necrosis (41), play a major role in switching the mechanism of cell death from apoptosis to necrosis (42). Apart from these, several studies have reported that curcumin induces apoptosis through ROS generation (43,44).

Inhibition of enzymatic activity by curcumin

Being an antioxidant, anti-inflammatory and anti-carcinogenic agent, curcumin has been shown to inhibit some enzyme activities that have important roles in cell regulation. Some of the in vitro experimental studies have shown that curcumin directly acts as a potent inhibitor of certain enzymes. It has been reported that curcumin inhibits the activity of different protein kinases such as protein kinase A (PKA), protein kinase C (PKC), cytosolic protamine kinase (cPK), phosphorylase kinase (PhK), autophosphorylation-activated protein kinase (AK), and pp60⁶⁰⁵ tyrosine kinase. Among these kinases, curcumin acted as a selective and potent inhibitor of PhK (45). The effect of curcumin has been tested on the enzyme activities of phospholipases such as ARF/GTPαS-dependent phospholipase D (PLD), phosphatidylinositol specific phospholipase C, phosphatidylcholine-phospholipase C, phospholipase A2 and sphingomyelinase in a cell free system. Curcumin inhibited enzyme activities of all phospholipases except sphingomyelinase. Amongst these, PLD was effectively inhibited at lower concentration of curcumin, which was further confirmed in intact mouse macrophage J774.1 cell model by inducing the cells with TPA (46).

Apart from its in vitro inhibitory action, curcumin has been shown to inhibit some of the enzyme activities in vivo by interfering with their gene expression level. Curcumin inhibited P18⁵ autophosphorylation and transphosphorylation by inhibiting P18⁵ tyrosine kinase, a potent oncoprotein that is overexpressed in breast cancers, under in vitro condition and completely depleted the protein in vivo and suppressed the growth of breast cancer cell line AU-565 (47). An inhibitory effect of curcumin on nitric oxide synthase (NOS) was observed when murine macrophage RAW 264.7 cells were treated with curcumin and its hydrogenated metabolites tetrahydrocurcumin,
hexahydrocurcumin, and octahydrocurcumin. Lipopolysaccharide (LPS) has been shown to induce the expression of iNOS by the activation NF-κB (48). Only curcumin completely suppressed the expression of iNOS mRNA level when macrophages were induced with LPS (49). Apart from these, curcumin has been shown to act as a novel inhibitor of class I histone deacetylase (class I HDACs) such as HDAC1, HDAC3, and HDAC8. Evidence suggests that a family of histone deacetylases may exist in order to regulate diverse cellular functions, including chromatin structure, gene expression, cell cycle progression, and oncogenesis (50). A curcumin induction study conducted on the Burkitt lymphoma cell line Raji, has shown that curcumin induced apoptosis by inhibiting the histone deacetylase enzymes HDAC1, HDAC3 and HDAC8 and up-regulating the expression of Ac-histone H4 (51). Telomerase, a reverse transcriptase enzyme highly expressed in tumor cells, activity was suppressed by curcumin and induced apoptosis in human chronic myelogenic leukemia (K-562) cells. The mode of curcumin inhibition of the enzyme activity was due to the suppression of translocation of telomerase reverse transcriptase (TERT) from cytosol to nucleus (52).

**Curcumin induces sphingolipid mediated cell signaling**

Sphingolipids have recently emerged as important bioactive molecules in cell regulation. They have important biological roles in cell stress responses, cell growth, apoptosis, angiogenesis, differentiation, and senescence. The sphingolipid metabolites ceramide, sphingosine, and sphingosine-1-phosphate have been shown to take an important part in the regulation of cell function. Intracellular ceramide and sphingosine levels are associated with growth arrest and apoptosis, whereas, sphingosine-1-phosphate is associated with suppression of apoptosis. *In vitro* studies of many stimuli such as heat, UV, α-radiation, TNF-α, and chemotherapeutic agents cause ceramide accumulation before committing to apoptosis. Ceramide is cleaved to sphingosine and free fatty acid by ceramidase enzymes, sphingosine is further metabolized by phosphorylation to sphingosine-1-phosphate by sphingosine kinase. Ceramidases are emerging as a key enzyme activity, as they play an important role in the regulation of the levels of ceramide, sphingosine, and sphingosine-1-phosphate and consequently these sphingolipid metabolite mediated biology.

Ceramide is generated via two main pathways; the *de novo* pathway, through the condensation of serine and palmitoyl CoA, and sphingomyelinase pathway, through the cleavage of sphingomyelin to ceramide and phosphatydilcholine. Capsaicin, another well studied phytochemical obtained from red chili pepper, induces apoptosis through ceramide generation via sphingomyelin hydrolysis (53). Recently, it has been demonstrated that curcumin treatment leads to significant generation of ceramide through the *de novo* pathway and apoptosis in the colon cancer cell line HCT116. When these cells are pre-treated with myriosin, a specific inhibitor of the *de novo* pathway, it attenuated curcumin induced ceramide generation, and markedly reduced cell death (54). The above mentioned evidence are indicative of possible roles for important sphingolipid metabolites in curcumin mediated cell death. Its mechanism of action remains incompletely understood and further investigations are needed to understand the biological role of sphingolipids in curcumin mediated cell death.

**Conclusion**

Our review attempts to appraise the molecular mechanisms of phytochemical action on cells. Most of the phytochemicals have been shown to induce cell growth arrest or apoptosis and thereby they act as chemopreventive agents.
Among these curcumin holds its prime position as it has been well studied and shown to induce cell growth arrest or apoptosis in a variety of malignant cell lines. Curcumin can be considered as a chemopreventive agent that can be developed as an anti-cancer drug. Complete removal of cancer without damage to the rest of the body is the goal of chemotherapy. The effectiveness of chemotherapy by using chemical drugs is often limited by cytotoxicity to the other tissues in the body. However, being consumed as dietary supplements for many centuries, curcumin can be considered as the safest chemical agent for chemotherapy. More biological and clinical investigations are needed to establish this phytochemical as an anti-cancer drug.

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References


