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Curcumin and its Allied Analogues: Epigenetic and Health Perspectives – a Review

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Abstract

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Curcumin (diferuoyl methane) is a yellow active ingredient present in turmeric. It is a homodimer of feruloylmethane that comprises a hydroxyl and methoxy group (heptadiene with two Michael acceptors), and α-, β-diketone. It contains various metabolites, i.e. hexahydrocurcumin (HHC), tetrahydrocurcumin (THC), octahydrocurcumin (OHC), dihydrocurcumin (DHC), curcumin sulphate, and curcumin glucuronide. Curcumin has been proven the most effective histone deacetylase (HDAC) inhibitor in HeLa nuclear extracts. It has the ability to affect the Akt, growth factors, NF-kB, and metastatic and angiogenic pathways. Curcumin has a strong therapeutic or preventive potential against several major human ailments, i.e. suppression of inflammation, cardiovascular, diabetes, tumorigenesis, chronic fatigue, antidepressant and neurological activities, depression, loss of muscle and bone, and neuropathic pain. In future, higher utilisation of curcumin as an active agent in food based products is required to curtail the human health disorders.

Keywords: turmeric; chemistry and metabolism; epigenetic role; anticancer; low toxicity

Brief overview

Turmeric has been mentioned by Marco Polo during his visit to China and India in 1208. Turmeric was introduced into Europe in the 13th century by Arab traders. During the 15th century, Vasco de Gama brought the turmeric to the subcontinent during the rule of British (Chattopadhyay *et al.* 2004). Turmeric is native to Southeast Asia countries and is obtained from the *Curcuma longa* roots whilst

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turmeric root is frequently used as food. For 4000 years, turmeric has been used to curtail various maladies in Chinese as well as in Indian Ayurvedic and Arabic medicines (Anand *et al.* 2007). It is composed of bioactive components such as curcumin and curcuminoids. Firstly, curcumin was isolated in 1815 from turmeric, whereas its chemistry was determined by Roughley and Whiting in 1973 (Aggarwal & Sung 2009). Curcumin is known as international food additive E100 and it is used to colour margarines and mayonnaise-based products. It is composed of natural analogue at 77%, followed by bis-demethoxycurcumin (3%), and demethoxycurcumin (17%). One methoxy group is absent in demethoxycurcumin, whereas methoxy group is not present on either side of the aryl rings of bis-demethoxycurcumin (Sandur *et al.* 2007).

Curcumin analogues and metabolite

Turmeric is composed of diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin analogues. Among these analogues, diferuloylmethane and bisdemethoxycurcumin show higher antioxidant activity than curcumin in some cases. Turmeric root contains approximately 5% of curcumin (Ireson *et al.* 2001; Okada *et al.* 2001; Strimpakos & Sharma 2008). During oral administration, it is converted into curcumin metabolites such as glucuronide and curcumin sulfonate, whereas during systematic administration of curcumin it is converted into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol (Pari & Murugan 2004; Pari & Amali 2005).

Curcumin contains curcumin sulphate, curcumin glucuronide metabolites, tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), dihydrocurcumin (DHC), and octahydrocurcumin (OHC). Hexahydrocurcumin (HHC) and octahydrocurcumin (OHC) metabolites are not more potent than THC. THC is more hydrophilic and colourless than curcumin and is obtained by partial hydrogenation of curcumin (Sugiyama *et al.* 1996). THC shows a higher antioxidant potential than curcumin and curcuminoids and neutralises *t*-butoxyl, alkoxy, and peroxyl radicals better. It also inhibits 2, 2'-azobis (2-amidinopropane) dihydrochloride (AAPH) induced red blood cell haemolysis and peroxides in rat liver microsomes and rabbit erythrocyte membrane ghosts (Khopde *et al.* 2000; Naito *et al.* 2002). THC suppresses the oxidative modification of low density lipoprotein (LDL) and prevents the hypercholesterolaemic rats from the oxidative stress (Okada *et al.* 2001). It also inhibits nitrolotriacetate-induced oxidative renal damage. An oral dose of THC at 80 mg/kg body weight (BW) for 15 days lowered the hepatotoxicity induced by the antibiotic erythromycin estolate in rats (Pari & Murugan 2004, 2006; Pari & Amali 2005). Murugan and Pari (2006) determined that the THC dose of 80 mg/kg BW for 45 days significantly increased the antioxidant enzyme level in streptozotocin-nicotinamide induced oxidative stress in rats. It also lowered the levels of glucose and prevented the abnormal changes in insulin levels of the blood of rats. Curcumin has a higher potential than THC to modulate ABC drug transporters and fails to suppress TNF-induced NF-κB activation in RAW and KBM-5 cells (Pan *et al.* 2000). THC shows a lower potential as compared to curcumin to protect from phorbol 12-myristate 13-acetate (PMA)-induced skin tumour promotion in rats. It also prevents from the inflammation of mouse ears and TPA-induced tumour promotion in mouse skin (Hong *et al.* 2004). Additionally, THC suppressed the formation of lipopolysaccharide (LPS)-induced COX-2 expression, prostaglandin E2, and liberated the arachidonic acid and its metabolite in RAW cells. It also showed chemo-preventive activity in colons of experimental animals by suppressing 1,3-dimethylhydrazine-induced putative preneoplastic aberrant crypt foci development (Kim *et al.* 2000).

Chemistry of curcumin

Curcumin was isolated from turmeric in 1815 by Vogel and Pelletier. The two German scientists Milobedzka and Lampe determined its chemical structure in 1910. The oral bioavailability of curcumin in the gastrointestinal is poor and produces curcumin sulphate, hexahydrocurcumin, tetrahydrocurcumin, curcumin glucuronide, and dihydrocurcumin (Lee *et al.* 2011). Curcumin has low bioavailability due to its enol-tautomer structure (Payton *et al.* 2007). It gives three protons that produce ions in a water solution, the enolic proton with pK_A of 8.5 while the other two phenolic protons have the pK_A value ranging from 10 to 10.5. The chemical degradation of curcumin by alkali due to the difference of media has been studied by numerous laboratories with different results (Bernabe-Pineda *et al.* 2004). The previous investigations of Tonnesen *et al.* (1987) determined the degradation products such as feruloylmethane and ferulic acid of curcumin, and they also studied the kinetics of degradation in a MeOH-aqueous

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buffer solution (phosphate buffer pH 6–9). Wang *et al.* (1997) also demonstrated that curcumin decomposed 90% at pH 7.2, and temperature 378°C within 30 min in 0.1 M phosphate buffer, and uncertainly categorised the decomposed product as *trans*-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal. From the decomposed products of curcumin, vanillin is recognised as a major product along with ferulic acid and feruloylmethane (Bernabe-Pineda *et al.* 2004).

The Tris, borate, phosphate, and carbonate buffer solutions were used for the first order of kinetics of degradation for curcumins I (diferuloylmethane), II (demethoxycurcumin), and III (bisdemethoxycurcumin) (Price & Buescher 1997). Among these analogues, bisdemethoxycurcumin has been proven most stable by having the rate order I > II > III. Curcumin has photodegradable activity in an isopropanol solution (Ireson *et al.* 2001, 2002).

It has lipophilic nature and quickly permeates cell membranes (Jaruga *et al.* 1998a). During apoptosis, curcumin affects the structural and functional properties of cellular membranes. However, the curcumin is contrasted by cellular responses with typical apoptotic cell death due to a loss of the membrane integrity, which was immediate, partially reversible, and cells recovered in a short time (Jaruga *et al.* 1998b). The explorations of Lodha and Baggha (2000) improved the solubility of curcumin through modifying its structure and also covalent bonding with sugar molecule. Curcumin exhibited anti-angiogenic activity, and the diketone group was changed with phenolic components and α-, β-unsaturated ketone was unsymmetrically replaced by substituted phenyls.

Pharmacokinetics of curcumin

Scientists explored the uses of curcumin in biliary diseases in 1937, antibacterial role in 1949, and its use as antidiabetic in 1972 (Sandur *et al.* 2007). Beevers and Huang (2011) determined the hydrolysis of curcumin diethyl disuccinate in human plasma and in phosphate buffer (pH 7.4) they followed pseudo first order kinetics. It also maintains plasma levels in humans (Han *et al.* 2011). In one study conducted in Greece Pandelidou *et al.* (2011) prepared a stable curcumin formulation that comprised egg phosphatidylcholine (EPC) liposomes. This formulation showed the 14% discharge of the compound in the foetal bovine serum after 96 h of incubation. Another study supported previous findings; they determined that the phospholipid lecithin formulation of standardised curcuminoids (Meriva®) increased the curcuminoid absorption up to 29 times as compared to an unformulated curcuminoid mixture, but on the other side with demethoxycurcumin they attained the maximum systemic bioavailability and absorption (Garcea *et al.* 2004). Nevertheless, μg of curcuminoid in plasma remained appreciably less than that required for the inhibition of anti-inflammatory targets identified by curcumin (Gonzales & Orlando 2008). Likewise, Shao *et al.* (2011) synthesised curcumin-loaded spherical core-shell structure nanoparticles composed of methoxy poly(ethylene glycol)-poly block copolymers (mPEG-PCL) in a laboratory. The encapsulation of curcumin by using mPEG-PCL nanoparticles liberates in a sustained manner has effectively transported into cells via intracellularly localised primarily around nuclei and endocytosis. Similarly, Bhawana *et al.* (2011) synthesised curcumin nanoparticles in the form of nanocurcumin (2–40 nm) that freely diffuse in water in the absence of surfactants. In an *in vitro* study, curcumin liberated from microparticles and was retained over 28 days, whilst a single subcutaneous injection sustained the curcumin concentration in the liver of mice for 30 days (Kawamori *et al.* 1999).

Curcumin embeds the utilising poly(epsilon-caprolactone) nanofibres and liberates the curcumin in a biphasic form with Higuchi kinetics. Liu *et al.* (2011) determined that the use of Gelucire 44–14 along with curcumin increased the permeation rate of curcumin as 1.86 fold across the excised rabbit cornea, and also promoted the curcumin ocular bioavailability as 1.77 fold. Likewise, Liu and Chang (2011) formulated a eucalyptol microemulsion vehicle (ethanol, water, polysorbate 80, eucalyptol) for transdermal delivery of curcumin that enhanced the percutaneous permeation rate of the compound up to 15.7 fold as compared to eucalyptol formulation. The free radical chemistry of curcumin is owing to its phenol rings that discussed the H-atom donation from the β-diketone moiety. The resonance-stabilised α-oxo-alkyl curcumin radical, with unpaired electron density distributed between three carbon and two oxygen atoms, adds oxygen to the central carbon atom to become a peroxyl radical (Bhaumik *et al.* 2000). The reaction of curcumin radicals with other free radicals produced the ferulic acid, vanillin, and curcumin dimers (Surh *et al.* 2001).

Curcumin lowers the lipid peroxidation and maintains the level of a range of antioxidant enzymes, i.e. catalase, glutathione peroxidase, and superoxide dismutase. Moreover, the therapeutic potential of curcumin prevented from the free radicals through enhancing

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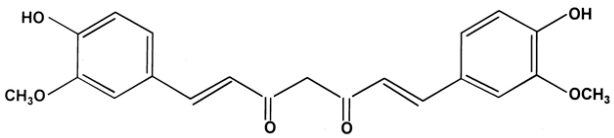

Figure 1. Curcumin

glutathione levels and its biosynthesis through Nrf2 (Surh *et al.* 2001; Peschel *et al.* 2007).

The oral administration of curcumin to the rats at the rate of 2 g/kg exhibited the maximum serum concentration of 1.35 ± 0.23 µg/ml at the time of 0.83 h, whilst the 0.006 ± 0.005 µg/ml serum concentration at 1 h was reported by using the same dose of curcumin in humans (Shoba *et al.* 1998). Likewise, Yang *et al.* (2007) determined that curcumin administration (500 mg/kg) showed the 1% bioavailability of curcumin in the plasma of freely moving rats. Similarly, 15 µg/ml curcumin was reported at the blood plasma level at 50 min after oral curcumin administration (1000 mg/kg) in rats (Chang *et al.* 2013). Moreover, the orally administered curcumin (4–8 g) in humans exhibited the peak plasma levels of 0.41–1.75 µM (Cheng *et al.* 2001). The previous findings of Sharma *et al.* (2004) showed that the oral dosing of curcumin (3.6 g) produced the plasma curcumin level of 11.1 nmol/l after an hour of dosing in a human clinical trial (Sharma *et al.* 2004). Furthermore, intravenous administration of unformulated curcumin (2 mg/kg) via the tail vain to rats showed better availability of curcumin 6.6 µg/ml in the blood plasma concentration (Sun *et al.* 2013).

Epigenetic role of curcumin – histone deacetylases and acetyltransferases

Almost 18 histone deacetylases (HDACs) have been recognised principally occupying 4 types (Xu *et al.* 2007b). HDAC enzymes are attached to DNA by multiprotein complexes such as co-activators and co-repressors. The concentration (50–500 µM) of curcumin has been proven as the most effective HDAC inhibitor in HeLa nuclear extracts and also at an IC_{50} of 115 µM (Bora-Tatar *et al.* 2009). Likewise, different concentrations of curcumin inhibited cell proliferation for 0, 24, 36, 48, 60, and 72 h in a dose- and time-dependent manner with an IC_{50} of 36 h at 24 µM in Raji cells. The Raji cells are the cell line of Epstein-Barr virus transformed lymphocytes with surface Fc receptors (Chen *et al.* 2007). The previous findings of Meja *et al.* (2008) illustrated that nanomolar concentrations of curcumin restored corticosteroid activity in oxidative monocytes through sustaining HDAC2 activity by protecting the oxidative degradation of HDAC2. These concentrations lowered the gene expression associated with protein degradation.

Histone acetyltransferases (HATs) such as histones, acetylates, and nonhistone targets participate in diverse processes, i.e. DNA repair, gene silencing, transcription activation, and cell cycle progression (Carrozza *et al.* 2003). Curcumin suppresses the p300/CBP HAT activity in *in vitro* and in *in vivo* studies (Dekker *et al.* 2009). Curcumin with an IC_{50} of almost 25 µM strongly inhibited the acetylation of histones H3 and H4 by p300/CBP in gel HAT assays, whilst p300/CBP linked factor HAT activity did not alter through the treatment of 100 µM curcumin (Morimoto *et al.* 2008). There are specific binding sites on p300/CBP for curcumin. These sites give a conformational change and lower the binding efficiency of acetyl CoA, histones H3 and H4 (Marcu *et al.* 2006). Additionally, curcumin suppresses the p300/CBP HAT activity dependent chromatin transcription (Morimoto *et al.* 2008). The findings of Kang *et al.* (2006) illustrated that curcumin activated the poly(adenosine diphosphate ribose) polymerase and caspase-3 mediated apoptosis by inducing histone hypoacetylation in brain glioma cell lines. Likewise, curcumin lowers acetylation of RelA by suppressing p300 that attenuates interaction with IjBa. Further, it lowers IjBa-dependent nuclear export of the complex by chromosomal region maintenance I-dependent pathway (Chen *et al.* 2001).

Curcumin has an inhibitory effect to covalently block the catalytic thiolate of C1226 of DNA methyltransferase I. The enol form of curcumin covalently blocked the catalytic thiol group in DNA methyltransferase I through the C3 keto-enol moiety of bisdemethoxycurcumin and demethoxycurcumin (Liu *et al.* 2009).

Curcumin and gene expression

Curcumin exhibits the health endorsing properties through its direct interaction with target proteins and also does the epigenetic modulation of target genes (Van Erk *et al.* 2004). In human colon cancer cells, curcumin produces gene expression changes in early response genes. Gene expression changes were produced after exposure to curcumin for 3–6 h that participated in the cell cycle (BUB1B, p16INK4, Rb, PLK, STK6, p53, STK12, cyclin E1, and cyclin G1), DNA repair (MSH3, ERCC2, and hMLH1), signal transduction (MAPK, STAT3, STAT5b, FGFR1, VEGF, and AKT), gene transcription (ATF4, HDAC1, and EGF1), xenobi-

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otic metabolism (CYP1B1, GSTT2, and GSTM4), and cell adhesion (integrins and annexin), whilst the cells with enhanced apoptosis were formed in the G2/M phase. The oral administration of curcumin changed the expression of metallothionein genes at 12–24 hours. It has also upregulated the tubulin genes after the administration of curcumin for 48 h at 100 lM, whilst it also downregulated the tubulin genes after the supplementation of curcumin for 3 h at 25 lM (Deeb *et al.* 2004). Curcumin regulated numerous genes with a > 4-fold increase and expressions were recorded as 8, 73, 181, 3, and 0 at 3, 6, 12, 24, and 48 h in the LNCaP prostate cancer mice. In the androgen-responsive LNCaP prostate cancer, curcumin has upregulated 181 genes and downregulated genes by > 4-fold cell line at 12 hours. On the other side, curcumin upregulated 27 genes and downregulated 13 genes in the C4–2B androgen refractory prostate cancer cell line (Sharma *et al.* 2004). Additionally, it also modulates the gene expression by interacting with diverse intracellular signal transduction pathways (Ehrlich 2009).

Health claims of curcumin and its anticancer role

Chemoprevention is a strategy to prevent from the cancerous effects before malignancy manifests via using natural and synthetic compounds (Surh 2003). Researchers have explored numerous bioactive components from fruits, vegetables, herbs and spices to show chemopreventive properties. Among these bioactive compounds, curcumin is a chemopreventive agent to curtail initiation and propagation stages of cancer (Duvoix *et al.* 2005).

The nuclear factor NF-κB is significant due to unique regulatory mechanisms, inducible expression patterns, and participation in several gene expression and signalling pathways. The activation of NF-κB factor is associated with the development of cancer in human body. Curcumin inhibits the NF-κB activation through TNF-α or H_2O_2, PMA, and also hampers the phosphorylation of IκKα as well as suppresses the degradation and phosphorylation of IκBα (Singh & Aggarwal 1995; Shishodia *et al.* 2005). Curcumin suppresses the translocation of NF-κB p65 in DCs and inhibits the LPS induced mitogen activated protein kinase (MAPK) activation (Kim *et al.* 2006). Likewise, it also lowers the LPS induced NF-κB activation or IL1 or TNF-α (Tomita *et al.* 2006). Lee *et al.* (2003) determined that curcumin has the ability to suppress the NF-κB binding activity which is reversible within 30 min after IFN-α supplementation. Curcumin mediates TRAIL-induced apoptosis through blocking IκBα degradation and phosphorylation and then abrogates NF-κB activation in LNCaP cancer cells (Deeb *et al.* 2004). Likewise, Wang *et al.* (2008) revealed that curcumin has the potential to bind the NF-κB DNA activity, suppress the degradation of IκBα upstream, and NF-κB-dependent expression of IL-6 downstream in WI-38 VA13 cells. It also inhibits the TPA-induced NF-κB activation by attenuating the consequent translocation of the p65 subunit and degradation of IκBα in HL-60 cells, as well as it lowers the TPA-induced activation of NF-κB (Hahm *et al.* 2004). Curcumin also blocks IKK activity, IκB serine 32 phosphorylation, IκBα degradation, RelA nuclear translocation, and cytokine-induced NF-κB DNA binding activity in HT-29, Caco-2 cells, and EC-6 cells (Renard *et al.* 2001).

Moreover, it abrogates the LPS-mediated TLR2 mRNA induction in mouse splenic macrophages and BCG-induced IL-8 production in human gingival fibroblasts and monocytes through suppressing NF-κB activation (Karunagaran *et al.* 2005). Ishita *et al.* (2004) determined that curcumin suppressed the HTLV-1 and NF-κB activation in T-cell lines through the abolished constitutive phosphorylation of Tax-induced NF-κB transcriptional and IκBα activities in primary ATL cells.

Curcumin has an anticarcinogenic effect on multiple targets such as cellular signalling molecules, apoptotic genes, adhesion molecules, transcription factors, angiogenesis regulators, and growth regulators (Aggarwal *et al.* 2003). It downregulates the production of tumour necrosis factors including IL-1β and TNF-α, as well as it also suppresses the activation of AP-1 and nuclear factor-κB (NF-κB) through hindering phosphorylation of I-κB by inactivation of I-κB kinase complex (Lee *et al.* 2012). It inhibits c-fos, c-jun, and activator protein-1 owing to its DNA binding activity. It also lowers the activity of multiple enzymes such as COX-2, cytochrome P450, protein kinase C, protein tyrosine kinases, and cyclooxygenase (Bush *et al.* 2001; Liu *et al.* 2006). Curcumin plays a significant role in arachidonic acid metabolism through lowering the COX-2 and hindering the phosphorylation of cytosolic phospholipase cPLA (2). It also suppresses 5-lipoxygenase (LOX) activity in HCT-15 and HT-29 human colon cancer cell lines (Hong *et al.* 2004; Ravindran & Babu 2009). It also lowers the baxxL and endogenous bcl-2 proteins and suppresses the activation of AP-1 and NFκB in DU145 cells (Mukhopadhyay *et al.* 2001).

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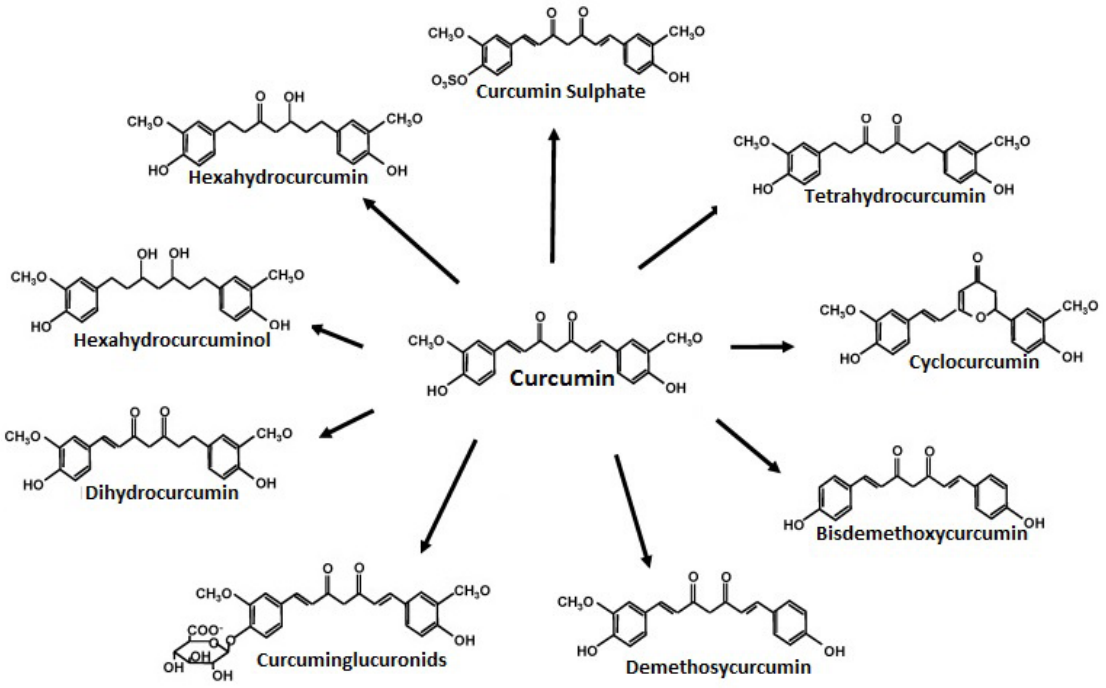

Figure 2. Curcumin and its analogues

Recently, Zheng *et al.* (2017) reported the preventive role of curcumin against human gastric cancer cell lines: SNU-1, SNU-5, and AGS via significantly impairing the tumour cell viability, inducing apoptotic cell death *in vitro*. Moreover, it also inhibits the levels of Wnt3a, phospho-LRP6, LRP6, phospho-β-catenin, β-catenin, surviving, and C-myc (Zheng *et al.* 2017). In human skin cancer cells lines, administration of curcumin mediated the modulation of several pathways, such as JAK-2/STAT3 via suppressing the melanoma cell migration, invasion and inducing apoptosis. The low oral bioavailability of curcumin has led to the development of curcumin analogues, such as EF24, with greater anti-tumour efficacy and metabolic stability. Likewise, curcumin has anticancer ability in cancer cells through modulation of miRNAs such as miR21 that is implicated in cell cycle regulation and apoptosis via downregulation of PTEN and PDCD4 proteins (Lelli *et al.* 2017). Similarly, curcumin has been found to show an anticancer potential in human pancreatic cancer cells via inhibiting cell growth, inducing apoptosis, causing cell cycle arrest and retarding cell invasion. Further, it also significantly suppressed the expression of Cdc20 in pancreatic cancer cells whereas downregulation of Cdc20 promoted curcumin-mediated anti-tumour activity (Zhang *et al.* 2017). Several studies reported that curcumin suppressed the survival and proliferation of DU145 cells in a dose- and time-dependent manner through inhibiting the expression of MT1-MMP, MMP2 proteins, and DNA-binding ability of NICD in human DU145 cells (Bondì *et al.* 2017; Yang *et al.* 2017).

Oxidative stress and curcumin

The pathogenesis of liver and lung diseases is associated with the production of free radicals in human body. The supplementation of corticosteroids was effective against chronic obstructive pulmonary and asthma disease (COPD) (Marwick *et al.* 2007). Curcumin restores histone deacetylase activity and is used to curtail lung diseases which are unresponsive to corticosteroids (Bruck *et al.* 2007). Nevertheless, the combination of curcumin with systemic corticosteroids should not be used because it may inhibit cytochrome P450 and UDP-glucuronosyl transferases. Curcumin lowers the thioacetamide and endotoxin induced liver dysfunction via inhibiting the expression of enzymes (iNOS), transcription factors NF-κB, tumour necrosis factor-a and IL-1β in mice (Shapiro *et al.* 2006). Moreover, it lowers the ritonavir-related vascular dysfunction, kidney toxicity and indomethacin-induced intestinal damage in porcine coronary arteries of rats (Farombi & Ekor 2006; Pari & Murugan 2006).

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Table 1. Biological effects of curcumin

	Disorders mechanisms	References
Anticancer	Inhibited the levels of Wnt3a, phospho-LRP6, LRP6, phospho-β-catenin, β-catenin, surviving, and C-myc	Zheng *et al.* (2017)
	Suppressed cell migration and invasion; Induced apoptosis and modulated the miRNAs such as miR21; Down regulated the PTEN and PDCD4 proteins	Lelli *et al.* (2017)
	Significantly suppressed the expression of Cdc20	Zhang *et al.* (2017)
	Inhibited the expression of MT1-MMP, MMP2 proteins and DNA-binding ability of NICD	Yang *et al.* (2017)
	Inhibited the NF-κB activation induced; Hampered the phosphorylation of IKKα; Suppressed the degradation and phosphorylation of IκBα	Singh & Aggarwal (1995); Shishodia *et al.* (2005)
	Suppressed the translocation of NF-κB p65	Tomita *et al.* (2006)
	Inhibited the LPS induced mitogen activated protein kinase (MAPK) activation; Lowered the LPS induced NF-κB activation or IL1 or TNF-α	Kim *et al.* (2006)
	Suppressed the NF-κB binding activity	Lee *et al.* (2003)
	Mediated TRAIL-induced apoptosis through blocking IκBα degradation and phosphorylation; Abrogated NF-κB activation in LNCaP cancer cells	Deeb *et al.* (2004)
	Suppressed the degradation of IκBα upstream, and NF-κB-dependent expression of IL-6 downstream in WI-38 VA13 cells	Wang *et al.* (2008a)
	Inhibited the TPA-induced NF-κB activation	Hahm *et al.* (2004)
	Blocked IKK activity, IκB serine 32 phosphorylation, IκBα degradation, RelA nuclear translocation, and cytokine-induced NF-κB DNA binding activity	Renard *et al.* (2001)
	Abrogated the LPS-mediated TLR2 mRNA induction	Karunagaran *et al.* (2005)
	Suppressed the HTLV-1 and NF-κB activation; Abolished constitutive phosphorylation of Tax-induced NF-κB transcriptional and IκBα activities in primary ATL cells	Ishita *et al.* (2004)
	Down regulated the production of tumor necrosis factors including IL-1β & TNF-α; Suppressed the activation of AP-1 and nuclear factor-κB (NF-κB)	Lee *et al.* (2012)
	Inhibited c-fos, c-Jun, and activator protein-1 owing to its DNA binding activity; Lowered the activity of multiple enzymes such as COX-2, cytochrome P450, protein kinase C, protein tyrosine kinases and cyclooxygenase	Bush *et al.* (2001); Liu *et al.* (2006)
	Lowered the COX-2 and hindering the phosphorylation of cytosolic phospholipase (cPLA (2); Suppressed 5-lipoxygenase (LOX) activity in HCT-15 and HT-29 human colon cancer cell lines	Hong *et al.* (2004); Ravindran & Babu (2009)
	Lowered the baxxL and endogenous bcl-2 proteins and suppresses the activation of AP-1 and NF-κB in DU145 cells	Mukhopadhyay *et al.* (2001)
Oxidative stress	Balanced the activity of antioxidant defense system	Nariya *et al.* (2017)
	Lowered the content of mtDNA and enhanced the content of Cyt B and NADH5 in spermatozoa	Zhang *et al.* (2017)
	Decreased the expression of phospho (p)-p38, p-checkpoint kinase 1 (ChK1), cyclin D1, and breast cancer associated gene 1 (BRCA1) protein; Inhibited glucose-regulated protein 78 and DNA damage	Dai *et al.* (2017)
	Inhibited Wnt/β-catenin signalling pathways	Wang *et al.* (2016)
	Restored histone deacetylase activity and used to curtail lung diseases which are unresponsive to corticosteroids	Bruck *et al.* (2007)
	Inhibited cytochrome P450 and UDP-glucuronosyl transferases; Lowered thioacetamide and endotoxin induced liver dysfunction via inhibiting the expression of enzymes (iNOS), transcription factors NF-κB, tumor necrosis factor-a and IL-1b	Shapiro *et al.* (2006)
	Lowered the ritonavir related vascular dysfunction, kidney toxicity and indomethacin-induced intestinal damage in porcine coronary arteries of rats	Farombi & Ekor (2006); Pari & Murugan (2006)
	Augmented antioxidant defense system and modulated the biochemical marker enzymes	Kalpana & Menon (2004)
	Lowered oxidative damage, and neutralising free radicals when they attack on lipids membrane	Halliwell & Gutteridge (2002)
	Inhibited SH-group oxidation and efficiently block thiol depletion	Chattopadhyay *et al.* (2004); Pari & Amali (2005)

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Table 1 to be continued

	Disorders mechanisms	References
Cardiovascular role	Neutralised free radical, exhibited metal chelating ability; Enhanced antioxidant enzymes concentration; Reduced gastrointestinal absorption and tissue Cd accumulation	Kukongviriyapan *et al.* (2016)
	Induced apoptotic death, reduced surface expression of intercellular adhesion molecule 1; Lowered adhesion of monocytes to endothelial monolayers	Kam *et al.* (2015)
	Downregulated expression of hypertrophy marker genes (ANF, β-MHC), apoptotic mediators (Bax, Cytochrome-c) and activity of apoptotic markers (Caspase 3 and PARP)	Ray *et al.* (2016)
	Suppressed the p300-induced hypertrophic responses and inhibits the acetylation of histones and GATA4 in cultured neonatal cardiomyocytes	Balasubramanyam (2004)
	Mediated the suppression of nuclear acetylation; Prevented from the p300-GATA4 formation in cardiac patients	Thompson (2004); Black (2006)
	Lowered hypertrophic responses in cardiomyocytes; Inhibited hypertrophy-responsive transcription factors; Suppressed acetylation of histones	Gardner (2003)
	Inhibited HAT mutp300- and TSA	Sano (2007)
	Protected from the development of atherosclerotic lesions	Olszanecki *et al.* (2005); Wongcharoen & Phrommintikul (2009)
	Inhibited hypertrophy-inducing transcription factors such as p300-histone transacetylase and down regulated nitric oxide synthase (NOS)	Wongcharoen & Phrommintikul (2009)
	Reduced the nitric oxide production through the mediation of AP-1, NF-κB; Induced HO-1 by activating Nrf2-dependent antioxidant response	Farhangkhoee *et al.* (2006)
	Inhibited the ATPase activity of the Ca^{2+}-ATPase of the cardiac and skeletal sarcoplasmic reticulum (SR) muscle	Frey & Olson (2003)
Anti-diabetic	Inhibited the PEPCK and G6Pase activities	Kim *et al.* (2009)
	Increased the phosphorylation of AMPK and its downstream target acetyl-CoA carboxylase (ACC)	Fujiwara *et al.* (2008)
	Inhibited intracellular reactive oxygen species (ROS) generation, VEGF-mediated PKC-β2 translocation, and vascular endothelial growth factor (VEGF) expression	Premanand *et al.* (2006)
	Inhibited the nitric oxide synthase (NOS) overexpression and NF-κB activation	Pari & Murugan (2005); Weber *et al.* (2006); Kowluru & Kanwar (2007)
	Exhibited anti-inflammatory potential in tumor necrosis factor (TNF)-alpha-treated HaCaT cells through inhibition of nuclear factor-κB (NF-κB) and mitogen activated protein kinase (MAPK)	Cho *et al.* (2007)
	Lowered sugar level in diabetic neuropathy	Mijnhout *et al.* (2006)
	Enhanced the activation of PPAR-γ; Increased the antioxidant level of pancreatic β-cells	Murugan & Pari (2006)
	Inhibitory effect on macrophage inflammatory protein-1a, tumour necrosis factor-a by phorbol myristate acetate (PMA), membrane cofactor protein-1 and IL-1b, alveolar macrophages and the production of interleukin (IL)-8	Literat *et al.* (2001)
	Inhibitory effect on hydrogen peroxide production and superoxide anion	Iqbal *et al.* (2003)
	Inhibited (VEGF), NF-κB signaling, proinflammatory cytokines (IL-1b) and increasing activity of chaperone molecules	Murugan & Pari (2006)
Alzheimer's disease	Enhanced the mitochondrial fusion activity, reduced fission machinery; Increased biogenesis and synaptic proteins; Modified the Aβ aggregation pathway	Reddy *et al.* (2016)
	Ameliorated Aβ-induced toxicity	Thapa *et al.* (2016)
	Lowered Aβ aggregation	Yang *et al.* (2005)
	Inhibited transcriptional activities and signalling cascades	Narayan (2004)
	Lowered the I-R induced changes; Reduced the infarct volume and edema (BDNF) in middle cerebral artery of rats	Thiyagarajan & Sharma (2004)
	Lowered the cognitive deficits and oxidative damage	Wu *et al.* (2003a); Thiyagarajan & Sharma (2004)

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Table 1 to be continued

	Disorders mechanisms	References
Hepatoprotective effects	Suppressed the IL-1β and TNF-α cytokines	Bruck *et al.* (2007)
	Modulated NF-κB activity	Oakley *et al.* (2005)
	Suppressed the hepatic fibrosis; Inhibited collagen a1 (I) gene expression & HSC activation	Bruck *et al.* (2007)
	Suppressed a-smooth muscle actin, collagen a1, and fibronectin (I); Increased the matrix metalloproteinase-2 and -9 expressions; Inhibited the connective tissue growth factor (CTGF) expression	Xu *et al.* (2003b)
	Modulated the intracellular signalling pathways i.e. JNK, PPAR-g, AP-1, ERK, and NF-κB	Zheng *et al.* (2007)
	Activated the PPAR-g through inhibiting NF-κB activity in HSCs	Park *et al.* (2000)
	Inhibited CTGF expression in HSCs; Suppressed the activation of ERK, MAP kinase and NF-κB	Hsu & Cheng (2007)
Antidepressant activity	Attenuated the activity of C6 glial cells monoamine oxidize (MAO)	Xu *et al.* (2005b)
	Enhanced the levels of brain-derived neurotrophic factor (BDNF)	Xu *et al.* (2005a)
	Increased the hippocampal neurogenesis; Prevented from the stress-induced decrease in serotonin 5-HT1A mRNA and BDNF protein levels; Reversed the chronic stress-induced reduction in BDNF protein levels	Xu *et al.* (2006)
	Reversed the glutamate-induced decrease in BDNF levels of cultured rat cortical neurons	Wang *et al.* (2008b)
	Inhibited the cyclooxygenase-2 (COX-2) isoenzyme and transcription of NF-κB; Reduced the release of inflammatory NO through blocking the synthesis of inducible nitric oxide synthase (NOS) enzyme	Chan *et al.* (1998b); Lim *et al.* (2001)
Wound healing	Enhanced the formation of granulation tissue through increasing collagen and fibronectin (FN) expressions	Mani *et al.* (2002)
	Improved the muscle regeneration through modulating NF-κB activity	Thaloor *et al.* (1999)
	Suppressed the hydrogen peroxide in human fibroblasts and keratinocytes; Neutralised the activity of free radicals and inhibits cell proliferation in curcumin treated rats	Gopinath *et al.* (2004)
	Increased the synthesis of hexosamine, collagen, nitrite, DNA and histologic; Improved the collagen deposition and also enhances in fibroblast	Jagetia & Rajanikant (2005)
Antiplatelet effect	Suppressed platelet-activating factor (PAF), ADP, epinephrine mediated platelet aggregation, collagen, and arachidonic acid (AA); Inhibited the AA and PAF mediated platelet aggregation	Kim *et al.* (2003); Lim *et al.* (2004)
	Mediated the AA-induced platelet aggregation and preferential inhibition of PAF shows suppressing effects on and Ca^{2+} signalling and TXA2 synthesis	Srivastava *et al.* (1995)
Osteoprosis, osteoarthritis and akin disease	Suppressed RANKL-induced osteoclastogenesis of rat monocyte-macrophage RAW264.7 cells	Suda *et al.* (1999)
	Induced the apoptosis in osteoclast rabbit, and inhibits the RANKL signalling and ultimately suppresses the RANKL-induced osteoclastogenesis in RAW 264.7 cells	Ozaki *et al.* (2000); Bharti *et al.* (2004)
	Improved the bone microarchitecture and enhancing the mineral density in APP-PS1 transgenic rats	Yang *et al.* (2011)
	Significantly prevented from paw inflammation	Ammon & Wahl (1991)
	Suppressed the COX-2 expression and also decreased the cellular protein kinases (JNK, protein kinase C), human epidermal growth factor receptors (EGFR & ErbB-2) and epidermal growth factor at the transcriptional level	Goel *et al.* (2001)
	Inhibited the NF-κB activation and hindered the c-jJun-AP-1 function	Kim *et al.* (2003)
	Decreased the expression of IL-6 and IL-8 pro-inflammatory cytokines	Pol *et al.* (2003)
	Showed inhibitory effect against different pro-inflammatory factors STAT3, NF-κB, and TNF	Vamvouris & Hadi (2006); Abdou & Hanout (2008)
	Lowered the density of CD8+ T-cells and PK levels	Heng *et al.* (2000)
	Suppressed the keratinocyte proliferation and prevented from the posriais activity	Pol *et al.* (2003); Kurd *et al.* (2008)
	Suppressed the lung fibroblasts through suppression of protein kinase C epsilon (PKC)	Tourkina *et al.* (2004)
	It induces apoptosis in scleroderma lung fibroblasts (SLFs) rats, and this effect was linked with the expression of PKC epsilon	Xu *et al.* (2007a)

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Table 1 to be continued

	Disorders mechanisms	References
Miscellaneous properties	Induced the heat-shock (HS) response; Suppressed proteasome activity in HeLa cells	Jana *et al.* (2004)
	Showed proteasomal activity in telomerase-immortalised mesenchymal bone marrow stem cells and human fibroblasts	Pandya *et al.* (2000); Padmaja & Raju (2004)
	Increased endothelial HO-1 expression; Stimulated the expression of Nrf2 through increasing redox	Asai & Miyazawa (2001)
	Sensitive inducible protein HO-1 expression and HO-1 activity	Balogun *et al.* (2003)
	Induced changes in human sperm mitochondrial transmembrane potential (MTP) and interferes with sperm energy metabolism, produced alterations in MTP	Balasubramanyam *et al.* (2004)
	Inhibited the human immunodeficiency virus (HIV) replication through suppressing HIV long-terminal repeats, HIV protease, HIV-1 integrase, repression of the acetylation of histone-nonhistone proteins, histone acetyltransferase dependent chromatin transcription, and p300-CREB-binding protein-specific acetyltransferase	Vajragupta *et al.* (2005)
	Lowered the lymphocytes infiltrating the thyroid gland, inhibited the synthesis of TNF-α, and leucotriens	Chan *et al.* (1998)
	Suppressed the induction of iNOS and COX-2	Brouet & Ohshima (1995)
	Inhibited TGF-band fibrogenesis	Chang (2001)
	Suppressed the myeloperoxidase (MPO) activity, infiltration of eosinophils, phorbole myristate acetate (PMA)-stimulated superoxide generation; Inhibited lipopolysacchride-stimulated TNF-a release, TGF- b1 activity, lactate dehydrogenase (LDH) activity, macrophages and neutrophils in lung tissue, c-Jun protein, expression of type I collagen and lung hydroxyproline content	Illek *et al.* (2000)
	Lowered the calcium concentrations that released the mutant cystic fibrosis transmembrane conductance regulator (CFTR) gene	Zeitlin *et al.* (2004)
	Inhibited 5a-reductase and growth of flank organs	Liao *et al.* (2001)
	Suppressed the human sperm motility and develops the novel intravaginal contraceptive	Rithaporn *et al.* (2003)
	Neutralised both 70% lethal effect of Crotalus venom and haemorrhagic activity of Bothrops venom	Araujo & Leon (2001)
	Suppressed GM-CSF, IL-4, and IL-5 production and inhibiting cytokines production that affect IgE synthesis, and eosinophil function	Ram *et al.* (2003)
	Inhibited the airway hyperreactivity, and OVA-induced airway constriction	Yeon *et al.* (2010)

Kalpana and Menon (2004) stated that curcumin augmented an antioxidant defence system and modulated the biochemical marker enzymes. It also lowers the levels of free radicals and induction of detoxification enzymes and provides protection against life style related disorders (Manikandana *et al.* 2004). Additionally, Halliwell and Gutteridge (2002) reported that administration of curcumin lowered oxidative damage, neutralising free radicals when they attack the lipid membrane. Curcumin acts as a free radical scavenger that inhibits SH-group oxidation and efficiently blocks thiol depletion (Chattopadhyay *et al.* 2004; Pari & Amali 2005).

Recently, Nariya *et al.* (2017) reported that curcumin significantly prevented from the oxidative stress indices in a dose- and duration-dependent manner by balancing the activity of the antioxidant defence system which is induced by lead acetate in human peripheral blood lymphocyte culture (Nariya *et al.* 2017). In another study conducted by Zhang *et al.* (2017) they observed that curcumin treatment in a leucocytospermia human patient significantly improved the sperm motility and decreased the level of H_2O_2. Further, it also lowered the content of mtDNA and enhanced the content of Cyt B and NADH5 in spermatozoa (Zhang *et al.* 2017). Similarly, curcumin lowered the expression of phospho(p)-p38, p-checkpoint kinase 1 (ChK1), cyclin D1, and breast cancer associated gene 1 (BRCA1) protein to attenuate the S-phase arrest in human hepatocyte L02 cells. Meanwhile, curcumin protected from the FZD induced ER stress via the inhibition of glucose-regulated protein 78 and DNA damage inducible gene 153/C/EBP-homologous protein (GADD153/CHOP) expression.

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Conclusively, curcumin prevented from the FZD induced cytotoxicity and S-phase arrest through activating the Nrf2/HO-1 pathway and inhibiting the p38 MAPK pathway and ER stress (Dai *et al.* 2017).

In an *in vitro* study in human adipose-derived mesenchymal stem cells (MSCs), curcumin prevented from the cell death caused by hydrogen peroxide (H_2O_2) exposure. Moreover, it also increases the osteoblast differentiation of human adipose-derived MSCs. Additionally, the inhibition of oxidative stress and Wnt/β-catenin signalling pathways are linked with curcumin treatment (Wang *et al.* 2016).

Cardiovascular role of curcumin

Heart failure is associated with an increase in pressure, a quick response to increase the wall stress needed to retain cardiac output. Hypertrophy is linked with the activation of many neurohormonal factors, i.e. endothelin-1 (ET-1), catecholamines, and angiotensin II (Molkentin & Dorn 2001; Lohse *et al.* 2003). Activation of transcription factors is mediated through acetylation control by an intrinsic histone acetyltransferase (HAT), p300 and histone deacetylases (Backs & Olson 2006; Miyamoto 2006). Curcumin suppresses the p300-induced hypertrophic responses and inhibits the acetylation of histones and GATA4 in cultured neonatal cardiomyocytes (Balasubramanyam 2004). It also mediates the suppression of nuclear acetylation through contributing to the repression of myocardial cell hypertrophy and prevents from the p300-GATA4 formation in cardiac patients (Thompson 2004; Black 2006).

Curcumin lowers the hypertrophic responses in cardiomyocytes through inhibiting the hypertrophy-responsive transcription factors, suppressing acetylation of histones, and protecting from the p300-GATA4 complex through inhibiting the p300 HAT activity (Gardner 2003). Sano (2007) determined that curcumin inhibited HAT mutp300 and TSA due to its strong antioxidant potential as well as prevented from the p300-GATA4 complex formation in animal models. It also protects from the development of atherosclerotic lesions (Olszanecki *et al.* 2005; Wongcharoen & Phrommintikul 2009). It averts heart failure in animal models and myocardial hypertrophy development, inhibits hypertrophy inducing transcription factors such as p300-histone transacetylase and downregulates nitric oxide synthase (NOS) (Morimoto *et al.* 2008; Wongcharoen & Phrommintikul 2009). Curcumin also reduces the nitric oxide production through the mediation of AP-1, NFkB, and many vasoactive factors. Curcumin induces HO-1 by activating the Nrf2-dependent antioxidant response in endothelial cells (Farhangkhoee *et al.* 2006).

Additionally, it also inhibits the ATPase activity of the Ca^{2+}-ATPase of the cardiac and skeletal sarcoplasmic reticulum (SR) muscle. The concentration of curcumin (1 and 10 μM) enhanced the Ca^{2+} transport level up to 20% whereas the 1–3 μM concentration of curcumin also increased the ATPase activity (Frey & Olson 2003).

In cadmium toxicity, curcumin and tetrahydrocurcumin administration can alleviate vascular dysfunction and high blood pressure in humans. Further, they protect the vascular endothelium by increasing nitric oxide ($NO^{\bullet}$) bioavailability and improving the vascular function. Curcumin also exerts an antioxidant potential against Cd toxicity directly and/or indirectly through neutralising free radicals, metal chelating ability, increasing the antioxidant enzyme concentration, regulating inflammatory enzymes, reducing the gastrointestinal absorption and tissue Cd accumulation (Kukongviriyapan *et al.* 2016). The earlier investigations of Kam *et al.* (2015) illustrated the preventive role of curcumin against EAhy926 human endothelial cells through multiple mechanisms such as (1) attenuation of microparticle release caused by TNF, (2) acceleration the cell death, (3) induction of apoptotic death, and (4) reduction of the surface expression of intercellular adhesion molecule 1 and adhesion of monocytes to endothelial monolayers (Kam *et al.* 2015).

Curcumin encapsulated by carboxymethyl chitosan (CMC) nanoparticle peptide during hypertrophy significantly improved the cardiac function by downregulating the expression of hypertrophy marker genes (ANF, β-MHC), apoptotic mediators (Bax, Cytochrome-c) and activity of apoptotic markers (Caspase 3 and PARP). Targeted curcumin treatment significantly lowered p53 expression and activation in diseased myocardium via the inhibited interaction of p53 with p300-HAT (Ray *et al.* 2016).

Antidiabetic role of curcumin

Diabetes mellitus (DM) Type 1 is an autoimmune disease associated with beta-cell destruction and lymphocytic infiltration of the pancreatic islets of Langerhans (Bloomgarden 2007; Dobretsov *et al.*

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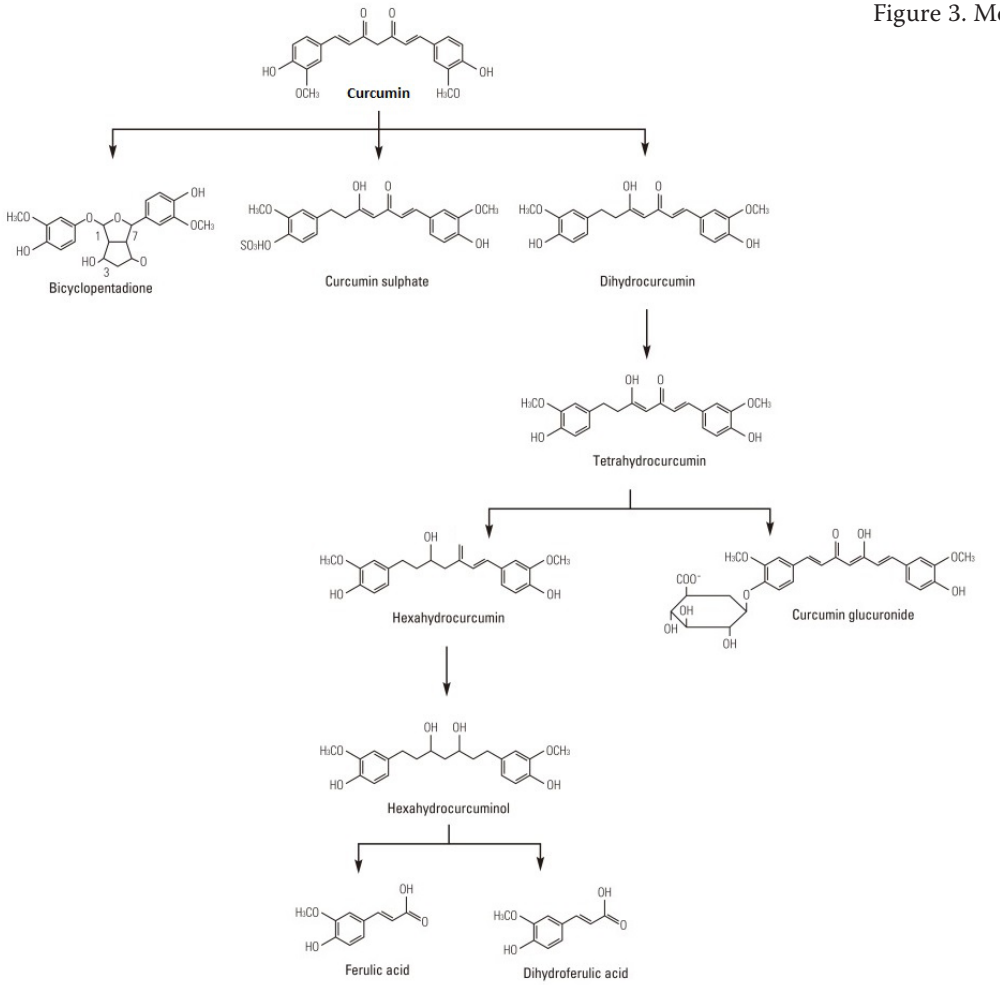
Figure 3. Metabolism of curcumin



2007). The β-cell damage is the production of reactive oxygen species due to the depletion of poly(ADP-ribose)polymerase-1 overactivation and free radical scavenging activity. These poly(ADP-ribose)polymerase-1 inhibitors are recognised as to prevent from diabetes along with having side effects (Cay *et al.* 2001). Curcumin has a chemopreventive potential against secondary diabetic complications, i.e. wound healing, retinopathy, reduction of advanced glycation, and diabetic nephropathy – renal lesions end products in rats. It inhibits the nitric oxide synthase (NOS) overexpression and NF-κB activation (Pari & Murugan 2005; Weber *et al.* 2006; Kowluru & Kanwar 2007).

Curcumin exhibits the anti-inflammatory potential in tumour necrosis factor (TNF)-α-treated HaCaT cells through the inhibition of nuclear factor-κB (NF-κB) and mitogen activated protein kinase (MAPK) (Cho *et al.* 2007). Similarly, Mijnhout *et al.* (2006) determined that curcumin is a more effective free radical scavenger and can lower the sugar level in diabetic neuropathy. In diabetic rats, curcumin enhances the activation of PPAR-γ and increases the antioxidant level of pancreatic β-cells (Murugan & Pari 2006). It also showed an inhibitory effect on macrophage inflammatory protein-1α, tumour necrosis factor-α by phorbol myristate acetate (PMA), membrane cofactor protein-1 and IL-1β, alveolar macrophages and the production of interleukin (IL)-8 (Literat *et al.* 2001). It also exerts a strong inhibitory effect on hydrogen peroxide production and superoxide anion (Iqbal *et al.* 2003). The previous findings of Murugan and Pari (2006) illustrated that curcumin reduced the diabetic nephropathy in streptozocin-treated rats through inhibiting VEGF, NF-κB signalling, proinflammatory cytokines (IL-1β) and increasing the activity of chaperone molecules.

Curcumin inhibits PEPCK and G6Pase activities in H4IIE rat hepatoma and Hep3B human hepatoma cells (Kim *et al.* 2009). In earlier findings of Fujiwara *et al.* (2008), they demonstrated that curcumin increased the phosphorylation of AMPK and its downstream

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target acetyl-CoA carboxylase (ACC) in H4IIE and Hep3B cells. Similarly, curcumin also induces apoptosis in human retinal endothelial cells (HREC) through inhibiting intracellular reactive oxygen species (ROS) generation, VEGF-mediated PKC-β2 translocation, and vascular endothelial growth factor (VEGF) expression (Premanand *et al.* 2006). In another study conducted by Sameermahmood *et al.* (2008), they demonstrated that curcumin has an inhibitory effect on stromal cell-derived factor-1 (SDF-1) α-induced HREC migration by reducing downstream PI3K/Akt signals and blocking the upstream Ca^{2+} influx (Sameermahmood *et al.* 2008). In the retina of STZ-induced diabetic rats, curcumin modulated the oxidatively modified DNA (8-OHdG), glutathione, SODC, and inflammatory parameters, including IL-1β, TNF-α, VEGF, and NF-κB, and may also inhibit the activation of nucleotide excision repair enzymes (Gupta *et al.* 2011).

Alzheimer's disease and curcumin

Alzheimer's disease (AD) is the most spreading neurodegenerative disorder in the aged people linked with a progressive loss of neurons from the brain. The development of neurofibrillary tangles and senile plaques in susceptible brain parts from the two neuropathological markers is responsible for AD (Citron 2002, 2004). The senile plaques (β-amyloid peptide) are formed from amyloid precursor protein (APP) through β- and γ-secretases. It is the abnormal proteolytic cleavage of APP which leads to an excess extraneuronal accumulation of Aβ that produce toxic effects in neurons as well as in glia (Cole *et al.* 2007; Baum *et al.* 2008). Due to its lipophilic nature, curcumin may cross the blood-brain barrier (BBB) and reach the brain. Due to its poor bioavailability, it is quickly metabolised through conjugation while an adequate concentration of curcumin reached in the brain can activate the signal transduction for lowering Aβ aggregation (Yang *et al.* 2005).

It inhibits transcriptional activities and signalling cascades (Narayan 2004). Thiyagarajan and Sharma (2004) investigated the neuroprotective effects of curcumin against cerebral ischemic injury in global and focal ischemia models in rats. After 30 min, oral administration of curcumin (0.2 g/kg) considerably lowered the I-R induced changes and reduced the infarct volume and oedema (BDNF) in the middle cerebral artery of rats. It also lowers the cognitive deficits and oxidative damage associated with aging as well as reduces the amyloid pathology in Alzheimer's disease (Wu *et al.* 2003; Ono *et al.* 2004; Thiyagarajan & Sharma 2004).

Recently, Reddy *et al.* (2016) have described the anticancer role of curcumin against human neuroblastoma (SHSY5Y) cells via enhancing the mitochondrial fusion activity, reducing fission machinery, and increasing biogenesis and synaptic proteins. It also elevated the mitochondrial function and cell viability (Reddy *et al.* 2016). β-amyloid (Aβ) containing plaques in the brain is responsible for the hallmark of Alzheimer's disease and serves as a biomarker for *post-mortem* confirmation of diagnosis. *In vitro*, bisdemethoxycurcumin (BDMC) showed the higher affinity to Aβ containing plaques in human cortical AD brain tissue. Subsequently, it showed significantly higher specific binding in cortical AD brain tissue (Veldman *et al.* 2016). Thapa *et al.* (2016) observed the neuroprotective effect of curcumin against human Aβ induced toxicity through modifying the Aβ aggregation pathway toward the formation of nontoxic aggregates and ameliorating Aβ-induced toxicity possibly through a nonspecific pathway (Thapa *et al.* 2016).

Hepatoprotective effects of curcumin

Liver damage is the replacement of normal hepatic tissue with the collagen-rich extracellular matrix that leads to cirrhosis. Carbon tetrachloride (CCl_4) is commonly used to induce an acute toxic liver injury in rats (Ramadori & Armbrust 2001). The inflammatory reaction occurred primarily due to TNF-α and interleukin-1β (IL-1β) and further, these cytokines can modulate the interleukin-6 (IL-6) effects (Simpson *et al.* 1997). They increase the levels of TNF-α and IL-1β in mice that cause the liver injury (Weber 2003; Oakley *et al.* 2005). The cytokines, i.e. IL-1β and TNF-α, promote the NF-κB activation that enhances the production of IL-1β and TNF-α and modifies the hepatocyte structure (Neuman 2003). Curcumin exerts beneficial effects on liver injury and cirrhosis through suppressing the IL-1β and TNF-α cytokines (Bruck *et al.* 2007).

Additionally, administration of curcumin exhibits positive effects on different inflammatory conditions by modulating the NF-κB activity (Oakley *et al.* 2005). Hepatic stellate cells (HSCs) have a significant role in the progression of fibrosis. In HSCs,

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curcumin exhibits anti-oxidative, antifibrogenic, anti-inflammatory, and anti-proliferative properties (Elsharkawy *et al.* 2005). The previous findings of Bruck *et al.* (2007) indicated that curcumin suppressed the hepatic fibrosis in rats through inhibiting collagen a1 (I) gene expression and HSC activation and lowered the oxidative stress. It also prevents from the formation of the extracellular matrix through suppressing a smooth muscle actin, collagen a1, and fibronectin (I). Curcumin increases the matrix metalloproteinase-2 and -9 expressions and inhibits the connective tissue growth factor (CTGF) expression (Xu *et al.* 2003b). Numerous intracellular signalling pathways, i.e. JNK, PPAR-g, AP-1, ERK, and NF-κB, are modulated by the administration of curcumin in HSCs cells (Zheng *et al.* 2007). Curcumin also activates the PPAR-g through inhibiting the NF-κB activity in HSCs (Park *et al.* 2000). Moreover, curcumin also inhibits CTGF expression in HSCs through suppressing the activation of ERK, MAP kinase, and NF-κB (Hsu & Cheng 2007).

Hepatotoxicity in humans which is induced by heavy metals such as cadmium, arsenic, copper, chromium, lead and mercury, caused histological injury, lipid peroxidation and glutathione (GSH) depletion. On the other side, curcumin protected from lipid peroxidation, depletion of antioxidant enzymes, and mitochondrial dysfunction. It has also the ability to scavenge the free radicals, and induce the Nrf2/Keap1/ARE pathway (Singh *et al.* 2012; García-Niño & Pedraza-Chaverrí 2014).

Antidepressant activity of curcumin

Depression is a debilitating psychiatric and proliferating health problem worldwide. There are several antidepressants such as specific serotonin-noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and selective reversible inhibitors of monoamine oxidase (RIMAs). These antidepressant drugs are used to curtail the depression symptoms along with their side effects (Luo *et al.* 2000). Curcumin as a safer drug is used effectively to curtail depression via attenuating the activity of C6 glial cells monoamine oxidase (MAO). It possesses the antidepressant effects in olfactory bulbectomy of mice (Xu *et al.* 2005b).

Generally, inhibitors of the monoamine oxidase enzyme enhance the content of neuronal monoamines that are associated with enhancing monoaminergic activity (Dar & Khatoon 2000). Monoamine oxidase is present on the outer membrane of mitochondria of the body's cells, and exists in two forms such as MAO-A and MAO-B and is involved in catalysing the oxidation of monoamines (Kulkarni *et al.* 2008). Xu *et al.* (2005a) demonstrated that curcumin has a potential to enhance the levels of brain-derived neurotrophic factor (BDNF) in rats. In another study conducted by Xu *et al.* (2005a) it was stated that curcumin (10–20 mg/kg) increased the hippocampal neurogenesis in stressed mice. It also prevented from the stress-induced decrease in serotonin 5-HT1A mRNA and BDNF protein levels in the hippocampus. Likewise, curcumin reverses the chronic stress-induced reduction in BDNF protein levels (Xu *et al.* 2006).

In an *in vitro* study, Wang *et al.* (2008b) determined that curcumin also reversed the glutamate-induced decrease in BDNF levels of cultured rat cortical neurons. It inhibits the cyclooxygenase-2 (COX-2) isoenzyme and transcription of NF-κB. It reduces the release of inflammatory NO through blocking the synthesis of inducible nitric oxide synthase (NOS) enzyme (Chan *et al.* 1998b; Lim *et al.* 2001).

Monoamine oxidase (MAO) enzyme is involved in catalysing the oxidation of monoamines. It exists in two isoforms, MAO-A and MAO-B. Curcumin is an inhibitor of monoamine oxidase (MAO) enzyme. MAO-B is the predominant form of the enzyme in the human brain and oxidizes dopamine, whereas norepinephrine and serotonin are the preferred substrates for MAO-A. Interestingly, curcumin possesses both MAO-A and MAO-B inhibiting properties (Kulkarni *et al.* 2008). In previous findings of Xu *et al.* (2005b) they investigated that curcumin modulated the level of dopamine, norepinephrine, and serotonin in the brain. These neurotransmitters are involved in various activities such as emotions, attentiveness, learning, sleeping, pleasure, locomotion, sleep, appetite, memory, temperature regulation, muscle contraction, cardiovascular functions, and endocrine regulation. Curcumin promotes hippocampal neurogenesis and has an ability to enhance the levels of brain-derived neurotrophic factor (BDNF). Xu and their colleagues determined that curcumin administration (10–20 mg/kg) increased the hippocampal neurogenesis in stressed animals (Xu *et al.* 2007a). Moreover, curcumin also reverses the glutamate-induced decrease in BDNF levels *in vitro* in cultured rat cortical neurons (Wang *et al.* 2008b).

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Curcumin enhanced wound healing

From prehistoric times, wounds have affected humans and the healing of wounds is an art as old as humanity. Chronic wounds increasingly affect the elderly patients and seriously reduce their quality of life (Kumar *et al.* 2005). Non-phagocytic cells also produce the free radicals due to the NADPH oxidase mechanism in wounded cells (Hunt *et al.* 2000). Transforming growth factor (TGF-β1) stimulates the expression of collagen and fibronectin by fibroblasts in wound healing and enhances the granulation tissue formation rate (Quaglino *et al.* 1990).

Curcumin treatment enhanced the formation of granulation tissue through increasing collagen and fibronectin (FN) expressions that led to greater neo-vascularisation, cellular content and faster re-epithelialisation through regulating the expression of nitric oxide synthase, TGF-β1, and its receptors of wound in hyperglycaemic rats (Mani *et al.* 2002). Additionally, in an *in vivo* study curcumin improves the muscle regeneration through modulating the NF-κB activity during trauma (Thaloor *et al.* 1999). Curcumin suppresses the hydrogen peroxide in human fibroblasts and keratinocytes. It also neutralises the activity of free radicals and inhibits cell proliferation in curcumin-treated rats (Gopinath *et al.* 2004). Likewise, it also increases the synthesis of hexosamine, collagen, nitrite, DNA, and histologic determination of wound biopsy specimens that improves the collagen deposition and also enhances in fibroblast (Jagetia & Rajanikant 2005). Phan *et al.* (2001) determined that the oral dose of curcumin (2.5 μg/ml) showed the significant protective effect against H_2O_2 to human dermal fibroblasts.

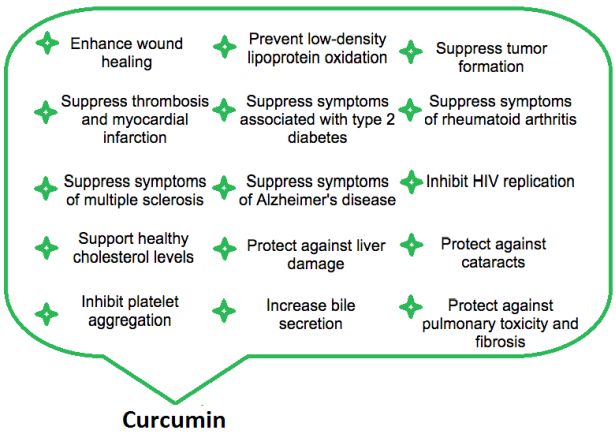

Figure 4. Health effects of curcumin

Lee (2006) reported that curcumin has an inhibitory effect on platelet aggregation induced by collagen and arachidonic acid. In addition, Mayanglambam *et al.* (2010) observed that curcumin also suppressed the platelet aggregation and dense granule secretion induced by GPVI agonists via interfering with the kinase activity of Syk (spleen tyrosine kinase) and subsequent activation of PLCγ2.

Antiplatelet effect of curcumin

Curcumin prevents from the platelet aggregation through suppressing platelet-activating factor (PAF), ADP, epinephrine mediated platelet aggregation, collagen, and arachidonic acid (AA). Administration of curcumin (20–25 μM) inhibited the AA and PAF mediated platelet aggregation (Kim *et al.* 2003; Lim *et al.* 2004). It also mediates the AA-induced platelet aggregation and preferential inhibition of PAF showed suppressing effects on Ca^{2+} signalling and TXA2 synthesis (Srivastava *et al.* 1995).

Curcumin against osteoprosis, osteoarthritis and skin disease

Osteoporosis is a complex process that is closely associated with the sequence of osteoclast-mediated bone resorption and osteoblast-mediated bone formation (Hussan *et al.* 2012). These unbalanced sequences decrease the bone mass and develop the bone disease, i.e. osteoporosis (Raisz 2005). Curcumin effectively controls the osteoclastogenesis through suppressing RANKL-induced osteoclastogenesis of rat monocyte-macrophage RAW264.7 cells (Suda *et al.* 1999). It induces the apoptosis in rabbit osteoclasts, and inhibits the RANKL signalling and ultimately suppresses the RANKL-induced osteoclastogenesis in RAW 264.7 cells (Ozaki *et al.* 2000; Bharti *et al.* 2004). Curcumin has the antiosteoclastogenesis activity via improving the bone microarchitecture and enhancing the mineral density in APP-PS1 transgenic rats (Yang *et al.* 2011).

Osteoarthritis (OA) is a chronic inflammatory disease and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat OA. NSAIDs suppress the prostaglandin synthesis through inhibiting COX-1 and COX-2 isoenzymes (Brooks 2002). Curcumin oral administration (0.03 mg/kg) for 14 days significantly prevented from paw inflammation in arthritic rats (Ammon & Wahl 1991).

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The findings of Goel *et al.* (2001) illustrated that curcumin suppressed the COX-2 expression and also decreased the cellular protein kinases (JNK, protein kinase C), human epidermal growth factor receptors EGFR and ErbB-2 and epidermal growth factor at the transcriptional level. Kim *et al.* (2003) determined that curcumin inhibited the NF-κB activation and hindered the c-jJun-AP-1 function. It also decreases the expression of IL-6 and IL-8 pro-inflammatory cytokines in human keratinocytes (Pol *et al.* 2003).

Curcumin plays a major role against different pro-inflammatory factors STAT3, NF-κB, and TNF that are involved in the skin disease psoriasis (Liu *et al.* 2006; Vamvouris & Hadi 2006; Abdou & Hanout 2008). Supplementation of curcumin lowered the density of CD8 + T-cells and PK levels in a psoriatic model as compared to control rats (Heng *et al.* 2000). Similarly, it also suppresses the keratinocyte proliferation and prevents from the psoriasis activity to rats (Pol *et al.* 2003; Kurd *et al.* 2008). The scleroderma is characterised by aberrations of extracellular matrix deposition, visceral fibrosis, and produced changes such as cellular and humoral immune abnormalities in the microvasculature. Curcumin suppresses the lung fibroblasts through the suppression of protein kinase C (PKC) epsilon (Tourkina *et al.* 2004). It induces apoptosis in scleroderma lung fibroblasts (SLFs) of rats, and this effect is linked with the expression of PKC epsilon (Xu *et al.* 2007a).

Miscellaneous properties of curcumin

Curcumin induces the heat-shock (HS) response and suppresses proteasome activity in HeLa cells of Swiss 3T3 mouse fibroblasts (Jana *et al.* 2004). Proteasome inhibition induced the HS response of mammalian cells in two ways: (1) suppression of the proteasome through curcumin concentrations up to 50 μM, (2) low levels of curcumin (up to 1 μM) produced an inhibitory effect on proteasome activity of human keratinocytes (Joe *et al.* 2004). It also showed proteasome activity in telomerase-immortalised mesenchymal bone marrow stem cells and human fibroblasts (Pandya *et al.* 2000; Padmaja & Raju 2004).

Haem oxygenase-1 (HO-1) is a redox-sensitive inducible stress protein that converts haem to iron, CO, and biliverdin (Motterlini *et al.* 2000; Motterlini *et al.* 2002). This protein plays an imperative role in haem oxygenase products which are linked with moderate cellular stress. Scapagnini *et al.* (2002) observed that curcumin is a potent inducer of HO-1 in neuronal cells and vascular endothelial cells. It increases endothelial HO-1 expression and thus protects cells against free radicals under severe hypoxic conditions (Asai & Miyazawa 2001). Curcumin stimulates the expression of Nrf2 by increasing the redox sensitive inducible protein HO-1 expression and HO-1 activity (Balogun *et al.* 2003). It induces changes in the human sperm mitochondrial transmembrane potential (MTP) and interferes with sperm energy metabolism. In another study, Balasubramanyam *et al.* (2004) determined that treatment with curcumin produced alterations in MTP that considerably inhibited the human sperm motility.

Curcumin inhibits the human immunodeficiency virus (HIV) replication through suppressing HIV long terminal repeats, HIV protease, HIV-1 integrase, repression of the acetylation of histone-non-histone proteins, histone acetyltransferase dependent chromatin transcription, and p300-CREB-binding protein-specific acetyltransferase (Vajragupta *et al.* 2005).

Long-term oral administration of curcumin to rats led to the hypoproliferation of thyroid epithelial cells, and also neutralised the hypothyroidism associated with aging of the thyroid gland in *in vitro* and in *in vivo* studies (Ferreira *et al.* 2000; Kim *et al.* 2003; Biswas *et al.* 2005). It also lowers the lymphocytes infiltrating the thyroid gland in rats through inhibiting the synthesis of TNF-α, IFN-γ, and leucotriens (Chan *et al.* 1998). Curcumin also suppresses the induction of iNOS and COX-2 (Brouet & Ohshima 1995).

It is a potent inhibitor of TGF-band fibrogenesis and considerably prevents from the fibrotic diseases in liver, intestine, kidneys, and body cavities (Chang 2001). The administration of curcumin at 0.2 g/kg body weight considerably suppressed the myeloperoxidase (MPO) activity, infiltration of eosinophils, phorbol myristate acetate (PMA)-stimulated superoxide generation, lipopolysaccharide-stimulated TNF-α release, TGF-β activity, lactate dehydrogenase (LDH) activity, macrophages and neutrophils in the lung tissue, c-Jun protein, expression of type I collagen and lung hydroxyproline content of rats (Illek *et al.* 2000). Curcumin inhibits a calcium pump in the endoplasmic reticulum through lowering the calcium concentration that releases the mutant cystic fibrosis transmembrane conductance regulator (CFTR) gene and enhances its odds of reaching the cell surface (Zeitlin *et al.* 2004).

The findings of Liao *et al.* (2001) illustrated that oral supplementation of water extracts of curcumin also exhibited 100% anti-fertility activity in mice

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through inhibiting 5α-reductase and growth of flank organs. It also suppresses the human sperm motility and develops the novel intravaginal contraceptive (Rithaporn *et al.* 2003). Curcumin neutralises both the 70% lethal effect of Crotalus venom and haemorrhagic activity of Bothrops venom in rats (Araujo & Leon 2001).

Bronchial asthma is one of the most chronic inflammatory diseases that are associated with eosinophilia, mass cell infiltration, and goblet cell hyperplasia. Curcumin controls the allergic diseases through dose-dependently suppressing GM-CSF, IL-4, and IL-5 production and inhibiting cytokine production that affect IgE synthesis, and eosinophil function (Ram *et al.* 2003). Additionally, it considerably suppresses the airway hyperreactivity, and OVA-induced airway constriction (Yeon *et al.* 2010).

Dose and safety

The amount of curcumin up to 12 g/day is better tolerated in humans. Curcumin has low bioavailability due to the first pass metabolism, low gastrointestinal absorption, poor aqueous solubility and rapid elimination (Cheng *et al.* 2001; Anand *et al.* 2007; Sharma *et al.* 2007). During the incubation of curcumin with rat liver microsomes, glucuronidation of curcumin is done on the phenolic hydroxyl group. This glucuronidation gives a lipophilic conjugate that is less stable than its unconjugated form and is excreted through the stool (Pfeiffer *et al.* 2007; Sharma *et al.* 2007). Tetrahydrocurcumin (THC) has a lower ability to inhibit NF-κB than curcumin, whereas it has a higher antioxidant potential than curcumin (Okada *et al.* 2001; Naito *et al.* 2002). Cheng *et al.* (2001) determined the plasma concentration peak at 1–2 h but undetectable at 12 h after oral supplementation of curcumin. Sharma *et al.* (2004) investigated the curcumin not only in plasma, but also in urine, at lower concentrations, whereas curcumin in serum is undetectable below oral doses of 4 grams. Vareed *et al.* (2008) determined that glucuronides are curcumin conjugates produced by human metabolism and detectable in plasma at higher concentrations than free curcumin with a peak at 4 h after oral dosing. The considered safe dose of dietary spice has been consumed up to 0.01 g/day for centuries. The human consumption of curcumin is up to 12 g/day having no side effects. Kurien *et al.* (2007) determined that heat treatment improved the water solubility of curcumin. Sharma *et al.* (2004) explored the minor side effects of curcumin namely diarrhoea and it is considered safe and well tolerated.

CONCLUSION

Turmeric has been used to increase the preservation and palatability of food moieties as well as to improve the storage condition. It consists of three analogues of curcumin, i.e. diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin (diferuoyl methane) was found to be the most potent, whilst in some cases bisdemethoxycurcumin was found to exhibit higher antioxidant activity. Researchers and scientists have reported that the mixture of all three components is more potent than either one alone. Nevertheless, systemically or intraperitoneally administered curcumin is metabolised into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. Curcumin has many pharmacological properties such as inhibiting the tumorigenesis, inflammation, antidepressant, diabetes, cardiovascular, and neurological activities.

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