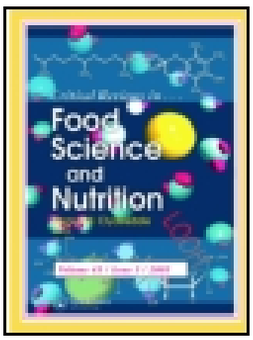

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

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Cellular and molecular mechanisms of curcumin in prevention and treatment of disease

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ABSTRACT

Curcumin is a naturally occurring polyphenolic compound present in rhizome of *Curcuma longa* belonging to the family zingiberaceae. Growing experimental evidence revealed that curcumin exhibit multitarget biological implications signifying its crucial role in health and disease. The current review highlights the recent progress and mechanisms underlying the wide range of pharmacological effects of curcumin against numerous diseases like neuronal, cardiovascular, metabolic, kidney, endocrine, skin, respiratory, infectious, gastrointestinal diseases and cancer. The ability of curcumin to modulate the functions of multiple signal transductions are linked with attenuation of acute and chronic diseases. Numerous preclinical and clinical studies have revealed that curcumin modulates several molecules in cell signal transduction pathway including PI3K, Akt, mTOR, ERK5, AP-1, TGF-β, Wnt, β-catenin, Shh, PAK1, Rac1, STAT3, PPARγ, EBPα, NLRP3 inflammasome, p38MAPK, Nrf2, Notch-1, AMPK, TLR-4 and MyD-88. Curcumin has a potential to prevent and/or manage various diseases due to its anti-inflammatory, anti-oxidant and anti-apoptotic properties with an excellent safety profile. In contrast, the anti-cancer effects of curcumin are reflected due to induction of growth arrest and apoptosis in various premalignant and malignant cells. This review also carefully emphasized the pharmacokinetics of curcumin and its interaction with other drugs. Clinical studies have shown that curcumin is safe at the doses of 12 g/day but exhibits poor systemic bioavailability. The use of adjuvant like piperine, liposomal curcumin, curcumin nanoparticles and curcumin phospholipid complex has shown enhanced bioavailability and therapeutic potential. Further studies are warranted to prove the potential of curcumin against various ailments.

KEYWORDS

Curcumin; mechanism of action; therapeutic use; pharmacokinetic; clinical trials; drug interaction

Introduction

Curcuma longa, also called as turmeric, is native to South Asia, Indonesia and India (Perrone et al. 2015). Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] (Figure 1), also known diferuloylmethane, is biologically active natural polyphenol derived from the rhizome of *C. longa* (Zingiberaceae family) (Pulido-Moran et al. 2016). *C. longa* is known by various synonyms based on its use and appearance, like Pita (leading to the name Lord Krishna based on wearing only the yellow clothes), Nisha (beautiful as a full moon night), Kanchani (looks like the gold), Gauri (brilliant), Mahaghni (antidiabetic), Krimighni (antihelmenthic and antibacterial) and Yoshit priya (gynecological disorders). In India, turmeric is commonly known as Haldi, in Korea as Gangwhang or Ulgeum and in Japanese as Gajyutsu or Ukon (Aggarwal, Surh, and Shishodia 2007). It is soluble in extremely acidic solvents or in alkali (Rao and Sudheer 2011). It is crystalline in nature with a bright orange-yellow color, hence used as colorant for food (Lestari and Indrayanto 2014). Curcumin is known to reverse various ailments of the nervous system, cardiovascular system, digestive system, respiratory system, endocrine system, renal system, etc (Figure 2). According to recent and well-designed clinical study, consumption of curcumin exerts beneficial effect against metabolic syndrome, skin diseases, cancer, gut inflammation, depression, arthritis, fatty liver disease and premenstrual syndrome (Mantzorou et al. 2018). Furthermore, the anti-inflammatory and antioxidant potential of curcumin supplementation for its beneficial effect against arthritis and metabolic syndrome has been reviewed (Hewlings and Kalman 2017). No major toxicity was reported upon oral curcumin administration, however some gastrointestinal upsets on record (Soleimani, Sahebkar, and Hosseinzadeh 2018). In the present review, the therapeutic potential of curcumin in clinical and preclinical studies with its mode of action has been summarized. In addition, the synergy, pharmacokinetics, clinical trials, safety and tolerability of curcumin has also been discussed.

Molecular targets of curcumin

Curcumin is known to interact with wide range of molecular targets and exert therapeutic potential against various ailments (Zhou, Beevers, and Huang 2011; Lin 2007) (Table

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1). Curcumin has been reported to bind directly to signaling molecules, such as carrier proteins, DNA methyltransferases 1, xanthine oxidase, human immunodeficiency virus (HIV)-1 integrase, filamenting temperature-sensitive mutant Z (FtsZ) protofilaments, glyoxalase I, proteasome, histone deacetylase, histone acetyltransferase, cell survival proteins, HIV-1 protease, protein reductases, protein kinases, inflammatory molecules and metal ions (Gupta et al. 2011). Curcumin treatment modulated β-secretase 1 (BACE-1), acetylcholinesterase (AChE) activity, chemokines, toll-like receptor (TLR), cyclooxygenase (COX), brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), c-Jun N-terminal kinase (JNK), insulin receptor substrate-1 (IRS-1), inhibitor of NF-kB (IkB), glutathione-S-transferase, endothelial haeme oxygenase-1 (HO-1), extracellular receptor kinases (ERKs), low density lipoprotein-receptor (LDL-R), activator protein 1 (AP-1), peroxisome proliferator-activated receptor-gamma (PPAR-γ), liver X receptor-β (LXR-β), retinoid X receptor (RXR)-α, c-Jun and tumor necrosis factor alpha (TNF-α) (Ray and Lahiri 2009; Hamaguchi, Ono, and Yamada 2010; Farooqui 2013; Tian et al. 2013). Curcumin treatment is reported to exert its beneficial effect through various kinases such as focal adhesion kinase (FAK), acid activated protein kinase C (AAPK), epidermal growth factor receptor-kinase (EGFRK), protein tyrosine kinase (PTK), mitogen-activated protein kinase (MAPK), protein kinase A (PKA), protein kinase B (PKB), ERK, p21-activated kinase (PAK), janus kinase (JAK), interleukin (IL)-1, Rak and pp60C-TK. Curcumin also demonstrates significant action *via* growth factors like fibroblast growth factor (FGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF). Cytokines such as IL-1β, IL-1, IL-6, IL-8, IL-12, TNF-α and monocyte chemoattractant protein-1 (MCP-1), and several transcription factors like nuclear factor kappa B (NF-kB), Ap-1, Notch-1, CREB-binding protein (CREB-BP), early growth response-1 (Egr-1), Wilms' tumor gene 1 (WT-1), β-catenin, hypoxia-inducible factor-1 (HIF-1), nuclear factor 2-related factor (Nrf-2) and estrogen response element (ERE) are also the molecular targets of curcumin (Kunnumakkara et al. 2017; Derosa et al. 2016; Sahebkar et al. 2016). Curcumin exerts beneficial effects through various receptor such as integrin receptor (IR), Fas receptor (Fas-R), EGFR, HER-2, IL-8R, C-X-C chemokine receptor type 4 (CXCR4), estrogen receptor-alpha (ER-α), endothelial cell protein C receptor, histamine (2)-receptor (H2R), LDL-R, androgen receptor (AR) and DR-5 (Kunnumakkara et al. 2017; Mehanny et al. 2016).

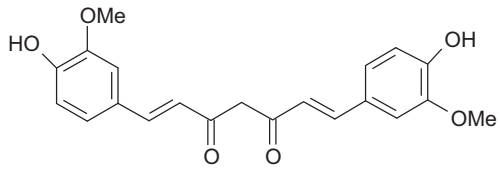

Figure 1. Chemical structure of curcumin.

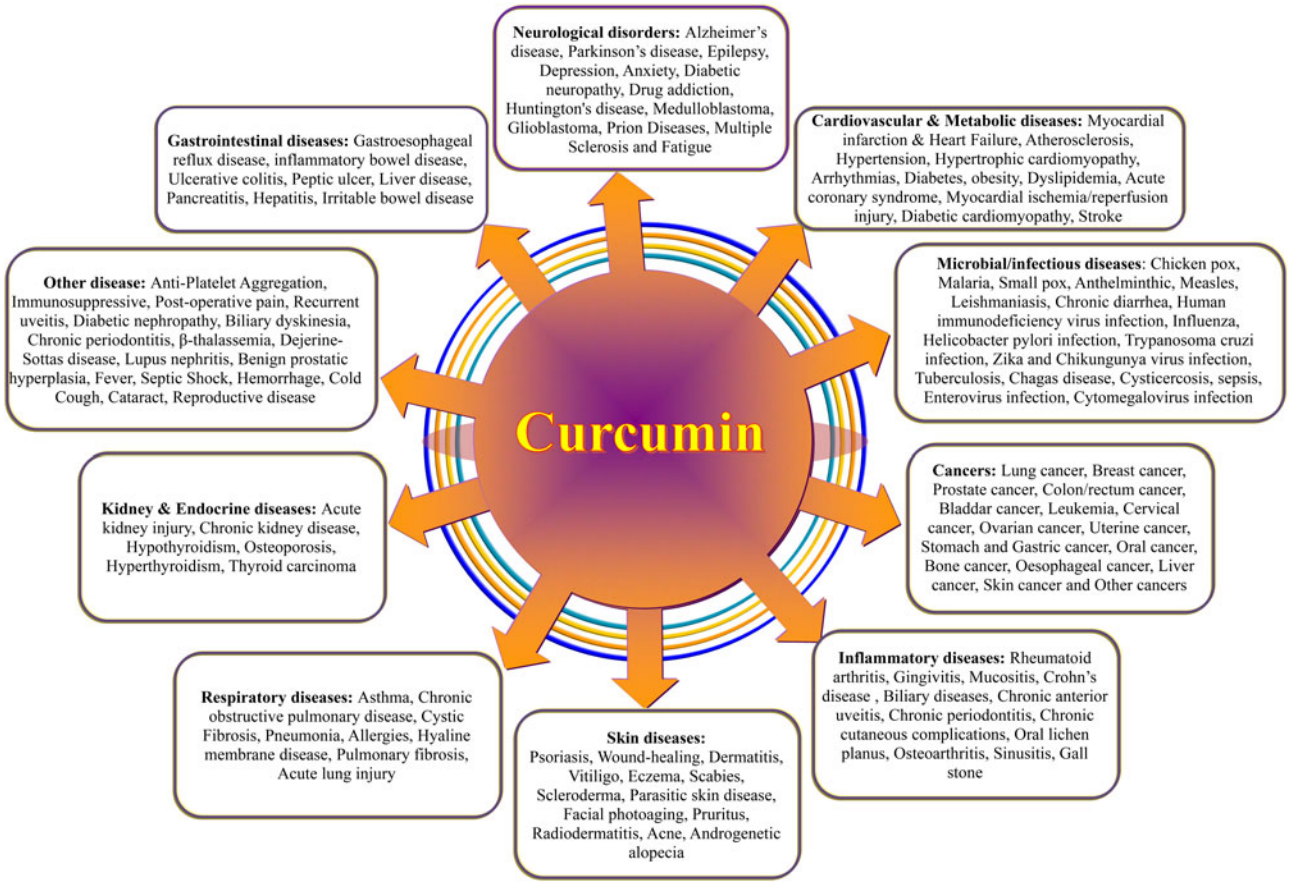

Figure 2. Multiple biological activities of curcumin.

Table 1. Cellular, molecular and biochemical mechanism of curcumin.

Diseases	Mechanism of curcumin at cellular, biochemical and molecular level	References
Alzheimer's disease	↑ABCA1 and ↑apolipoprotein A1 (apoA-1), ↑adult neurogenesis, ↑bditTLR4, ↑bditTLR7, ↑BDNF, ↑endothelial HO-1 gene, ↑glutathione-S-transferase activity, ↑LDL-R, ↑LXR-β, ↑monoacylglycerol acyltransferase-3, ↑microglial labeling, ↑NMDA(2B), ↑p-CaMKII, ↑p-NMDAR1, ↑PPAR-γ, ↑postsynaptic density-95 (PSD-95), ↑p-TrkB, ↑RXR-α, ↑SOD activity, ↑synaptic transmission, ↑TLR10, ↑TLR3, ↑TLR5, ↑TLR8, ↑TLR9, ↓A11-positive oligomers, ↓AChE activity, ↓AP-1, ↓apoptosis, ↓APP and BACE-1, ↓Aβ40, ↓Aβ42, ↓caspase-3, ↓caspase-8, ↓chemokines (IL-8, MCP-1 and MIP-1β), ↓c-Jun, ↓Cox-2, ↓Egr-1, ↓eicosanoids, ↓glial fibrillary acidic protein, ↓IkB phosphorylation, ↓IL-1β, ↓iNOS, ↓inflammation, ↓IRS-1, ↓JNK, ↓microglial activation, ↓NFκB, ↓NO, ↓oxidative damage, ↓oxidative stress, ↓phosphorylated tau, ↓phosphorylation of ERKs, ↓ROS, ↓serum cholesterol, ↓secretory phospholipase A 2, ↓synaptophysin loss, ↓TNF-α and ↓β-secretase	Ray and Lahiri 2009; Hamaguchi, Ono, and Yamada 2010; Farooqui 2013; Tian et al. 2013
Parkinson's disease	↑Bcl-2, ↑Bcl-xL, ↑Cu/Zn SOD, ↑dopamine and DOPAC levels, ↑gamma glutamyl cysteine ligase levels, ↑macroautophagy induction, ↑Nrf2/ARE pathway, ↓AP-1 pathway, ↓caspase 3, ↓iNOS, ↓apoptosis, ↓c-Jun phosphorylation, ↓cytochrome c release, ↓DNA damage, ↓GSH depletion, ↓hepcidin levels, ↓IkB kinases 1 and 2, ↓IL-6, ↓JNK phosphorylation, ↓LPO, ↓mitochondrial complex I, ↓mitochondrial depolarization, ↓mitochondrial dysfunction, ↓mTOR/p70S6K signaling, ↓neuroinflammation, ↓NFκB activation, ↓nitrosative stress, ↓oxidative stress, ↓proteasome inhibition, ↓protein aggregation, ↓ROS, ↓SOD and CAT, ↓STAT3 pathway, ↓synphilin-1 aggregation, ↓TNF- α and ↓α-synuclein	Jiang et al. 2013; Mythri and Srinivas Bharath 2012
Depression and anxiety	↑5-hydroxytryptamine (5-HT) 1A receptor, ↑5-HT4 receptor, ↑5-hydroxyindoleacetic acid, ↑AC (2 & 8) activity, ↑BDNF, ↑cAMP, ↑CAT, ↑dopamine, ↓serum corticotropin-releasing factor, ↑GSH, ↑HSP70, ↑MAPK, ↑noradrenaline, ↑p-ERK, ↑PI3K, ↑PSD-95, ↑serotonin, ↑synaptophysin, ↑TrkB, ↓corticosterone levels in serum, ↓COX-2, ↓hippocampal cell death, ↓hypothalamic-pituitary-adrenal axis (HPA axis) activity, ↓IL-1β, ↓IL-6, ↓iNOS, ↓LPO, ↓LOX, ↓long-term depression (LTD), ↓MAO-A/B, ↓MDA, ↓neurodegeneration, ↓neuroinflammation, ↓neurosteroids, ↓NFκB, ↓nitrite level, ↓nitrosative stress, ↓iNOS, ↓ROS, ↓TNF-α and ↓reactive nitrogen species (RNS)	Farooqui 2013; Lopresti 2017
Cardiovascular diseases	↑Akt, ↑Bcl-2, ↑cathepsin, ↑connexin 43, ↑ERK1/2, ↑GSH, ↑HDL cholesterol, ↑HO-1, ↑HSP27, ↑JAK/STAT3, ↑NO-cGMP axis, ↑PI3K, ↑SIRT1, ↑SOD, ↓AdBMP2-induced expression of HAT p300, ↓angiotensin II type 1 receptor, ↓apoptosis, ↓calcineurin, ↓cardiac hypertrophy, ↓cardiac troponin I, ↓caspase-3, ↓collagen deposition, ↓extracellular matrix remodeling, ↓Egr-1, ↓GATA4 and myocyte enhancer factor-2c overexpression, ↓gelatinase B expression, ↓GSK-3β, ↓H_2O_2, ↓histone acetylation, ↓histone H3 acetylation, ↓IL-1, ↓IL-6, ↓IL-8, ↓JNK, ↓LDL receptor-1, ↓macrophages and inflammation, ↓MAPK pathway, ↓MDA, ↓misfolding of L325R channels, ↓MMP-2, ↓MMP-9, ↓myocardial dysfunction, ↓NAD(P)H oxidase, ↓NF-kB, ↓Nkx2.5, ↓PARP, ↓p-cAMP-dependent kinases, ↓pERK, ↓release of lysosomal enzymes, ↓ROS, ↓TGF-β, ↓TNF-α, ↓total serum cholesterol, ↓TRL2, ↓ventricular fibrillation, ↓ventricular premature beats, ↓ventricular tachycardia and ↓β-catenin expression	Wongcharoen and Phrommintikul 2009; Jiang et al. 2017
Metabolic diseases	↑adiponectin, ↑Akt, ↑AMP-activated protein kinase (AMPK), ↑CAT, ↑erythrocyte antioxidants, ↑GLUT4, ↑glutathione reductase, ↑glycogen storage, ↑GPx, ↑GSH, ↑GST, ↑HDL, ↑hepatic glycerol kinase activity, ↑hepatic glycogen, ↑HO-1 expression, ↑HOMA-β, ↑insulin signaling, ↑IRS-1, ↑N-acetyl-β-D-glucosaminidase, ↑NADPH/NADP ratio, ↑Nrf2 activation, ↑plasma insulin, ↑PPAR-γ, ↑skeletal muscle lipoprotein lipase, ↑SOD, ↑transcription factor 7-like 2, ↑visfatin, ↓acyl-CoA-cholesterol acyltransferase, ↓blood glucose, ↓cholesterol, ↓COX-2, ↓C-peptide, ↓damage of pancreatic islets, ↓gluconeogenic enzyme activity, ↓glucose-6-phosphatase, ↓HbA1c, ↓HMG CoA reductase activity, ↓HOMA-IR, ↓ICAM-1, ↓IL-6, ↓insulin resistance, ↓LDL, ↓leptin, ↓LOX-1, ↓MCP-1 release, ↓mitochondria dysfunction, ↓NF-kB, ↓nitric oxide, ↓oral glucose tolerance test (OGTT), ↓oxidative stress, ↓phosphoenolpyruvate carboxykinase, ↓PKA, ↓PKC activity, ↓plasma free fatty acid, ↓protein carbonyls, ↓protein-tyrosine phosphatase-1β, ↓resistin, ↓sorbitol dehydrogenase, ↓T- and B-lymphocytes activity, ↓TBARS, ↓TGF- β1 expression, ↓TNF-α, ↓triglyceride levels, ↓urinary MDA, ↓urine volume and ↓VEGF	Pulido-Moran et al. 2016; Zhang et al. 2013b; Jiménez-Osorio, Monroy, and Alavez 2016; Blaslov 2017
Liver disease	↓Akt, ↓albumin, ↓alkaline phosphatase, ↓ALT, ↓AP-1 proteins, ↓AST, ↓CDKs, ↓c-fos, ↓c-jun, ↓c-myc, ↓COX-1, ↓EGF-receptor tyrosine kinase, ↓ELK, ↓ERK, ↓ERK1/2 pathway, ↑GSH, ↑HO-1, ↓growth factor receptors, ↓IKK IkB kinase (IKK) β, ↓ILs, ↓iNOS, ↓inflammation, ↓JNK MAPK, ↓LPO, ↓LOX, ↓MAPKs, ↓metalloprotease-1, ↓NF-kB activation, ↓NIK, ↓PGD2, ↓PGE1, ↓PGE2, ↓PGF2α, ↓phospholipase 2, ↓PI3K, ↓PKC, ↓ROS, ↑SOD, ↓TBARS, ↓TGF-β, ↓TNF-α, ↓xanthine dehydrogenase and ↓xanthine oxidase	Pulido-Moran et al. 2016; Nabavi et al. 2014; Rivera-Espinoza and Muriel 2009; Liang et al. 2017
Ulcerative colitis	↓AP-1, ↑carbonic anhydrase, ↓COX-2, ↓ERK, ↓IFN-γ, ↓IL (1α, 1β, 2, 6, 12, 17, 23), ↓inflammatory cytokine, ↓iNOS, ↓LOX, ↓MPO, ↓NFkB activation, ↓p38	Baliga et al. 2012; Hanai and Sugimoto 2009; Yildirim et al. 2016

(*continued*)

Table 1. Continued.

Diseases	Mechanism of curcumin at cellular, biochemical and molecular level	References
	MAPK, ↓PGE2, ↓PGJ2, ↑PPAR-γ, ↓Th1 cytokine, ↑Th2 cytokine, ↓TLR-4 and ↓TNF-α	
Respiratory diseases	↑Cathepsins, ↑cystic fibrosis transmembrane conductance regulator, ↑collagenase, ↑elastase, ↑GSH, ↑HDAC2, ↑HO-1, ↑Nrf2/HO-1 pathway, ↑SOD, ↑surfactant protein D, ↑TIMPs, ↑Treg cells, ↓adhesion molecules, ↓alveolar edema, ↓AP-1, ↓calcitonin gene-related peptide, ↓COX-2, ↓C-reactive protein, ↓fibrosis, ↓glutathione S-transferase, ↓IL-1β, ↓IL-5, ↓IL-6, ↓IL-8, ↓inflammation, ↓inflammatory cells in bronchoalveolar lavage fluid, ↓iNOS, ↓interstitial fibrosis, ↓lipid peroxidation, ↓lymphocytes, ↓macrophage chemotactic protein-1, ↓macrophages, ↓MDA, ↓MMP-2, ↓MMP-9, ↓necrosis and alveolar hemorrhage, ↓neutrophils, ↓NF-kB, ↓oxidative stress, ↓ROS, ↓TGF- β/SMAD3 pathway, ↓TGF- β1, ↓T helper 17 cells and ↓TNF-α	Noorafshan and Ashkani-Esfahani 2013; Lelli, Pedone, and Sahebkar 2017
Cancer	↑8-hydroxy deoxyguanosine, ↑alkaline phosphatase (ALP), ↑apoptosis, ↑ATPase, ↑BAD, ↑Bcl-Xs, ↑caspase-3, ↑CHOP, ↑chromatin condensation, ↑cleavage of PARP, ↑cytochrome c, ↑cytotoxic effects, ↑DEF-40, ↑mitotic spindle structure disruption, ↑DR-5, ↑ERE, ↑glucose-6-phosphatase, ↑GPX, ↑GSH, ↑GST, ↑JNK, ↑micronucleation, ↑Nrf-2, ↑p53, ↑p53-dependent Bax expression, ↑PPAR-γ, ↑ROS, ↑TBARS, ↑TIMP-1, ↑ubiquitinated exosomal proteins, ↑mitochondrial membrane potential ($\Delta\Psi$m), ↓AAPK, ↓apoptosis antagonizing transcription factor-1, ↓ALT, ↓AP-1 activation, ↓AR, ↓aryl hydrocarbon receptor, ↓AST, ↓ATFase, ↓ATPase, ↓Bcl-2, ↓Bcl-XL, ↓β-FGF, ↓bilirubin, ↓capillary density, ↓capillary vascularity, ↓CD31, ↓Cdc2, ↓*c*-myc, ↓COX-1, ↓COX-2, ↓CREB-BP, ↓connective tissue growth factor, ↓CXCL, ↓CXCR-4, ↓cyclin D, ↓cyclin D1, ↓cytochrome P450 1A1, ↓DNA polymerase, ↓EGF, ↓EGFR, ↓EGFR-K, ↓endothelial leukocyte adhesion molecule-1 (ELAM-1), ↓endothelial protein C-receptor, ↓ERK, ↓ERK1/2, ↓ER-α, ↓FAK, ↓Fas R, ↓fibronectin migration, ↓farnesyl protein transferase, ↓glutamate-cysteine ligase, ↓gamma-glutamyl transpeptidase, ↓GlCL, ↓GST placental form, ↓H2R, ↓HAT, ↓HGF, ↓HIF1, ↓HSP-70, ↓hTERT, ↓inhibitory apoptosis protein (IAP)-1, ↓ICAM, ↓IL-1, ↓IL-12, ↓IL-2, ↓IL-5, ↓IL-6, ↓IL-8, ↓inhibition of IL-2-stimulated-NK cell activation, ↓iNOS, ↓invasion of cells, ↓IR, ↓ITR, ↓JAK, ↓Ki-67, ↓laminin migration, ↓LDLR, ↓LOX pathway, ↓MAPK, ↓MCP, ↓MDA, ↓MDRP, ↓migration of cell, ↓MIP, ↓MMP-2, ↓MMP-9 secretion, ↓NF-kB (p65), ↓NF-κB activation, ↓NGF, ↓notch1 intracellular domain 1, ↓Notch1 signaling, ↓p21^{ras}, ↓PAK, ↓proliferating cell nuclear antigen, ↓PDGF, ↓P-gp function, ↓PhP D, ↓PKB, ↓PTK, ↓Src-2, ↓STAT-1, ↓STAT-3, ↓STAT-4, ↓STAT-5, ↓phenol sulfotransferase, ↓telomerase activity, ↓TGF-β1, ↓TMMP-3, ↓TNF-α, ↓tyrosine kinase activity of p185neu, ↓uPA, ↓vascular cell adhesion molecule (VCAM), ↓VEGF, ↓WT-1, ↓β-catenin, ↓FGF, ↓ICAM-1 and ↓IL-1R	Anand et al. 2008; Darvesh, Aggarwal, and Bishayee 2012; Qadir, Naqvi, and Muhammad 2016; Panda et al. 2017
Urinary/kidney diseases	↓tubular fibrosis, ↓oxidative injury, ↓inflammation, ↓ischemic kidney injury, ↓snail-1, ↓ILs, ↓MMPs, ↑Mn-SOD, ↓cleaved caspase-1, ↓NLRP3, ↑Nrf2, ↑SphK1-S1P signaling pathway, ↓triglyceride accumulation, ↓PKC-α, ↓PKC-β1, ↑p38MPAK-HSP25 pathway, ↓Egr-1, ↓c-fos, ↓p-ERK, ↓p-MEK, ↓B-raf, ↓Ras, ↑Raf-1, ↑NGFI-A binding (NAB)-2, ↓TGF-β signaling, ↓MDA, ↑GPx, ↓fibronectin, ↓COX-2, ↓TNF-α, ↓NF-kappaB p65, ↓p22-phox and ↓p67-phox	Lu et al. 2017; Noorafshan and Ashkani-Esfahani 2013; Gao et al. 2011
Inflammatory diseases	↑Bcl-2, ↑JAK2/STAT3 pathway, ↑Treg cells, ↓acute phase proteins, ↓AP-1, ↓caspase-3, ↓COX-2, ↓cyclinD1, ↓eIF-2α dephosphorylation, ↓eosinophil peroxidase, ↓GATA3, ↓GATA4, ↓IL-10, ↓IL-1β, ↓IL-4, ↓IL-5 , ↓IL-6, ↓IL-8, ↓iNOS, ↓JNK/NF-kB, ↓Keap-1, ↓keratinocyte chemoattractant, ↓MCP-1, ↓MDA, ↓migration inhibition protein, ↓MIP-1α, ↓MIP-1β, ↓MIP-2, ↓mitochondrial dysfunction, ↓MMP-3, ↓MMP-8, ↓MMP-9, ↓MPO activity, ↓NO, ↓Notch1/2 receptors, ↓Nrf-2, ↓p300/CREB-specific acetyltransferase, ↓p300-HAT activity, ↓p-Akt, ↓p-ERK, ↓PI3K/Akt/NF-κB signaling, ↓p-JNK, ↓p-MAPK, ↓p-NF-kB, ↓p-p38, ↓p-PI3K, ↓p-PKC, ↓proteasome, ↓serum IgE, ↓TGF-β1, ↓TLR4, ↓TLR4-MAPK/NF-κB pathways, ↓TNF-α, ↓VCAM-1 and ↓VEGF	He et al. 2015c; Ghosh, Banerjee, and Sil 2015
Skin diseases	↑GST P1, ↑HO-1, ↑Nrf2 binding, ↑Nrf2/ARE pathway, ↑TGF-β1, ↑GF-β- induced factor, ↓density of epidermal CD8+ T cells, ↓endothelial cell growth supplement, ↓Egr-1, ↓GSH, ↓IFN-γ production, ↓IL-1β, ↓IL-6, ↓IL-8, ↓inflammation, ↓keratinocyte transferrin receptor, ↓MMP-2, ↓MMP-9, ↓parakeratosis, ↓protamine kinase (PK), ↓PKC δ, ↓proteasome activity and ↓protein oxidation	He et al. 2015c; Thangapazham, Sharma, and Maheshwari 2007; Goel et al. 2008
Microbial diseases	↑bacterial membrane damage, ↑disruption of folic acid metabolism, ↑IL-12, ↑IL-18, ↑IL-8, ↑p53 level, ↑p-IκB, ↑polymyxin B resistance protein genes, ↑PPAR-γ, ↑proinflammatory cytokines, ↑salmonella pathogenicity island (SPI) genes, ↑salmonella iron transporter and manganese transporter genes, ↑TNF-α, ↓Akt-SREBP-1 pathway, ↓AP-1, ↓bacterial assembly of FtsZ protofilaments, ↓bacterial cell division, ↓bacterial cell proliferation, ↓gut microbiota, ↓haemagglutination, ↓HBV replication, ↓HCV replication, ↓HIV-1 and HIV-2 proteases, ↓HIV-1 integrase, ↓HIV-1 LTR-directed gene expression, ↓HSV-1 replication, ↓IKK kinase, ↓JunD in HTLV-1-infected T-cell lines, ↓MMP-3 & 9, ↓penicillin-binding protein 2α expression, ↓Salmonella SPI-1 genes, ↓shikimate dehydrogenase, ↓Tat protein acetylation, ↓Tat-mediated transactivation of HIV-1 LTR, ↓transcription of HPV-18, ↓UPS dysregulation and ↓viral oncoproteins of E6 and E7	Marathe et al. 2011; Teow et al. 2016; Zorofchian Moghadamtousi et al. 2014

(*continued*)

Table 1. Continued.

Diseases	Mechanism of curcumin at cellular, biochemical and molecular level	References
Reproductive diseases	↑glucose-6-phosphate dehydrogenase, ↑GSH, ↑GPx activity, ↑plasma testosterone levels, ↑sperm count and viability, ↑sperm motility, ↑γ-GT, ↓dysmenorrhea, ↓leydig cells damage, ↓MDA, ↓morphologic defects, ↓NO, ↓oxytocin-induced uterine contraction, ↓premature labor and ↓spermatozoa defects	Noorafshan and Ashkani-Esfahani 2013

Curcumin is known to modulate various cellular signaling cascade like the phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR), ERK5/AP-1, TGF-β signaling, Wnt/β-catenin, PAK1/Ras-related C3 botulinum toxin substrate 1, TLR-4/MyD-88, signal transducers and activators of transcription (STAT) 3 pathway, PPARγ-C/EBPα pathway, nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome, p38MAPK etc (Shanmugam et al. 2015).

Role of curcumin in multiple diseases

Neurological disorders

Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by the presence of hyperphosphorylated tau protein in neurofibrillary tangles, selective neuronal loss, progressive memory and cognitive impairment (Campbell and Gowran 2007). The molecular pathogenesis of AD involves extracellular deposition of beta-amyloid (Aβ) peptides in the hippocampus and curcumin is known to reduce Alzheimer's pathology (Serafini et al. 2017) possibly due to its anti-aggregatory properties (Cole, Teter, and Frautschy 2007). In a clinical study, curcumin administration (1 or 4 g, 6 months trial) significantly increased the levels of antioxidant vitamin E without inducing any adverse events in patients with AD (Baum et al. 2008). In preclinical studies, curcumin is known to reduce Aβ oligomer and fibril formation (Yang et al. 2005; Xiong et al. 2011), inhibit the neurotoxicity of Aβ in the brain (Jiang et al. 2012; Sun, Zhao, and Hu 2013), suppress Aβ-induced inflammation (Lim et al. 2001; Lu et al. 2014) and markedly reduce the levels of IL-1β (Griffin et al. 2006) and inducible nitric oxide synthase (iNOS) (Begum et al. 2008) in transgenic mouse brain. Several studies demonstrated dose-dependent neuroprotective effect of curcumin against Aβ-induced toxicity. Curcumin exhibited anti-aggregatory effect against Aβ plaque formation by metal chelation (Huang et al. 2004; Tamagno et al. 2005), anti-oxidant effects (Hamaguchi et al. 2009), cholesterol lowering effects (Fassbender et al. 2001; Refolo et al. 2001), inhibition of presenilin-2 and/or by increasing degrading enzymes such as insulin-degrading enzyme and neprilysin (Wang et al. 2014). Curcumin potentiate heat shock proteins production in response to cellular stress, which protects neuronal cells from Aβ neurotoxicity and prevent Aβ aggregation and accumulation (Scapagnini et al. 2006; Ohtsuka and Suzuki 2000; Cummings et al. 2001). Curcumin ameliorates Aβ induced neurotoxicity through overexpression of histone deacetylase (HDAC2) and inhibition of Aβ-induced tau hyperphosphorylation involving phosphatase and tensin homolog (PTEN)/Akt/glycogen synthase kinase 3 (GSK-3) pathway and stimulating the protective Wnt/β-catenin pathway in human neuroblastoma SH-SY5Y cells (Huang et al. 2014). Due to various effects of curcumin, such as antioxidant, anti-inflammatory, metal-chelation, decreased β-amyloid plaques, Aβ oligomerization, tau phosphorylation, decreased microglia formation and delayed degradation of neurons, the overall memory dysfunction in Alzheimer's disease has improved (Hamaguchi, Ono, and Yamada 2010; Mishra and Palanivelu 2008).

Parkinson's disease

Parkinson's disease is a type of movement disorder associated with deficiency of brain neurotransmitter called dopamine. In animal study, chronic curcumin administration (50, 100 or 200 mg/kg, p.o., for 3 weeks) significantly ameliorated behavioral alterations like locomotor activity and motor-coordination in mouse model of Parkinson's disease. In the similar study, curcumin administration reduced oxidative damage and mitochondrial dysfunction in brain homogenate by reducing AChE activity. Curcumin administration decreased malondialdehyde (MDA) and nitrite while increased superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) levels in the brain homogenate of rotenone induced mouse model of Parkinson's disease (Khatri and Juvekar 2016). It has been demonstrated that curcumin administration alleviate motor dysfunction and increase tyrosine hydroxylase activity in rotenone induced Parkinson's disease rat model. Curcumin administration phosphorylates Nrf-2 and Akt thereby attenuated oxidative damage of dopaminergic neuron (Cui, Li, and Zhu 2016). Moreover, dietary curcumin supplementation 0.5% or 2.0% (w/w) attenuated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity in mice *via* increasing the expression of glial cell line-derived neurotrophic factor and TGF-β1 in nigrostriatal dopaminergic system and thus slowing the progression of Parkinson's disease (He et al. 2015b). Curcumin administration increased monoaminergic neurotransmitters such as norepinephrine and dopamine in hippocampal homogenate and alleviated hippocampal damage in 6-hydroxydopamine induced Parkinson's disease in rat. In addition, curcumin treatment upregulated the expression of BDNF, TrkB and PI3K in the hippocampus (Yang et al. 2014). Curcumin treatment (200 mg/kg, for 1 week) significantly attenuated loss of tyrosine hydroxylase, sustained SOD1 level and diminished activation of microglia and astrocytes in the striatum of hemiparkinsonian mice

(Tripanichkul and Jaroensuppaperch 2013). Curcumin administration (50 mg/kg/day, i.p., for five consecutive days) significantly attenuated the phosphorylation of JNKs, translocation of Bax to mitochondria, cytochrome c mediated apoptosis and dopaminergic neuronal loss in the substantia nigra pars compacta of a MPTP mouse model of Parkinson's disease (Pan et al. 2012). In *in vitro* studies, pretreatment with bioconjugate curcumin monoglucoside protected the N27 dopaminergic neuronal cells against rotenone induced neurotoxicity and exerted antioxidant potential. In addition, it showed anti-apoptotic effects by decreasing phosporylation of JNK3 and c-jun, which leads to decrease the activity of caspase 3. Curcumin monoglucoside downregulated NOS2 and upregulated NAD(P)H dehydrogenase [quinone] 1 (NQO1) in neuronal cells. Experiment on *Drosophila* model revealed that, bioconjugate curcumin monoglucoside administration exerts better survival rate and locomotor activity, ameliorate dopamine content and antioxidant activity in rotenone treated group. Bioconjugate curcumin monoglucoside showed improved bioavailability and alleviated rotenone induced Parkinson's disease (Pandareesh et al. 2016). It has been reported that, curcumin activated human umbilical cord-derived mesenchymal stem cells (hUC-MSC-CUR) increased the expression of microtubule associated protein-2 and tyrosine hydroxylase and, downregulated iNOS and nitric oxide (NO) levels in PC12 cells. In addition, hUC-MSC-CUR treatment significantly upregulated the expression of NGF, IL-6 and IL-10 in 1-Methyl-4-phenylpyridine induced Parkinson's disease cell model (Jinfeng et al. 2016). Curcumin pretreatment decreased the production of TNF-α, IL-6 and reactive oxygen species (ROS), while increased IL-10 expression and glutathione levels in 1-methyl-4-phenylpyridinium ion-(MPP(+)-) stimulated primary astrocytes. In addition, curcumin treatment downregulated the levels of TLR-4, interferon regulatory transcription factor (IRF)-3, NF-κB, myeloid differentiation primary response gene 88 (MyD88) in MPP(+)-stimulated astrocytes (Yu et al. 2016). Curcumin pretreatment (1–10 μM) dose-dependently inhibited salsolinol and/or rotenone induced upregulation of caspase-3 and apoptosis in SH-SY5Y cells (Qualls et al. 2014). Curcumin treatment is known to reduce the accumulation of A53T α-synuclein *via* downregulation of the mammalian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase (p70S6K) pathway and induction of macroautophagy in SH-SY5Y cells (Jiang et al. 2013). Experimental data have conclusively proved that, curcumin exhibits antioxidant and anti-inflammatory potential, reduces protein aggregation, decreases mitochondrial dysfunction, decreases dopamine and DOPAC depletion, decreases iron-positive cells and restores dopaminergic neuronal function in substantia nigra thereby ameliorating motor dysfunctions in Parkinson's disease (Mythri and Srinivas Bharath 2012; Shahpiri et al. 2016).

Epilepsy

Epilepsies are heterogeneous group of disorders of central nervous system characterized by paroxysmal cerebral dysrhythmia, seizures and convulsions. These are the most prevalent episodic brain disorders affecting more than 50 million people globally (Koshal, Jamwal, and Kumar 2017; Pearson-Smith and Patel 2017). In animal study, chronic treatment with curcumin (200 mg/kg, i.p., for 24 days) alleviated epileptiform discharge in pentylenetetrazol-kindled rats *via* blocking the action of neuronal nitric oxide synthase (Zhu et al. 2015). Study revealed that chronic curcumin administration (100 mg/kg, p.o., for 40 days) significantly downregulated IL-1β, IL-6, TNF-α and MCP-1 expression in cortex and hippocampus of pentylenetetrazole model of chronic epilepsy. In addition, curcumin markedly reduced glial activation in cortex and hippocampus of epileptic rats (Kaur et al. 2015). Curcumin supplementation attenuated generation of ROS, lipid peroxides, protein carbonyls and mitochondrial dysfunction in hippocampus and cortex of pentylenetetrazole treated epileptic rats (Kaur et al. 2015). Kainate-induced temporal lobe epilepsy in rats was significantly reversed by curcumin administration (100 mg/kg/day, p.o., for 1 week). In the similar study, curcumin administration significantly decreased nitrite, nitrate and MDA levels thereby reduced oxidative damage and inflammation in the hippocampal region of epileptic rats (Kiasalari et al. 2013). Curcumin pretreatment (100 or 200 mg/kg, p.o., for three days) dose dependently reduced the intensity and frequency of seizure on lithium-pilocarpine induced status epilepticus in rats *via* decreasing oxidative stress in the striatum and hippocampus (Ahmad 2013). In addition, curcumin administration increased norepinephrine level in brain homogenate of pentylenetetrazole-kindled mice. Curcumin treatment (50, 100 or 200 mg/kg) dose dependently attenuated total nitrite level and AChE activity in the brain homogenate of pentylenetetrazole kindled mice (Choudhary et al. 2013). Recent experimental evidence demonstrated that curcumin exert anticonvulsant effect *via* activation of adenosine A1 receptor (Akula and Kulkarni 2014), downregulation of nitric oxide synthase, deactivation of lactate dehydrogenase as well as increasing SOD and GSH levels in brain homogenate of epileptic rodents (Du et al. 2012). Chronic curcumin administration (50, 100 or 200 mg/kg, p.o., 35 days) dose dependently attenuated seizure score on pentylenetetrazole-kindled mice and the effect of curcumin was comparable to chronic diazepam treatment (3 mg/kg). In addition, curcumin administration decreased MDA and increased GSH levels in the brain homogenate of pentylenetetrazole-induced kindled mice (Agarwal et al. 2011). Curcumin administration (100 or 200 mg/kg, ip) significantly prevented kainic acid induced seizures as well as oxidative stress in rats (Gupta, Briyal, and Sharma 2009). A recent study reported that, oral curcumin administration (400 mg/kg, p.o.) had no effect on electrically induced status epilepticus in rats because it does not reach the brain at significant levels (Drion et al. 2016). It has been reported that poor oral bioavailability of curcumin is a major hindrance toward its anti-epileptic action. Liposomal formulation of curcumin (25 or 50 mg/kg) significantly attenuated generalized and myoclonic seizures against electroshock and pentylenetetrazole induced seizures in mice (Agarwal et al. 2013). The suggested anti-epileptic mechanisms of curcumin effects are decreasing inflammatory cytokines, blocking the action of

nitric oxide synthase, reducing glial cells activation, attenuating oxidative stress, activating adenosine A1 receptor, etc (Akula and Kulkarni 2014; Agarwal et al. 2011). The antiepileptic effect of curcumin has been studied only in animal models and these findings will provides the step toward the clinical study in future.

Depression and anxiety

Depression and anxiety are different neurological disorders, but depressive patients often experience symptoms like anxiety disorder, such as irritability, nervousness, and problems in concentrating and sleeping. Depression and anxiety disorders have its own pathophysiology as well as behavioral and emotional symptoms. In a double blind, cross-over clinical trial, curcumin administration (1 g/day for 30 days) significantly reduced anxiety like behavior, while did not modulate depressive like behavior in obese individuals (Esmaily et al. 2015). Chronic curcumin administration (500 mg, twice daily for eight weeks) is associated with elevated urinary level of substance P and thromboxane B2 as compared to the placebo group. In addition, curcumin administration ameliorated the plasma endothelin-1 and leptin which is associated with greater reductions in IDS-SR30, a major depressive episode (Lopresti et al. 2015). In a randomized, double-blind, placebo-controlled trial, curcumin treatment (500 mg twice daily) for 4 to 8 week provides partial improvement in people with major depressive disorder (Lopresti et al. 2014). A recent meta-analysis data suggest that, curcumin supplementation appears to be efficacious, safe and well-tolerated antidepressant and anxiolytic in patients (Ng et al. 2017). In animal study, curcumin treatment is reported to attenuate depressive phenotype during chronically stressed condition *via* several mechanisms *viz*., reduction in adrenal gland to body weight ratio, reduction in serum corticosterone level, reduction in adrenal cortex thickness as well as upregulation of BDNF and COX-2 expression and reduction in (pCREB/CREB) levels in brain. Curcumin administration increased the level of synaptophysin and BDNF in amygdala alongside reduced depressive like behavior in chronically stressed rats (Zhang et al. 2014). Curcumin treatment is known to inhibit the release of glutamate in synaptosome and induce activation of GluN2B N-methyl-D-aspartate receptor (NMDAR) subunits resulting in antidepressant like action (Zhang et al. 2013c; Lin et al. 2011). Curcumin administration significantly reduced anxiety like effect in ovariectomized (Morrone et al. 2016) and stressed rats (Haider et al. 2015). The general mechanism of action of curcumin treatment includes, inhibition of brain monoamine oxidase (MAO)-A/B activity, modulation of serotonin receptor, amelioration of brain dopamine, serotonin and noradrenaline levels, increase the neurotrophic factor, enhance neuronal growth, increase neuroprotection, reduce neuroinflammation, apoptosis and oxidative stress (Lopresti 2017; Choi et al. 2017). The antidepressants and anxiolytic mechanism of curcumin at molecular level includes ↑BDNF, ↓activation of NF-κB, ↓TNFα and IL-6, ↑5-HT, ↑noradrenaline, ↑dopamone, ↑AChE activity, ↓central 5-$HT_{1a/1b}$ receptors, ↓plasma corticosterone, ↑adenylyl cyclase activity and cAMP, ↑mRNA of adenylyl cyclase subtypes AC 2, AC 8, and CREB (Bahramsoltani et al. 2015; Farzaei et al. 2016c).

Neuropathy

Neuropathy is a common term that refers to the malfunctions of nerves. It is caused by alcoholism, autoimmune diseases, diabetes, infections, tumors, vitamin deficiencies etc. Diabetic neuropathy is a type of neuronal damage, associated with chronic diabetes, characterized by demyelination and deterioration of nerve fibers, alterations in the microvasculature and loss of sensory fibers that leads to pain, foot ulcers, amputations, depression, phobias, anorexia, loss of memory and reduction in complex reasoning skills (Patel and Udayabanu 2013). In animal study, curcumin treatment (50 mg/kg, for 8 weeks) upregulated BDNF in frontal cortex and hippocampus alongside reduced oxidative damage in the hippocampus of diabetic *db/db* mice (Franco-Robles et al. 2014). Curcumin administration significantly increased $Na^{(+)}$-$K^{(+)}$-ATP activity, reduced lactate dehydrogenase (LDH) activity and lactic acid content as well as stimulates $Ca^{(+)}$-$Mg^{(+)}$-ATP activity in brain homogenate of alloxan induced diabetic mice. In addition, curcumin administration ameliorated energy metabolism in the brain homogenate of diabetic mice (Miao, Cheng, and Li 2015). Curcumin administration (60 mg/kg, p.o., for two weeks) downregulated the expression of glucose transporter (GLUT) type 3, muscarinic receptor type 3, α7-nicotinic receptor and AChE in brainstem and cortex of streptozotocin induced diabetic rats. In addition, it reduced the expression level of insulin receptor and choline acetyltransferase in brainstem. Curcumin treatment upregulated the gene expression of choline acetyltransferase, SOD and insulin receptor in cortex. It is known to upregulate the expression level of muscarinic cholinergic receptor 1 in brainstem and cerebral cortex (Kumar et al. 2013) as well as attenuate cognitive deficits in streptozotocin induced diabetic rats (Kumar et al. 2011). Curcumin treatment (60 mg/kg, p.o., for 15 days) downregulated the expression level of dopaminergic D1 and D2 receptor in the cortex. In addition, curcumin administration significantly upregulated dopaminergic D1 receptor and downregulated D2 receptor in the cerebellum of diabetic rodents. Curcumin treatment upregulated phospholipase C and transcription factor cAMP response element-binding protein expression in the cerebellum and cortex of streptozotocin induced diabetic rats resulting in amelioration of emotional and cognitive performance (Kumar et al. 2010). Curcumin administration (60 mg/kg, p.o., for 16 days) upregulated the glutamate decarboxylase while downregulated Bax, caspase 3 and caspase 8 expressions in the cerebral cortex. In addition, curcumin administration attenuated NMDA and AMPA receptor mediated oxidative stress and excitotoxicity in the cerebral cortex of streptozotocin induced diabetic rats (Jayanarayanan et al. 2013). Curcumin supplemented (0.5%) with animal's diet decreased β-d-glucuronidase activity (Chougala et al. 2012), nitric oxide level, total oxidant status, MDA level and oxidative stress index in streptozotocin induced diabetic rats (Acar et al. 2012). Curcumin treatment at the dose of 100 mg/kg for 8 weeks downregulated the

expression of caspase-12, nerve growth factor (NGF), neurotrophin-3 (3-NT), transforming growth factor beta-activated kinase 1, GLUT-4, NADPH oxidase and p-5′ AMP-activated protein kinase α1 while decreased oxidative stress in the cerebrum of streptozotocin induced diabetic rats (Lakshmanan et al. 2011). Curcumin administration significantly downregulated the expression of AChE, α7 nicotinic acetylcholine receptor, muscarinic cholinergic receptor 1, muscarinic cholinergic receptor 3, insulin receptor and glucose transporter type 3 in the cerebellum of streptozotocin induced diabetic rats (Peeyush et al. 2009). Curcumin (60 mg/kg, p.o., for 10 weeks) exhibits anticholinesterase activity in cerebral cortex and ameliorate spatial memory functions in diabetic rats. In addition, curcumin treatment reduced inflammation and oxidative stress in the hippocampus and cerebral cortex of streptozotocin induced diabetic rats (Kuhad and Chopra 2007). Curcumin treatment (15, 30 or 60 mg/kg, p.o., for 4 weeks) reduced thermal hyperalgesia as well as attenuated the nitrite levels in brain homogenate of streptozotocin induced diabetic mice (Sharma et al. 2006). Chronic diabetes has been reported to induce complications such as central and peripheral neuronal dysfunction. Curcumin might prove to be a better therapy for diabetic neuropathy due to its antioxidant and anti-inflammatory potential, which needs further investigation.

Drug addiction

In animal study, poly(lactic-co-glycolic acid) (PLGA)-curcumin nanoparticles (nanocurcumin) (6 or 20 mg/kg, p.o.) prevented opioid antinociceptive tolerance in mice. In addition, mice treated with nanocurcumin (2, 6 or 20 mg/kg, p.o.) reduced morphine mediated acute opioid dependence. Administration of nanocurcumin (20 mg/kg p.o.) significantly attenuated the chronic morphine induced tolerance and physical dependence in mice. Nanocurcumin (20 mg/kg, p.o.) administration significantly downregulated p-calcium/calmodulin-dependent kinase IIα (p-CaMKIIα) expression in prefrontal cortex of mice treated with morphine, resulting in reversal of opioids induced tolerance and dependence (Hu et al. 2015b). Dendrosomal curcumin (12.5 mg/kg, i.p.) significantly reduced the behavioral signs of morphine withdrawal syndrome in rats. Curcumin mitigates morphine withdrawal and tolerance through downregulation of cAMP-response element binding protein and BDNF transcription in dorsal root ganglion. A recent report suggested that curcumin inhibits DNA methyl transferases and histone acetyltransferases activity, and attenuates morphine withdrawal signs in rats (Ghaemi-Jandabi et al. 2015). Preclinical data have conclusively proved that, curcumin administration reduce drug addiction and withdrawal symptoms, possibly through modulation of histone acetyltransferases, DNA methyl transferases activity, CREB, BDNF (Ghaemi-Jandabi et al. 2015) and CaMKIIα (Hu et al. 2015b) expressions, therefore clinical studies are warranted to assess the therapeutic potential of curcumin in this field.

Huntington's disease

Huntington's disease is an inherited psychiatric problem associated with defective behavior, communication, feeding and movements. In animal study, curcumin administration (50 mg/kg, p.o., for three weeks) significantly ameliorated locomotor activity and motor function in quinolinic acid induced Huntington's disease. In addition, curcumin administration decreased MDA and nitrite levels while increased the reduced GSH levels in striatum. It also significantly decreased the levels of TNF-α, IL-1β and IL-6 in striatum of quinolinic acid induced neurodegeneration. Further, curcumin administration significantly increased nor-adrenaline, dopamine, serotonin, gamma-aminobutyric acid (GABA) and adenosine, while decrease 3, 4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and glutamate levels in the brain of quinolinic acid treated rats (Singh and Kumar 2016). Solid lipid nanoparticles of encapsulated curcumin (40 mg/kg, p.o., 7 days) increased NADH dehydrogenase, succinate dehydrogenase, cytochrome oxidase, F1F0 ATPase alongside reduced lipid peroxidation (LPO), ROS and protein carbonyl generation as well as reduced mitochondrial swelling in striatum of 3-nitropropionic acid-induced Huntington's disease rats. Curcumin nanoparticles significantly prevented hypolocomotion *via* reversal of mitochondrial dysfunctions (Sandhir et al. 2014). In KI mice curcumin supplementation since conception showed downregulated huntingtin aggregates while upregulated D1 and dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) receptor expression in striatum alongside improvement in rearing deficits. Dietary curcumin ameliorated neuronal deficits associated with CAG 140 knock-in mice and reduced the symptoms of Huntington's disease (Hickey et al. 2012). Curcumin treatment attenuated polyQ-mediated cytotoxicity in transgenic *Drosophila* with mutant Htt exon 1 fragment and reduced apoptotic cell death resulting in protection against Huntington's disease (Chongtham and Agrawal 2016). In summary, curcumin administration reduced Huntington's disease *via* several mechanisms including antioxidant, anti-inflammatory, anti-apoptotic activity, modulating neurotransmitters level, reducing huntingtin aggregates etc.

Glioblastoma

Glioblastoma, is the most common, aggressive and malignant tumor that arise from astrocytes. In animal study, curcumin treatment decreased the activation of PI3K/Akt and NF-kB, downregulated Bcl-XL, induced dysfunction of mitochondria, arrested G2/M cell cycle and inhibited the proliferation and migration of glioblastoma cells as well as reduced brain tumors in model of rat C6 glioma (Zanotto-Filho et al. 2012). Curcumin treatment downregulated PI3K, NF-κB, AP-1 while upregulated apoptotic signaling components like caspase 3, p53 and p21 in glioblastoma cell. Curcumin administration increased the survival rate of glioblastoma affected rodents (Rodriguez et al. 2016). In *in vitro* studies, curcumin nanoparticles inhibited the proliferation of glioblastoma neurosphere lines, embryonal tumor lines and U87 GBM cells *via* G2/M apoptotic induction and G2/M

arrest (Lim et al. 2011; Klinger and Mittal 2016). Curcumin (40 μM for 24 h) induced apoptosis and G2/M cell cycle arrest by upregulating the expression of caspase-3, cyclin G2, Fas ligand (FasL), forkhead box protein O1 and downregulating cyclin-dependent kinases (CDK)-1 expression and forkhead box protein O1 phosphorylation in U87 human glioma cells (Cheng et al. 2016). Dendrosomal preparation of curcumin (20 μM) significantly downregulated the expression of OCT4A (octamer binding protein 4), SOX-2 (SRY [sex determining region Y]-box 2) and OCT4B1, and induced overexpression of miR-145 alongside reduced cellular proliferation in U87MG cells (Mirgani et al. 2014). Curcumin treatment significantly upregulated the expression of receptor activator of NF-kB (RANK) and inhibited STAT3 in human glioblastoma U251 cells which might useful for epigenetic therapy in glioma (Wu et al. 2013a). Curcumin treatment reduced the phosphorylation of intracellular STAT3 alongside reduced the transcription of c-Myc and Ki-67 resulting in inhibition of human glioblastoma cell proliferation (Senft et al. 2010). Curcumin treatment (8 μg/ml, 16 μg/ml or 32 μg/ml) significantly upregulated the expression of p53, p21 and downregulated cell division cycle 27 (CDC27) after 48 h in glioblastoma cell lines. In addition, curcumin downregulated B-cell lymphoma 2 (Bcl-2), and upregulated Bax and caspase 3 expression in glioblastoma DBTRG cells (Su, Wang, and Chiu 2010). Additionally, curcumin induced the levels of p16, p21, p53, ElK-1, Egr-1, caspase 3, caspase 8, caspase 9, ERK, JNK, Bid, smac/Diablo, Bax, Cyt-c, LC3-II and H3 and H4 acetylation, while effectively supressed cyclin D1, pRB, Cdc2, STAT-3, AP-1, NF-κB, c-myc and ki, Ku 80, Ku70, protein kinase C (PKC), methylguanine-DNA methyltransferase, excision repair cross-complementing-1 (ERCC-1), histone acetyltransferase (HAT), telomerase (hTERT), p70S6K, MMP-1, matrix metalloproteinases (MMP)-3, MMP-9, MMP-14, CD105, cluster of differentiation 31 (CD31), XIPAs, Bcl-xL and Bcl-2 levels in glioblastoma cells. The suggested mechanisms of curcumin effects against glioblastoma are cell cycle arrest, suppression of proliferation, inhibition of glioma cell angiogenesis and invasion, and induction of apoptosis (Luthra and Lal 2016).

Cardiovascular diseases

Myocardial infarction and heart attack

A heart attack occurs when the oxygenated blood supply to a section of heart muscle suddenly diminished. It is characterized by shortness of breath, chest pain, discomfort in the upper part of the body, sweating, dizziness, lightheadedness, nausea and vomiting. In clinical study, curcumin administration (4 g/day beginning from 3 days before the surgery and continued up to 5 days after surgery) significantly attenuated myocardial infarction associated with coronary artery bypass grafting *via* antioxidant and anti-inflammatory effects (Wongcharoen et al. 2012). In animal study, curcumin supplementation (10, 20 or 30 mg/kg) significantly reduced oxidative stress, apoptosis and infract size *via* stimulating janus kinase 2/signal transducer and activator 3 of transcription (JAK2/STAT3) signaling pathway thus protects myocardium in ischemia reperfusion rats (Liu et al. 2017). In another study, curcumin administration (150 mg/kg) downregulated the NF-κB expression, upregulated PPAR-γ and Bcl-2 expression, thereby attenuated apoptosis and inflammation in rats with myocardial infarction injury (Lv et al. 2016). Curcumin is reported to protect hypoxia-induced cardiomyocytes apoptosis *via* downregulation of specific protein 1 (SP1) and upregulation of miR-7a/b expression in mice (Geng et al. 2016). It is known to reduce fibrosis by activating cardiac NAD-dependent deacetylase sirtuin (SIRT)-1 expression during myocardial infarction in mice (Xiao et al. 2016). Curcumin treatment inhibited the activity of MMPs, reduced MDA level, restored extracellular matrix degradation and decreased deposition of collagen in ischemic/reperfused myocardium of rats. In addition, curcumin supplementation downregulated phospho-Smad2/3 and TGFβ1 expression while upregulated mothers against decapentaplegic homolog 7 expression in the infarcted myocardium, which might prove to be effective for the management of heart attack (Wang et al. 2012). In *in vitro* study, curcumin attenuated apoptosis and induce autophagy by upregulating Bcl-2 and downregulating the expression levels of beclin-1, Bax, SIRT1 and Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) in hypoxia/reoxygenation-induced H9c2 myocytes (Huang et al. 2015b). These findings revealed that, curcumin reverse myocardial infarction and heart attack *via* its antioxidant, anti-inflammatory and anti-apoptotic properties.

Coronary atherosclerosis

Atherosclerosis is a disease where the coronary arteries become narrowed and hardened due to excessive accumulation of cholesterol plaque around the artery wall. In randomized controlled trial, administration of *C. longa* extract (standardized to 250 mg curcuminoids) for 6 months increased the level of adiponectin in serum, decreased pulse wave velocity and reduced the level of leptin, uric acid, triglyceride, total body fat, visceral fat and insulin resistance alongside lowered the atherogenic risks in type 2 diabetic population (Chuengsamarn et al. 2014). In animal study, curcumin administration reported to possess anti-atherosclerotic activity by downregulating the expression of lipocalin-2 in apolipoprotein E knockout mice (Wan et al. 2016). Curcumin supplementation downregulated monocyte chemotactic protein-1, P-selectin, vascular cell adhesion molecule-1, intracellular adhesion molecule-1 and MMP (1, 2 and 9) expressions, exerting anti-atherosclerotic activity. It oxidized LDL and lowered lipid levels in the serum of hypercholesterolemic rabbits (Um et al. 2014). Another mechanistic study revealed that curcumin supplementation suppresses the expression of CD36 and aP2 in macrophages of atherosclerotic mice (Hasan et al. 2014). In murine macrophage line RAW264.7, curcumin reduced ox-LDL-induced TNF-α, IL-1β, IL-6 production and apoptosis along with upregulation of ATP-binding cassette transporter (ABCA1) and CD36 expressions, thereby inducing lipid disposal and removal. It was observed that curcumin

administration ameliorates cholesterol uptake and its esterification (Chen et al. 2015). The anti-atherosclerotic mechanism of curcumin treatment includes the protection against oxidation and inflammation, inhibition of platelet aggregation, modulation of cholesterol homeostasis, lowering LDL-cholesterol and raising high density lipoprotein (HDL)-cholesterol, reducing lipid peroxidation, triglycerides and proinflammatory cytokines (Kapakos, Youreva, and Srivastava 2012).

Hypertension

Hypertension is a condition in which the pressure on blood vessels is greater than the normal pressure. A clinical study demonstrated that turmeric (standardized to 22.1 mg of active curcumin) supplementation (3 capsules daily for three months) attenuated hematuria, proteinuria and systolic blood pressure associated with refractory or relapsing nephritis in patients without any adverse events (Khajehdehi et al. 2012). In animal study, curcumin administration downregulated the expression angiotensin I receptor in vascular smooth muscle cells. In addition, curcumin reduced angiotensin II-induced high blood pressure in C57Bl/6J mice associated with downregulated expression of angiotensin I receptor and decreased vasoconstriction in the mesenteric artery (Yao et al. 2016). Administration of curcumin nanoparticles decreased the thickness of right ventricle and downregulated the ventricular TNF-α, IL-1β, myosin heavy chain-β, nitrotyrosine and fibronectin expression resulting in protection of pulmonary arterial hypertension induced by monocrotaline in rats (Rice et al. 2016). Treatment with curcumin (50 or 100 mg/kg, for 6 weeks) ameliorated blood flow in hind limb, decreased hypertension and reduced vascular resistance. In addition, it decreased the level of circulating angiotensin converting enzyme and induced vascular relaxation in hypertensive rats. Further, curcumin administration upregulated eNOS expression, decreased superoxide enzyme level and downregulated p47phox NADPH oxidase expression in vascular tissues, which is known to be responsible for 2kidney-1clip induced hypertension in rats (Boonla et al. 2014). In another study, curcumin treatment increased the expression of eNOS, decreased oxidative stress, restored glutathione redox ratio in aortic tissues along with decrease in plasma protein carbonyls, MDA and urinary nitrate/nitrite levels in cadmium intoxicated mice resulting in antihypertensive effect (Kukongviriyapan et al. 2014). In conclusion, curcumin supplementation effectively reduce hypertension *via* blocking angiotensin I receptor, reducing circulating angiotensin-converting enzyme, inducing vasodilation and mediating nephroprotection.

Arrhythmias

Arrhythmias (also called dysrhythmia) occur when the electrical impulse to the heart becomes irregular. In experimental study, clinicopathological evidence indicates that, curcumin treatment reduces cardiac dysrhythmias, ventricular fibrillation and tachycardia by attenuating oxidative stress in mesenteric vessels of rats during ischemia-reperfusion injury (Broskova et al. 2013). Curcumin supplementation reduced atrial arrhythmias *via* its anti-inflammatory activity and protected ventricular arrhythmias by modulating Ca^{2+} homeostasis (Broskova et al. 2013; Schoonderwoerd et al. 2008; Phrommintikul and Chattipakorn 2006). In *in vitro* study, curcumin administration inhibited human ether-a-go-go-related gene (hERG) potassium channels, resulting in cardiac repolarization prolongation, which might associated with the observed antiarrhythmic effects (Hu et al. 2012). Paradoxically, clinical report represented that curcumin treatment for one month causes complete atrioventricular block and after withdrawal of curcumin no further cardiac disturbances was observed (Lee et al. 2011). The suggested antiarrhythmic mechanisms of curcumin are the modulation of Ca^{2+} homeostasis, blockade of potassium channels as well as anti-inflammatory and antioxidant effects.

Stroke

Stroke, sometimes called a "brain attack", occurs when blood circulation to a part of the brain is blocked or ruptured. In animal studies, curcumin pre- and post-treatment significantly improved CAT, glutathione peroxidase (GPx) and SOD, while reduced TNF-α, IL-6, MDA and xanthine dehydrogenase levels in forebrain tissue. In addition, curcumin treatment significantly reduced apoptotic index induced by bilateral common carotid artery occlusion/reperfusion in rats (Altinay et al. 2017), increased the numbers of BrdU-positive cells, BrdU/doublecortin-positive cells, activated notch signaling pathway and stimulated neurogenesis during stroke (Liu et al. 2016). Curcumin pretreatment (200 mg/kg, i.p., for 7 days) significantly decreased MDA, NO, TNF-α, IL-1β, caspase-3, while increased SOD and GPx levels in the spinal cord of ischemia-reperfusion injury in rats. Further, curcumin administration reduced oxidative stress, inflammation and apoptosis in spinal cord as well as reversed locomotor deficit in rats (Gokce et al. 2016). Curcumin administration (50 mg/kg, single i.p. injection, 1 h after the onset of focal cerebral ischemia) upregulated eukaryotic initiation factor 4 A, adenosylhomocysteinase, isocitrate dehydrogenase, ubiquitin carboxy-terminal hydrolase L1, while downregulated pyridoxal phosphate phosphatase expressions in the cerebral cortex of rat (Shah et al. 2016a). Curcumin treatment (50 mg/kg, i.p., for five days) downregulated TNF-α, IL-6, Ac-p53 and Bax, while upregulated Bcl-2 and SIRT1 expression in brain. In addition, curcumin increased mitochondrial cytochrome *c* levels, mitochondrial complex I activity, mitochondrial membrane potential, while decreased cytosolic cytochrome *c* levels in brain resulting in reversal of mitochondrial dysfunction in transient middle cerebral artery occlusion/reperfusion stroke model of rat (Miao et al. 2016). Curcumin administration (300 mg/kg, i.p.) reversed ischemic brain injury induced cerebral infarct size in rats by downregulation of NAD(P)H: quinone oxidoreductase-1 expression, reduction of Akt phosphorylation, upregulation of NQO1 expression and amelioration of nuclear factor-erythroid 2-related factor 2 binding to antioxidant response element as well as reduction of oxidative

stress status (Wu et al. 2013b). Curcumin administration (300 mg/kg, i.p., at the beginning of reperfusion) significantly reduced cerebral infract volume, cortical MDA, caspase-3, cytochrome *c* levels, while increased the expression of Bcl-2 in cerebral cortex of rat (Zhao et al. 2010). Curcumin also (100 mg/kg, i.p.) upregulated brain Nrf-2 and HO-1 expressions, reduced water content of brain, infract volume and behavioral dysfunctions in rats against focal cerebral ischemia (Yang et al. 2009). Curcumin administration (100 mg/kg, for 5 days prior and 3 days after middle cerebral artery occlusion) increased the SOD activity in cerebral cortex and corpus striatum, inhibited brain LPO and reversed motor dysfunction in rats (Shukla et al. 2008). Curcumin treatment (300 mg/kg, 2 ml/kg injection through sublingual vein after reperfusion) diminished mortality, reduced infarct volume and cerebral damage, reduced the brain water content, downregulated iNOS expression and ameliorated neurological deficit as well as prevented blood-brain barrier damage in focal cerebral ischemic rats (Jiang et al. 2007). In *in vitro* study, curcumin treatment reduced LDH release, IL-1β, p-p38, NF-kB, MAPK and p-IkB level in oxygen-glucose deprivation mediated injury in brain microvascular endothelial cells of rats (Dong et al. 2014). Mechanistically, curcumin administration reduced oxidative stress, inflammation, apoptosis, mitochondrial dysfunction, cerebral infract size and volume thereby ameliorates neurogenesis and behavioral performance in experimental stroke models. Therefore, curcumin may be a promising supplementary phytoconstituent for stroke in the future.

Metabolic syndrome

Diabetes

Diabetes mellitus, commonly referred to as diabetes, is a chronic metabolic disorder characterized by hyperglycemia, glycosuria, negative nitrogen balance, polydipsia and sometimes ketonemia. In a randomized, double-blind, placebo-controlled trial, oral curcumin extract supplementation (three capsules per day, each curcumin capsule has curcuminoid content of 250 mg) for nine months ameliorated β-cell function, lowered C-peptide and increased homeostasis model assessment-β, reduced insulin resistance and increased the adiponectin level in type 2 diabetic subjects as compared to placebo group (Chuengsamarn et al. 2012). In another clinical study, curcumin administration (as nanomicelle, 80 mg/day for 3 months) lowered the level of HbA1c and fasting blood glucose as well as partially reduced LDL-cholesterol and body mass index in diabetic subjects (Rahimi et al. 2016). A recent meta-analysis revealed that, curcumin or combined curcuminoids supplementation effectively lowered the level of fasting blood glucose in individuals with some degree of dysglycemia. In addition, isolated curcumin supplementation significantly decreased HbA1c as compared to placebo and suggested its beneficial role as adjuvant in the treatment of dysglycemic patients (de Melo, Dos Santos, and Bueno 2018). In animal study, curcumin administration is reported to reduce glucose intolerance through induction of glucagon-like peptide-1 secretion in rats (Kato et al. 2017). In addition, curcumin administration is known to reduce insulin resistance by downregulating phosphorylation of IRS-1 serine residue and upregulating phosphorylation of IRS-1 tyrosine in the skeletal muscle of rats fed with high fructose. Curcumin treatment also reduced glucose intolerance, hyperinsulinemia and homeostasis model assessment-insulin resistance (HOMA-IR) level. Curcumin treatment decreased C reactive protein and TNF-α levels besides downregulated the protein kinase theta (PKCθ) and COX-2 protein expressions. Additionally, curcumin significantly downregulated extracellular kinase 1/2 (ERK 1/2) and p38 protein expressions in skeletal muscle. Further, curcumin treatment ameliorated the activity of GPx and attenuated the activation of inflammatory cascades (Maithilikarpagaselvi et al. 2016). Curcumin treatment significantly reduced systolic blood pressure, LDL-cholesterol, triglycerides, aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol, glycemia, total oxidative status, MDA and nitrative stress in streptozotocin-induced diabetic rats (Bulboacă, D Bolboacă, and Suci 2016). A recent study demonstrated that, curcumin administration (100 mg/kg, p.o., daily for 8 weeks) attenuated splenic damage and improved immunity in streptozotocin-induced diabetic rats *via* antioxidant, anti-inflammatory and anti-apoptotic mechanisms (Figure 3) (Rashid et al. 2017). Curcumin treatment is known to attenuate diabetes and its associated complications like liver disease, adipocyte dysfunctions, pancreatic beta cell dysfunction, vascular dysfunction, nephropathy, neuropathy, retinopathy etc (Zhang et al. 2013b). In cell culture studies, curcumin treatment suppressed palmitate-mediated insulin resistance, inhibited the ubiquitin-proteasome system, reduced the endoplasmic reticulum (ER) protein aggregation and activated the autophagy signaling in human umbilical vein endothelial cells (Ye et al. 2017). The suggested anti-diabetic mechanisms of curcumin effects are ameliorating β-cell dysfunction, insulin signaling, glucagon like peptide-1 secretion, and reducing glucose intolerance, hyperglycemia, hyperinsulinemia, HOMA-IR level, hyperlipidemia, islet apoptosis and necrosis etc (Maithilikarpagaselvi et al. 2016; Bulboacă, D Bolboacă, and Suci 2016; Zhang et al. 2013b). Therefore, these finding demonstrate that curcumin supplementation in diabetic population may be beneficial.

Obesity

Obesity is a condition in which excessive body fat accumulation increases the risk of health problems. Clinically, chronic administration of curcuminoids (comprising curcumin, bisdemethoxycurcumin and demethoxycurcumin) in the form of capsules containing 500 mg curcuminoids plus 5-mg bioperine (1 g/day, p.o., for 4 weeks) significantly decreased serum pro-oxidant-antioxidant balance, oxidative stress burden (Sahebkar et al. 2013), serum triglycerides (Mohammadi et al. 2013), VEGF, IL-1β and IL-4 in obese patients (Ganjali et al. 2014). In animal study, curcumin treatment reduced the level of triglyceride and LDL-cholesterol alongside increased HDL-cholesterol, which is known to ameliorate lipoprotein metabolism. Curcumin administration

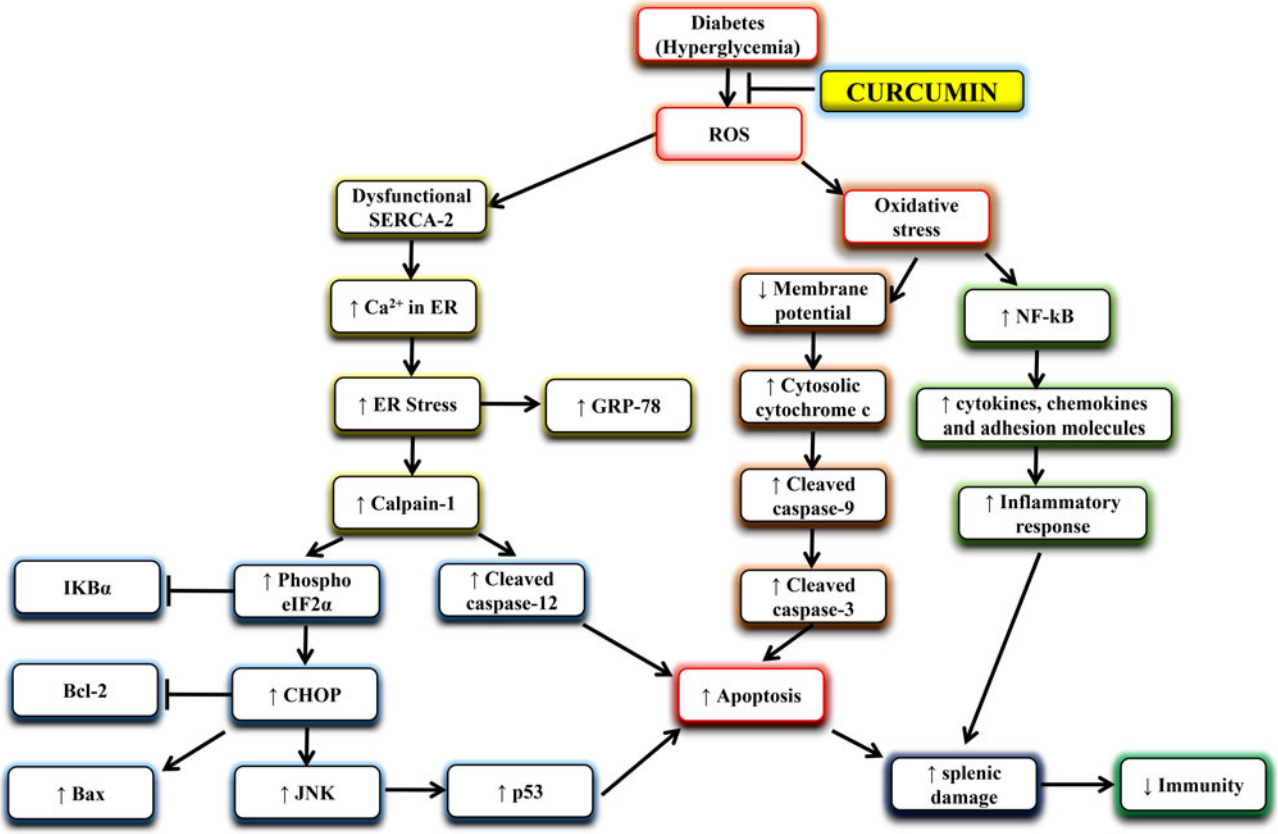

Figure 3. Molecular mechanism of curcumin against diabetes mediated splenic damage. Curcumin treatment blocked hyperglycemia associated apoptosis and splenic complications by reducing SERCA-2 dysfunction, ER stress, Calpain-1, CHOP, JNK, p53 and caspases levels. Curcumin also alleviated diabetes mediated oxidative stress and inflammation.

(0.05% w/w of diet) markedly decreased the plasma level of free fatty acid and triglyceride in the hamsters fed with high-fat diet (10% coconut oil and 0.2% cholesterol w/w) (Ganjali et al. 2017). Curcumin administration (200 mg/kg, dissolved in 0.1% carboxy methyl cellulose, for 10 weeks) significantly decreased body weight, adipose weight, liver weight, plasma levels of triacylglycerol, lipid ratios, hepatic fat accumulation while increased HDL in fructose-fed rats (Maithilikarpagaselvi et al. 2016). Curcumin administration alone (80 mg/kg/day, p.o., for 12 weeks) significantly downregulated the hepatic expression of sterol regulatory element-binding proteins-1, sterol regulatory element-binding proteins-2, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, mevalonate kinase, 24-dehydrocholesterol reductase, 7-dehydrocholesterol reductase, lanosterol synthase, sterol-C4-methyl oxidase-like (Sc4mol), squalene synthase, proprotein convertase subtilisin/kexin type 9, LDL-receptor, acetyl-coenzyme A carboxylase-1, ATP citrate lyase, acyl-CoA synthetase, fatty acid synthase, fatty acid desaturase-1, fatty acid desaturase-2, stearoyl-coenzyme A desaturase-1, glycerol-3-phosphate acyltransferase, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase-1 in high fat diet-induced obese mice. In addition, curcumin administration upregulated the hepatic phosphorylation of IRS-1, IRS-2 and Akt at serine 473 resulting in reversal of obesity in mice (Ding et al. 2016). Curcumin administration (200 mg/kg body weight) with high fat diet for 10 weeks significantly decreased the hepatic ERK and p38 signaling pathway activation as well as reduced body weight in rats (Maithili Karpaga Selvi et al. 2015). Curcumin (1 g/kg) along with high fat diet containing 60% of total calories from fat (5.1 kcal/g diet) administration for 16 weeks significantly decreased hepatic lipids levels, lipid peroxidation, reactive oxygen species levels and upregulated the expression of hepatic heme oxygenase-1 in rats (Öner-İyidoğan et al. 2014). Curcumin (100 or 400 mg/kg) along with high fat diet for 8 weeks effectively reduced serum fetuin-A levels and hepatic triglycerides level in obese rats (Öner-İyidoğan et al. 2013). Curcumin is known to inhibit NF-κB activation and macrophage infiltration in adipose tissue. In addition, curcumin downregulated the expression of the plasminogen activator inhibitor type-1, TNF-α and MCP-1 while upregulated the expression of adiponectin in adipocytes (Bradford 2013). In *in vitro* assay, curcumin downregulated the expression of axin, GSK-3β, CK1-α, AP-2 (mature adipocyte marker) and upregulated the expression of Fz2 (Wnt direct receptor), Wnt10β, LRP5 (Wnt co-receptor), c-Myc and cyclin D1 in 3T3-L1 cells. In addition, curcumin inhibited the phosphorylation of MAPK, JNK, p38 and ERK thereby rescue the differentiation of 3T3-L1 cells into adipocytes (Ahn et al. 2010). Curcumin treatment inhibited mitotic clonal expansion process and downregulated the expression of PPAR-γ, kruppel-like factor 5 and C/EBPα resulting in reduced adipocyte differentiation (Kim et al. 2011). Mechanistically, curcumin administration inhibits NF-κB activation and macrophage infiltration, reduces the expression of

plasminogen activator inhibitor type-1, MCP-1, TNFα, very low density lipoprotein (VLDL), cytokines and leptin alongside induced HO-1, fatty acid oxidation, APO-A1 and adiponectin level. In addition, curcumin treatment reduces the incidence of obesity and its associated risk factors, mainly due to its antioxidant and anti-inflammatory activities (Alappat and Awad 2010).

Endocrine diseases

Hypothyroidism

Thyroid hormones play a vital role in the regulation of digestive and cardiac functions, brain development, muscle control, maintenance of bones as well as metabolism. In animal study, upregulated expression of hepatic glutathione reductase, GPx-1 and CAT were mitigated by concomitant administration of curcumin and vitamin E in 6-propyl-thiouracil induced hypothyroid rats. In addition, curcumin and vitamin E supplementation reduced the enhanced activity of MnSOD-2, GPx-1 and suppressed activity of glutathione reductase in mitochondrial fraction. It was concluded that curcumin and vitamin E supplementation modulate hepatic antioxidant gene expression during hypothyroidism (Subudhi and Chainy 2012). Curcumin administration significantly reduced the level of LPO in cerebellum and cerebral cortex of 6-propyl-2-thiouracil-induced hypothyroidism in rats. In addition, curcumin reversed the decreased level of translated products SOD1 and SOD2 in rats with hypothyroidism (Jena et al. 2012). Interestingly, an earlier study suggested that, vitamin E and curcumin administration restore the activity of serum transaminase, altered rectal temperature and hepatic histoarchitecture in rats with hypothyroidism induced by 6-n-propyl-2-thiouracil (Subudhi et al. 2009).

Hyperthyroidism

In animal study, curcumin administration reduced lipid peroxidation in the cerebral cortex of l-thyroxine induced hyperthyroid rats. Interestingly, curcumin reduced the activity of SOD, SOD1 and SOD2 in cerebral cortex, while enhanced the SOD and SOD1 activity in the cerebellum of hyperthyroid rat (Jena, Dandapat, and Chainy 2013). In another study, curcumin and vitamin E administration reversed the reduced levels of hepatic SOD and CAT. Besides, curcumin administration upregulated the expression of glutathione peroxidase-1 and glutathione reductase in rat liver. In the same study, co-treatment of curcumin along with vitamin E alleviated oxidative stress and liver damage in l-thyroxine induced hyperthyroid rats (Subudhi and Chainy 2010). Further, l-thyroxine induced hyperthyroidism and its associated increase in activity of ALT and AST in rat serum were reduced by curcumin and vitamin E treatment resulting in hepatoprotection (Subudhi et al. 2008). These finding suggest that, curcumin administration exerts neuromodulatory and hepatoprotective activity during hyperthyroidism mainly due to its antioxidant effect.

Osteoporosis

Osteoporosis is a disease that causes bones to become more weak and fragile. In animal model, curcumin administration ameliorated microarchitecture of tibia bone through downregulation of MMP-9 expression, inhibition of osteoprotegerin (OPG)/RANK ligand/RANK signaling and the activation of microRNA-365 in dexamethasone treated mice (Li et al. 2015a). It has been indicated that MiR-365 act as an upstream regulator of MMP-9 during osteoporosis. Mechanistically curcumin treatment ameliorated bone deteriorations through the activation of miR-365 *via* suppressing MMP-9 (Li et al. 2015a). One study revealed that, curcumin administration increased the ratio of osteoprotegerin to receptor activator for NF-kB ligand, ameliorated the proliferation of osteoblasts and activated the Wnt signaling thereby alleviated osteoporotic symptoms induced by glucocorticoid in rats (Chen et al. 2016). Curcumin treatment (100 mg/kg for 2 month) increased bone mineral density, downregulated the ratio of Bax/Bcl-2, downregulated cleaved poly-ADP-ribose polymerase (PARP) and cleaved caspase-3, upregulated p-ERK1/2 expression as well as reduced femoral osteoblast apoptosis in glucocorticoid-induced osteoporosis rat model (Chen et al. 2016). Recently, report suggests that curcumin reversed hind-limb suspension-induced bone loss in rats *via* upregulation of vitamin D receptor expression and attenuation of oxidative stress (Xin et al. 2015). In *in vitro* studies, curcumin treatment ameliorates the viability of Saos-2 cells, reduces apoptosis, improves the mitochondrial membrane functions and its potential, upregulates GSK3β and protein kinase B (Akt) phosphorylation. These evidences of curcumin administration supporting its potential for management of osteoporosis (Dai et al. 2017). Curcumin reduce the risk of osteoporosis *via* several mechanisms including reduction of apoptosis, amelioration of mitochondrial membrane function, PKB phosphorylation, microRNA-365 activation, osteoblasts proliferation etc.

Gastrointestinal diseases

Inflammatory bowel disease

Inflammatory bowel disease, including ulcerative colitis and Crohn's disease, is recognized as chronic inflammatory state of the gastrointestinal tract. It is characterized by diarrhea, abdominal pain, bleeding, anemia, and weight loss. Crohn's disease can affect the whole gastrointestinal tract, while ulcerative colitis usually involves colonic mucosa (Farzaei et al. 2016a). In a randomized, double-blind trial, administration of NCB-02 enema (contain 140 mg of curcumin) once daily for 8 weeks showed better improvement in disease activity when observed through endoscopy study in patients with mild-to-moderate distal ulcerative colitis (Singla et al. 2014). Further, in a multi-centred, double-blind, placebo-controlled trial, curcumin treatment (1 g after breakfast and 1 g after the evening meal with mesalamine or sulfasalazine for 6 months) appeared to be a safe and promising drug candidate for maintaining remission in ulcerative colitis patients (Hanai et al. 2006). In animal study, curcumin administration reversed inflammation of the colonic mucosa,

restored colonic length, and reduced colonic weight and colonic damage. In addition, curcumin increased the number of T regulator (Treg) cells while suppressed the secretion of IL (2, 6, 12 and 17) and TNF-α. Curcumin is known to downregulate the expression of co-stimulatory molecules CD254 [RANKL], CD54 [ICAM-1], CD205, CD256 [RANK], TLR4 and CD252[OX40 L] against 2, 4, 6-trinitrobenzene sulfonic acid induced colitis in mice (Zhao et al. 2016b). In a recent experimental study, curcumin administration demonstrated therapeutic potential through downregulation of colonic TNF-α, myeloperoxidase (MPO), p-38MAPK and p-p38MAPK expressions in mouse murine ulcerative colitis model (Khoury et al. 2015). Curcumin treatment is known to reduce interferon (IFN)-γ, COX-1, COX-2, TNF-α, NF-κB and iNOS expression. Further, it was reported that curcumin treatment reduces inflammation of colon due to inhibition of chemokinesis and neutrophil chemotaxis (Wan et al. 2014). Moreover, curcumin mitigated inflammatory bowel disease *via* influencing MAPK, ERK pathways, increasing antioxidants, inducing free radical scavenging and MPO inhibition (Baliga et al. 2012). Mechanistically, curcumin treatment reduced ulcerative colitis by inhibiting neutrophil chemotaxis, suppressing the secretion of inflammatory cytokines and inducing antioxidant effects. In a pilot study, administration of curcumin (350 mg, t.i.d. for 1 month followed by 350 mg q.i.d. for another 2 month) reduced the inflammatory response in Crohn's disease condition. In addition, it reduced the erythrocyte sedimentation rates and Crohn's Disease Activity Index in patients (Holt, Katz, and Kirshoff 2005).

Irritable bowel syndrome and visceral hypersensitivity

Irritable bowel syndrome, a disorder of the intestines frequently marked by abdominal pain, bloating, and changes in the bowel habits. Visceral hypersensitivity is a complex process that may occur within the central or peripheral nervous systems, and plays a major role in the etiology of irritable bowel syndrome symptoms (Farzaei et al. 2016b). Clinically, oral administration of CU-FEO (Curcumin 42 mg and Fennel essential oil 25 mg/capsule, b.i.d., for 30 days) significantly ameliorated the symptoms and quality of life in irritable bowel syndrome patients (Portincasa et al. 2016). In animal study, oral administration of curcumin (40 mg/kg, for 21 days) reversed the visceral nociceptive response to graded intensity of colorectal distension and pellet output associated with chronic acute combined stress mediated depressive- and anxiety- like behaviors in rats. Mechanistically, curcumin treatment increased the levels of serotonin, BDNF and pCREB in the hippocampus, while these levels were reduced in the colonic of chronic acute combined stressed rats (Yu et al. 2015). The 5-HT1A receptor is known to be involved in the mode of action of curcumin for the management of visceral hypersensitivity in rats with irritable bowel syndrome. In addition, curcumin administration causes remarkable decrease in visceromotor response to colorectal distension in rats (Farzaei et al. 2016b).

Peptic ulcer

Peptic ulcer is painful sores on the lining of esophagus, stomach or small intestine. Recently, a randomized double-blind placebo-controlled study demonstrated that adjunctive therapy of curcumin (500 mg/day for 4 weeks) with anti-helicobacter regimen ameliorated the symptoms of dyspepsia in peptic ulcer patients (Khonche et al. 2016). In animal study, curcumin administration reduced the restraint stress and water immersion stress-induced gastric lesions by increasing gastric blood flow and attenuating pentagastrin- or histamine- stimulated secretion of gastric acid. In addition, the expression levels of iNOS, COX-2 and TNF-α was significantly downregulated in gastric mucosa of curcumin administered rats exposed to restraint stress and water immersion stress, resulting in gastroprotective effect (Czekaj et al. 2016). Curcumin (10, 50 or 100 mg/kg orally for three days) dose dependently reduced LPO and gastric ulcer area and restored GPx, CAT and SOD levels in gastric mucosa of naproxen treated rats (Kim et al. 2016b). Curcumin treatment reversed stress mediated gastric ulceration in rats by reducing the hemorrhage of gastric mucosa, increasing gastric pH values and attenuating ulcer index which is associated with downregulation of histone H3 acetylation at H^+, K^+-ATPase promoter gene (He et al. 2015a). Curcumin treatment decreased pepsin activity, total acid output and ulcer index alongside reduced MDA level, ameliorated mucin, CAT, NO and SOD in gastric mucosa of indomethacin-induced ulcer in rats (Morsy and El-Moselhy 2013). Additionally, curcumin ameliorated indomethacin-induced gastric ulcer by inducing angiogenesis and collagenization of gastric tissue *via* upregulation of TGF-β, MMP-2, membrane type 1-MMP and VEGF expressions in ulcerated tissues (Sharma et al. 2012). The biological mechanism of curcumin to combat peptic ulcer is mainly due to its antioxidant and anti-inflammatory activities. The gastroprotective effect is also due to inhibition of acid release, amelioration of blood flow, angiogenesis and collagenization of gastric tissue (Sharma et al. 2012; Yadav et al. 2013).

Liver diseases

Alcoholic liver disease is damage to the liver and alteration of its function due to alcohol abuse. In animal study, curcumin administration (60 mg/kg for 4 weeks) inhibited the biosynthesis of unsaturated fatty acids and fatty acids synthesis in ethanol treated mice. In addition, ethanol induced hepatic steatosis was reversed by curcumin treatment (Guo et al. 2017). Animal studies have shown that curcumin administration reduced the ethanol-induced increase in MDA content, decreases the levels of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), and increases the GSH levels. In addition, it is known to reduce fatty liver, oxidative stress, inflammation and necrosis (Nabavi et al. 2014; Nanji et al. 1999; Ghorbani, Hajizadeh, and Hekmatdoost 2016).

Non-alcoholic fatty liver disease is an umbrella term for a variety of pathological conditions including steatosis, fibrosis, cirrhosis and steatohepatitis, caused by accumulation of fat in the liver. It is closely correlated with metabolic

syndrome, obesity, overweight and type 2 diabetes in pediatric and adult individuals (Nabavi et al. 2014). In randomized placebo-controlled trial, curcumin administration (70 mg/day for two months) significantly reduced the liver fat content, triglycerides, LDL-cholesterol, serum levels of total cholesterol, body mass index, ALT, AST, glycated hemoglobin and glucose in patients with nonalcoholic fatty liver disease as compared to placebo group (Rahmani et al. 2016). Additionally, curcumin upregulated the expression of adiponectin precursor and reduced its methylation in experimental model of fatty liver disease (Park et al. 2016). In methionine and choline feed deficient mouse model, curcumin administration inhibited the activation of NF-kB and reduced the inflammatory recruitment in steatohepatitis (Leclercq et al. 2004). Curcumin administration downregulated the intrahepatic expression of procollagen type I, CD11b, tissue inhibitor of metalloprotease (TIMP)-1, monocyte chemoattractant protein-1 and α-smooth muscle-actin in methionine and choline feed deficient mouse model of steatohepatitis alongside reduced the oxidative stress in cultured stellate cells (Vizzutti et al. 2010).

Drug-induced hepatotoxicity is rare but potentially life threatening adverse drug reaction. Hepatotoxicity is a common side effect of over 1000 drugs, toxins and herbs, which require its withdrawal from pharmaceutical market due to its association with morbidity and mortality (Khoury et al. 2015). In animal study, curcumin administration reduced the serum hepatic markers *viz.*, AST, ALT and MDA thereby attenuated lipopolysaccharide/d-galactosamine induced liver damage in rats. In the same study, curcumin administration reduced the NF-κB activation and TNF-α level in liver and serum. Furthermore, curcumin upregulated Nrf-2-dependent antioxidant defense genes like quinone (NQO-1), NAD(P)H dehydrogenase, glutamate-cysteine ligase and heme oxygenase-1 which is responsible for the hepatoprotective activity (Xie et al. 2017). Curcumin administration ameliorated the barrier integrity of intestine, reduced ectopic fat deposition in liver and modulated the gut microbiota which in turn reversed hepatic steatosis in high fat diet fed rats (Feng et al. 2017). Curcumin administration elicited hepatoprotective effect *via* reversal of reduced GPx, CAT and SOD levels in tartrazine induced liver injury. In addition, it reduced the intracellular vacuolization, dilation of central vein and sinusoids as well as necrosis in hepatotoxic rats (El-Desoky et al. 2017). Recent experimental evidence suggests that curcumin administration reduced Gr1hi monocytes infiltration in liver, downregulated the expression of MCP-1, TNF-α and TGF-β1 in mouse model of CCl_4 induced liver fibrosis (Huang et al. 2016b).

Primary biliary cirrhosis is a chronic autoimmune disease characterized by progressive inflammation and destruction of the bile ducts which subsequently causes liver scarring, cirrhosis and fibrosis (Nabavi et al. 2014). It was reported that curcumin administration prevents bile duct ligation induced cirrhosis in rats *via* inhibition of oxidative stress and downregulation of TGF-β (Reyes-Gordillo et al. 2008). Curcumin administration (200 mg/kg, for 3 weeks) ameliorated the functional properties of hepatocytes and downregulated the expression of NF-κB and iNOS in liver of biliary duct ligated rats (Barta et al. 2015).

Hepatitis B virus (HBV) is a small DNA member of the genus *Orthohepadnavirus* (Hepadnaviridae family) that causes liver infections resulting in hepatic disorders like cirrhosis and hepatitis (Nabavi et al. 2014). A recent *in vitro* study demonstrated that curcumin treatment time- and dose-dependently reduce the expressions of HBV surface antigen and e-antigen in HBV transfected HepG2.2.15 cell line. In addition, curcumin inhibited replication of HBV gene *via* down-regulation of cccDNA-bound histone acetylation (Wei et al. 2017). Study revealed that curcumin treatment inhibits HBV *via* downregulation of the metabolic coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). It has been reported that combination of nucleotide/nucleoside analog with curcumin can synergistically reduce the replication of HBV (Nabavi et al. 2014; Mouler Rechtman et al. 2010).

Hepatitis C is a liver disease caused by hepatitis C virus (HCV), a member of the *Flaviviridae* family. HCV causes liver fibrosis, chronic hepatitis and cirrhosis (Nabavi et al. 2014). It was reported that co-incubation of HCV with curcumin and its derivatives potently inhibits the entry of all major HCV genotypes, except tetrahydrocurcumin, which support the importance of α, β-unsaturated ketone groups in the anti-viral efficacy. Curcumin affects the membrane fluidity resulting in impairment of viral binding and fusion thereby inhibits cell-to-cell transmission in human liver cells (Colpitts et al. 2014). Co-administration of curcumin and IFN-α profoundly inhibited HCV replication in Huh7 cells and found to be effective against HCV infections (Kim et al. 2010). Moreover, curcumin exhibited anti-HCV activity by inducing HO-1 and modulating ERK and NF-κB activities in Huh7.5 cells expressing the HCV genotype 1 b subgenomic replicon (Chen et al. 2012).

Mechanistically, curcumin shows hepatoprotective action due to its antioxidant effects and inhibitory activity against NF-κB that is known to regulate different pro-fibrotic and pro-inflammatory cytokines. Additionally, curcumin supplementation reduced liver marker enzymes, cholesterol levels and replication of hepatitis B and C viruses (Nabavi et al. 2014).

Respiratory diseases

Asthma

Asthma is a chronic lung disease involving the inflamed, swell and narrowed airways that produce extra mucus, which causes breathing difficulties. Clinically, curcumin administration (500 mg/day for 30 days) ameliorated the mean forced expiratory volume one second values resulting in alleviation of airway obstruction alongside improved haematological parameters in asthmatics (Kunnumakkara et al. 2017). In animal study, intranasal curcumin administration attenuated the pulmonary fibrosis and inflammation of airway by downregulation of MMP-9, eotaxin, TIMP-1 and α-smooth muscle actin expressions in the lung tissue of ovalbumin-induced chronically asthmatic mice (Chauhan,

Dash, and Singh 2017). In another study, curcumin administration reduced inflammatory markers like IL-4 and INF-γ levels in lung tissue alongside reduced asthma symptoms by activation of Wnt/β-catenin signaling pathway in ovalbumin challenged mice (Yang et al. 2017c). Further, intranasal curcumin administration suppressed the activation of JNK54/56, ERK 42/44 and p38 MAPK resulting in inhibition of COX-2 expression and prostaglandin (PG) D2 release, which is known to reduce airway obstruction, inflammation and asthma progression in ovalbumin challenged mouse model of asthma (Chauhan et al. 2016). Evidence suggested that lipopolysaccharide exposure causes increase in level of IgE, IL-4, IL-5, histamine and MPO resulting in exacerbation of airway inflammation in rats and these effects were efficiently reversed by intranasal curcumin administration (Kumari, Dash, and Singh 2015). Curcumin treatment is reported to attenuate the production of IgE, accumulation of inflammatory cells and hyperplasia of goblet cell alongside ameliorated the secretion of mucus and hyperresponsiveness of airway in asthmatic mice. In addition, curcumin administration increased the activity of HO-1 and Nrf-2 while reduced p-IκB and NF-κB levels in the lung tissue of ovalbumin challenged female specific pathogen-free BALB/c mice (Liu et al. 2015). Their mechanism of action is associated essentially due to its anti-oxidative and anti-inflammatory activities in asthma. At molecular and cellular levels, curcumin treatment reduces asthma symptoms mainly due to inhibition of histamine release, attenuation of IgE, inhibition of COX-2 enzyme and suppression of JNK54/56, ERK 42/44 and p38 MAPK activation (Chauhan et al. 2016; He et al. 2015c).

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that causes obstruction in airflow and difficulty in breathing. In animal study, curcumin administration is known to ameliorate right ventricular hypertrophy index and right ventricular systolic pressure *via* activation of suppressor of cytokine signaling (SOCS) 3/JAK2/STAT signal transduction in lung tissue of rat with chronic obstructive pulmonary disease (Lin, Chen, and Liu 2016). Curcumin treatment downregulated macrophage inflammatory protein (MIP)-2α, IL-8 and MCP-1 expressions while upregulated histone deacetylase 2 expression, ameliorated methylation of H3K9 and reduced H3/H4 acetylation in type II alveolar epithelial cells during cigarette smoke exposure induced chronic obstructive pulmonary disease in rats (Gan et al. 2016). Further, it was reported that, curcumin administration reduce TNF-α, IL-6, IL-8 level, macrophages count, neutrophil numbers and total cell numbers alongside reversed ultrastructural damage and emphysema in bronchoalveolar lavage fluid of cigarette smoke exposure combined intratracheally administered lipopolysaccharide induced chronic obstructive pulmonary disease in rats. Additionally, curcumin downregulated alveolar epithelia p66Shc and p-p66Shc expression, which is associated with protection of alveolar epithelial injury (Zhang et al. 2016c). We conclude that curcumin suppresses the progression of chronic obstructive pulmonary disease by inhibiting the inflammation of airways. These findings suggest that curcumin could be used to protect chronic obstructive pulmonary disease in human and animals.

Pneumonia

Pneumonia is an inflammatory condition caused by bacteria, viruses or fungi in one or both lungs. In animal model, curcumin treatment reduced pneumonia in female C57BL/6J mice caused by *Staphylococcus aureus via* inhibiting the pore-forming activity of α-hemolysin, an extracellular protein secreted by bacteria that is known to induce the lung infection (Wang et al. 2016a). Further, curcumin significantly reduced *S. aureus*-mediated lung edema, barrier disruption, vascular leakage and pneumonia. In addition, curcumin administration significantly reduced neutrophils infiltration and attenuates plasminogen activator inhibitor-1 activation, resulting in reduction of chemokines and cytokines in *staphylococcus aureus*-infected mouse model of pneumonia (Xu et al. 2015). Thus, continued studies of the potent anti-inflammatory, anti-microbial, anti-oxidant agent, curcumin, will likely use to reverse or slow the progression of pneumonia, ultimately, leading to novel treatments for pulmonary dysfunction in critically ill patients (Avasarala et al. 2013).

Allergies

Allergies, also known as allergic diseases, are a number of conditions in which the immune system reacts abnormally to a foreign substance. In a randomized, double-blind study, chronic curcumin administration (500 mg/day, p.o., for consecutive 2 months) significantly alleviated rhinorrhoea, sneezing and nasal congestion in patients by reducing nasal airflow resistance. In addition, curcumin administration suppressed TNF-α, IL-4 and IL-8, while increased the production of soluble intercellular adhesion molecule and IL-10 (Wu and Xiao 2016). In animal model, intranasal curcumin administration (2.5 or 5 mg/kg, for four days) suppressed the level of IgE in the serum of asthmatic mice. Further, it reduced the level of secretory phospholipase A2, COX-2, nitric oxide, IL-4 and IL-6 in bronchoalveolar lavage fluid. In addition, curcumin administration downregulated the expression of p38, COX-2, p-ERK and p-JNK in the lungs tissue of ovalbumin challenged mice (Chauhan et al. 2016). Study revealed that curcumin treatment significantly reduce histamine release and downregulate TNF-α, IL-1β, IL-6, IL-8, p-ERK, p-p38, p-JNK, p-IkBα and NF-kB p65 expressions in mast cells. Besides it decreased the levels of IgE, histamine, TNF-α, Src kinases, Fyn, Lyn and Syk in the serum of mice with allergic rhinitis induced by ovalbumin (Zhang et al. 2015b). Curcumin supplementation significantly attenuated lipopolysaccharide induced allergic asthma by reducing airway inflammation and decreasing IgE level, histamine release and oxidative stress in mice (Kumari, Dash, and Singh 2015). Further, curcumin administration inhibited intestinal mastocytosis, expression of Th2 cytokines, intestinal anaphylaxis and activation of NF-κB in ovalbumin

challenged mice (Kinney et al. 2015). It reduced IgE production, attenuated goblet cell hyperplasia and inflammatory cell accumulation, alleviated airway inflammation and stimulated Nrf- 2/HO-1 pathway in lung tissues of ovalbumin challenged mice (Liu et al. 2015). It was reported that, curcumin pretreatment significantly reverse the upregulated expression of Notch1, Notch2 receptors and erythroid transcription factor (GATA)-3 in the lung tissues of ovalbumin challenged allergic asthmatic mice (Chong et al. 2014). Further, curcumin mitigated ovalbumin-induced allergy in mice *via* decreasing iNOS, IL-4 and IL-5 production (Chung et al. 2012). These findings suggest that, the anti-allergic mechanism of curcumin is essentially due to its anti-inflammatory and anti-oxidative activities. At cellular and molecular levels, curcumin treatment reduces allergic symptoms mainly due to attenuation of IgE, inhibition of histamine release, inhibition of COX-2 enzyme, stimulation of Nrf- 2/HO-1 pathway etc (Chong et al. 2014; Kurup and Barrios 2008; Lee et al. 2008).

Cancer

Lung cancer

Animal study revealed that curcumin administration reduced ultra-histoarchitecture and histoarchitecture abnormalities against benzo[a]pyrene induced lung carcinogenesis in mice (Wang et al. 2016c). In *in vitro* studies, curcumin treatment is reported to induce miR-98 and supressed MMP-2 and MMP-9 which leads to inhibition of lung cancer in A549 cell line (Liu et al. 2017). Curcumin-loaded PLGA-PEG-Fe_3O_4 nanoparticles downregulated the expression of hTERT, induced cytotoxicity and attenuated proliferation in A549 cell line, and suggested as effective target for lung cancer therapy (Sadeghzadeh et al. 2017). Curcumin treatment reduced CD133-positive cells, reduced the formation tumorsphere, downregulated the expression of lung cancer stem cells markers like Oct4, aldehyde dehydrogenase isoform 1A1, CD133, CD44 and Nanog alongside induced apoptosis and inhibited proliferation of lung cancer cells. In addition, it reduced lung cancer *via* inhibition of sonic hedgehog and Wnt/β-catenin signaling pathways (Zhu et al. 2017). Curcumin treatment inhibits hepatocyte growth factor induced epithelial-mesenchymal transition and angiogenesis by inhibiting PI3K/Akt/mTOR signal transduction regulated by c-Met in human lung cancer cell line A549 (Jiao et al. 2016). Recent evidence suggest that curcumin treatment effectively prevented lung cancer metastasis and growth by downregulating microRNA (miR)-let 7c and miR-101 mediated expression of enhancer of zeste homolog 2 along with downregulation of Notch1 expression in human lung cancer cell lines (A549 and NCI-H520) (Wu et al. 2016).

Breast cancer

Clinical trial study recommended that, administration of curcumin (6 g/day for seven consecutive days in every 3 weeks) in combination with docetaxel to be safe, effective and well tolerated for advanced and metastatic breast cancer (Bayet-Robert et al. 2010). *In vitro* models revealed that curcumin treatment is known to induce cytotoxicity through apoptosis induction and inhibit the viability of MCF-7 cells *via* caspase-3 and 9 activations. It reduced the expression of miR-21 by upregulating the PTEN/Akt signaling in breast cancer cells (Wang et al. 2017). Experimental evidence suggested that curcumin administration downregulate the expression of estrogen receptor-alfa (ER-α) and tumor suppressor protein exerting antiproliferative effects in T-47D human breast cancer cells (Hallman et al. 2017). Besides, curcumin treatment reduced hypermethylation of glutathione S-transferase (GST) pi 1 (Kumar, Sharma, and Rathi 2017) and deleted in liver cancer 1 (DLC1) (Liu et al. 2017), downregulated the Sp1 and DNA methyltransferase 1 expressions, resulting in inhibition of proliferation of human breast cancer cells (Liu et al. 2017). A recent study revealed that curcumin treatment downregulated the expression of Fibronectin, Twist1 Vimentin, AXL, Slug, β-catenin, N-cadherin and E-cadherin thereby inhibited the migration and invasion of cancer in breast cancer cell lines (Gallardo and Calaf 2016). Curcumin inhibits NF-κB signaling resulting in inhibition of cell growth and invasion in MDA-MB-231 human breast cancer cell line (Yodkeeree et al. 2010). Further, curcumin arrested the cell cycle at the late S and G2M phase alongside induced ROS mediated apoptosis, accumulated p16/Rb and P53/p21 in breast cancer cells (Calaf et al. 2011; Wang et al. 2016d).

Prostate cancer

In a pilot phase II study, curcumin (6000 mg per day for 7 consecutive days) along with docetaxel and prednisone showed therapeutic potential against castration-resistant prostate cancer with good patient acceptability and tolerability (Mahammedi et al. 2016). *In vitro* models revealed that, curcumin treatment downregulated PGK1 *via* upregulation of miR-143 alongside increased the expression of FOXD3, resulting in inhibition of proliferation and migration of prostate cancer cell (Cao et al. 2017). Curcumin treatment is known to induce transferrin receptor protein 1 (TfR1) and iron regulatory protein 1 (IRP1) expression which leads to induced autophagy and apoptosis in castration-resistant prostate cancer cells (Yang et al. 2017a). It has been reported that curcumin treatment inhibited MT1-MMP and MMP-2 expressions in DU145 cells thus reduced the metastasis and survival of prostate cancer cells mediated by Notch-1 signaling cascade (Yang et al. 2017b). Curcumin treatment induced the arrest of G0/G1 cell cycle phase alongside inhibited the regulatory proteins cyclin D1 and CDK-2. Besides, it upregulated the expression of p21, p27 and p53 while downregulated Bcl-2 expression. Further, curcumin treatment is known to activate caspase (3, 8 and 9) (Sha et al. 2016) while decreased Akt, MMP (2 and 9), Bcl-2, Bcl-XL and tumor volume in prostate cancer (Jordan et al. 2016). Curcumin treatment is reported to increase HDAC (1, 4 and 8), apoptosis, production of ROS and Nrf-2 expression, while decrease VEGF, HIF1-α, GSK-3β, Akt, prostate-specific antigen (PSA) level, PSA mRNA expression, HAT activity and cellular proliferation in LNCaP cell lines.

In PC-3 cells, curcumin reduced GSH level, pro-survival factors, Bcl-2, antiapoptotic gene, CXCR-4 and IL-6 expressions while increased DNA fragmentation, p38 MAPK level, ceramide accumulation, JNK level and caspase (3, 8 and 9) activity. Besides, curcumin treatment reduced Bcl-2, CXCL chemokine (C-X-C motif) ligand (CXCL) (1 and 2) and metastatic related gene in C4-2B cell line (Jordan et al. 2016).

Colorectal cancer

Clinically, curcumin administration (3 g/day orally for one month) converted advanced colon cancer derived regulatory T cells to T helper 1 cells *via* increasing IFN-γ production and repression of Foxp3 expression in colon cancer patients (Xu, Yu, and Zhao 2017). In a nonrandomized, open-label clinical trial, oral curcumin (2 g or 4 g per day for 30 days) administration reduced the number of aberrant crypt foci and prevented the colorectal neoplasia (Kunnumakkara et al. 2017; Carroll et al. 2011). *In vitro* models revealed that treatment with curcumin induced apoptosis, arrested the cell cycle at the G1 phase, decreased the cell population as well as inhibited the proliferation and mutation of COLO 320DM cells (Dasiram et al. 2017). Additionally, curcumin treatment stimulated 5′ AMP-activated protein kinase, suppressed the phosphorylation of p65 NF-κB, downregulated MMP-9 and urokinase-type plasminogen activator (uPA) expression as well as reduced the binding ability of NF-κB DNA in LoVo and SW480 cells leading to inhibition of colon cancer invasion (Tong et al. 2016). Curcumin treatment downregulated chemokine receptor 4 expression, upregulated naked cuticle homolog 2 expression and supressed Wnt signaling. In addition, curcumin treatment downregulated vimentin and upregulated E-cadherin expression, which leads to inhibition of proliferation and epithelial mesenchymal transition in SW620 human colon cancer cells (Zhang et al. 2016d). Evidence suggested that curcumin treatment downregulated the expression of p-glycoprotein (Neerati, Sudhakar, and Kanwar 2013) and upregulated PPAR-γ protein (Liu et al. 2015), the potential mechanism by which curcumin can be used for the treatment of colon cancer (Neerati, Sudhakar, and Kanwar 2013).

Bladder cancer

In animal model, curcumin suppressed the invasion and growth of bladder cancer *via* induction of apoptosis and arresting G1/S phase transition in N-methyl-N-nitrosourea induced bladder tumor in rats (Pan et al. 2017). Curcumin treatment suppressed the N-methyl-N-nitrosourea-induced urothelial tumor in rats. In cell lines studies, curcumin treatment is known to downregulate the expression of insulin-like growth factor (IGF)-2 and reduces the IGF1R and IRS-1 phosphorylation in T24 and UMUC2 bladder cancer cells. In this regards curcumin functions through suppression of IGF-2-mediated PI3K/AKT/mTOR signal transduction (Tian et al. 2017). Curcumin treatment reversed the transition of epithelial-mesenchymal cells *via* reducing ERK5/AP-1 signaling pathway in SV-40 human urothelial cells which might be the potential drug candidate for prevention of bladder cancer (Liu et al. 2017). In human bladder cancer cell lines, curcumin treatment exert multiple effects like inhibition of MMP-2/9, generation of ROS, upregulated the expression of HO-1, increased the hypomethylation of the miR-203, upregulated the expression of miR-203, inhibited Aurora A promotor activity, downregulated histone H3 activation, induced G2/M phase cell cycle arrest, decreased the expression of cyclin D1 and COX-2, decreased VEGF level, decreased c-myc, decreased Bcl-2 expression, downregulated Survivin protein, upregulated the expression of p53 and Bax, induced fragmentation of DNA, downregulated cyclin A expression and decreased NF-kB expression thereby inhibited the cancer cell invasion, viability of cancerous cells and growth (Imran et al. 2016; Saini et al. 2011).

Leukaemia

Clinically, curcumin administration (3×5 g for 6 weeks) possessed potent chemosensitizing effect in chronic myeloid leukemia patients, where the patients receiving both curcumin and imatinib exhibited better prognosis with decreased NO levels as compare to the patients receiving imatinib alone (Ghalaut et al. 2012). In animal study, curcumin treatment significantly decreased tumor growth in the chronic myeloid leukemia xenograft mice *via* release of exosomes enriched miR-21 in plasma (Taverna et al. 2015). In cell line studies, curcumin treatment upregulated apoptosis inducing factor, caspase-3, cleaved PARP-1 while downregulated Bcl-2 resulting in induction of apoptosis in lymphoblastic leukemia cells (Mishra, Singh, and Narayan 2016). Curcumin incubation (10 µM, for 6 days) increased the level of ROS, induced genomic instability, mediated reversal of p15 promoter methylation and induced apoptosis in Raji cells (Sharma et al. 2014). Curcumin treatment (40 µmol/L, for 48h) downregulated the protein expression of nuclear NF-κB P65 as well and its translocation alongside inhibited proliferation of acute myeloid leukemia in KG1a and Kasumi-1 cells (Rao et al. 2015). Also, curcumin treatment (25 µM, for 24–48 h) arrested cell cycle in the S-phase, increased the number of annexin V-FITC(+)/PI(-) cells and inhibited the proliferation of SHI-1 cells. In addition, curcumin upregulated FasL and downregulated NF-κB, ERK, Bcl-2, MMP-2 and MMP-9 expressions. Further, curcumin induced the activation of MAPK, p38, caspase-3 and JNK resulted in inhibition of SHI-1 cell invasion (Zhu et al. 2016). Curcumin treatment downregulated the expression of VEGF and decreased the phosphorylation of AKT. Curcumin mediated increased miR-196b levels caused downregulation of Bcr-Abl expression in chronic myelogenous leukemia cells (Taverna et al. 2015). Curcumin incubation downregulated Mcl-1 expression and associated with apoptosis in human myeloma cell lines (Gomez-Bougie et al. 2015). Curcumin treatment simultaneously inhibited RAF/MEK/ERK and AKT/mTOR pathway activation resulting in induction of apoptosis and inhibition of proliferation in human leukemia THP-1 cells (Guo et al. 2014). Curcumin incubation increased the generation of intracellular ROS, depletion of intracellular GSH, activation of caspase enzyme, loss of

mitochondrial membrane potential resulting in anti-proliferative and apoptotic effects on JURKAT cells (Gopal, Paul, and Paul 2014). Mechanistically, curcumin downregulated the expression of DNA methyltransferase 1, Sp1 and p65 which is known to induce p15(INK4B) promoter hypomethylation, reactivation of p15(INK4B) tumor suppressor gene, G1 cell cycle arrest and apoptosis in acute myeloid leukemia cell lines. In addition, curcumin reduced tumor growth in mice implanted with human AML MV4-11 cell line (Yu et al. 2013). Curcumin incubation supressed class I histone deacetylases resulting in upregulation of SOCS1 and SOCS3 expression in the K562 and HEL cells (Chen et al. 2013). Curcumin treatment is reported to activate JNK/ERK/AP-1 pathways, induce apoptosis in human monocytic leukemia THP-1 cells (Yang et al. 2012). Curcumin stimulated autophagy, induced apoptosome complex formation, activated caspase-3 enzyme, induced Bid cleavage, downregulated Bcl-2 expression and upregulated beclin 1 expression, resulting in apoptotic and autophagic death in chronic myeloid leukemia cell line K562 (Jia et al. 2009). Furthermore, curcumin treatment significantly downregulated TICAM1, TNFSF10, TNFalphaIP3, TNF, TLR3, STAT1, RELB, RAF1, PPM1A, NFKBIA, NFKB1, NFKB2, MYD88, MAP3K1, MALT1, IRAK2, IL-1A, IL-1B, IL-6, IL-8, IKBKE, IKBKB, intracellular adhesion molecule-1 (ICAM-1), F2R, CSF2, CD40, CCL2 and CARD4, while upregulated TNFRSF7, TLR-9, TLR-2, TICAM2, IL-10, IFNG, FOS, CSF3, CASP1 and AGT expressions in K562 human leukemia cells (Reuter et al. 2009).

Cervical cancer

Curcumin administration (500 or 12,000 mg/day for 3 months) reduced the risk of cervical cancer and is found to be safe and well tolerated chemotherapeutic in phase I clinical trial (Cheng et al. 2001). In animal model, curcumin nanoparticles suppressed nuclear β-catenin, decreased oncogenic miRNA-21 and abrogated E6/E7 HPV expression in orthotopic mouse model of cervical cancer (Zaman et al. 2016). Curcumin administration (1000 or 1500 mg/kg, for 30 days) significantly downregulated the expression of VEGF, COX-2, EGF-R and inhibited angiogenesis and tumor growth in cervical cancer xenografts model of nude mice (Yoysungnoen-Chintana, Bhattarakosol, and Patumraj 2014). In cell line studies, curcumin treatment (13 μM) upregulated the expression of early-onset breast cancer 1, O6-methylguanine-DNA methyltransferase, mediator of DNA damage checkpoint 1, p-H2A.XSer140 and p-p53 as well as induced translocation of p-H2A.XSer140 and p-p53 from cytosol to nuclei, resulting in chromatin condensation and induction of DNA damage in HeLa human cervical cancer cells (Shang et al. 2016a). Treatment with poly (lactic-co-glycolic acid) based curcumin nanoparticle effectively arrested the cell cycle, inhibited cell growth and induced apoptosis in Caski and SiHa cervical cancer cell lines (Zaman et al. 2016). Curcumin activated ATF6, PERK, IRE-1α and elevated the levels of ROS intracellularly as well as induced apoptosis and inhibited the proliferation of cervical cancer cells (ME180, C33A, HeLa and CaSki) (Kim et al. 2016a). Curcumin counteracts estradiol induced proliferation of cervical cancer *via* induction of apoptosis in cervical cancer cells (Singh and Singh 2011). Incubation with curcumin (20 μM, for 72 h) reversed the hypermethylation and reactivation of the RARβ2 gene in cervical cancer cell lines (Jha et al. 2010). Curcumin (50 or 100 μM, 24 h) dose dependently reduced the phosphorylation of ERK, increased the activity of caspase 3 and caspase 9, upregulated AIF, Bax, cytochrome *c* while downregulated Bcl-XL, Bcl-2 in cervical cancer cells. Curcumin treatment downregulated the expression of cyclin D1, iNOS and COX-2 in HeLa, SiHa and Ca Ski cells, and acts as an anti-proliferative agent (Singh and Singh 2009).

Thyroid carcinoma

In cell line studies, curcumin treatment upregulated E-cadherin while downregulated vimentin and MMPs expressions along with reduced metastasis, cell spreading and cell migration in human papillary thyroid carcinoma cells. Curcumin suppressed TGF-β1 mediated transcription, activation and secretion of matrix metalloproteinases. It also inhibited TGF-β1 induced Smad2 and Smad3 phosphorylation in human papillary thyroid carcinoma BCPAP cells (Zhang et al. 2016a). Curcumin treatment induced DNA damage in thyroid carcinoma BCPAP cells *via* upregulation of H2A.X phosphorylation at Ser139 and ATM-mediated activation of Chk2-Cdc25C-Cdc2 pathway. Moreover, curcumin induced caspase mediated apoptosis in BCPAP cells (Zhang et al. 2016b). Curcumin-based zinc compound is reported to ameliorate p53 reactivation in thyroid cancer cells (Garufi et al. 2015). Curcumin downregulated the expression of HIF-1α and its binding to hypoxia response element in K1 papillary thyroid cancer cells. In addition, curcumin upregulated the expression of E-cadherin, inhibited the activity of MMP-9 (Zhang et al. 2013a) and weakened K1 cells migration resulting in anti-metastatic effect (Tan et al. 2015). Curcumin treatment reduced the phosphorylation of PI3K and Akt pathway, and downregulated the expression of MMP-1/7 and COX-2 leading to inhibition of cell migration, growth and invasion of thyroid cancer cells (FTC133) (Xu, Qin, and Liu 2014). Curcumin instigate the production of ROS, reduce mitochondrial membrane potential and altered intracellular calcium concentration thereby mediate apoptotic induction in papillary thyroid cancer cell line K1 (Song et al. 2012).

Skin cancer

Skin cancer is an abnormal growth of the skin cells. Curcumin decreased the phosphorylation of IRS-1, ILGF-1 receptor, Akt, 4EBP1 and S6K in the mouse keratinocyte cells alongside exerted significant anticancer activity against 7,12-dimethylbenz(a)anthracene (DMBA)-tetradecanoyl phorbol-13-acetate induced skin cancer in mice (Kim et al. 2014). In *in vitro* studies, curcumin treatment is reported to upregulate mmu-miR-205-5p expression, block proliferating cell nuclear antigen, downregulate Bcl-2 expression and suppress JAK-2/STAT3 pathway which in turn induction of

apoptosis and inhibition of proliferation and invasion (Lelli, Pedone, and Sahebkar 2017). Curcumin treatment arrested the G2/M phase of cell cycle as well as induced autophagy in human melanoma cells (A375 and C8161). In addition, curcumin reduced the activation of P70S6K, and downregulated AKT and mTOR expressions which might offer plausible target in the treatment of human melanoma (Zhao et al. 2016a). In another study, curcumin decreased the invasion of squamous cell carcinoma by suppressing STAT3 signaling pathway in A431 cells (Wu, Lu, and Cui 2015). Curcumin induced the opening of mitochondrial permeability transition pore and melanoma cell death in WM-115 melanoma cells (Qiu et al. 2014). Curcumin inhibited NF-κB pro-survival pathway, upregulated the p53 tumor suppressor protein and downregulated Bcl-2 expression resulting in apoptosis and reversal of skin cancer (Chinembiri et al. 2014).

Medulloblastoma

Medulloblastoma is the common malignant brain tumor in pediatrics. In animal model, curcumin inhibited tumor growth and increased the survival rate in Smo/Smo transgenic medulloblastoma mice (Lee et al. 2011). In cell line studies, curcumin treatment arrested G2/M phase of cell-cycle, activated GSK-3β and suppressed Wnt/β-catenin pathway resulting in inhibition of proliferation in DAOY medulloblastoma cell line (He et al. 2014). Curcumin treatment upregulated the PTEN gene expression and downregulated the expression of E2F1, CDK2 and cyclin E1 gene resulting in growth arrest at G2/M phase in medulloblastoma cells. In addition, curcumin treatment increased caspase-3/7 activity, overexpressed Bax while downregulated Bcl-2, Bcl-Xl and surviving expression, which leads induced apoptosis of human medulloblastoma cells (Bangaru et al. 2010). Curcumin treatment inhibits telomerase activity and gene expression of hTERT resulting in telomere shortening in medulloblastoma cell lines (A172, KNS60, U251MG and ONS76) (Khaw et al. 2013). Curcumin phosphorylates Cdc27, a component of the anaphase promoting complex/cyclosome, which is known to ubiquitinate securing and cyclin B, resulting in proteolysis and apoptosis of DAOY medulloblastoma cell (Lee and Langhans 2012). Further, it was reported that, curcumin treatment induced apoptosis and cell cycle arrest possibly through downregulation histone deacetylase 4 and enhanced tubulin acetylation. Curcumin treatment inhibited the sonic hedgehog-glioma associated oncogene-1 pathway *via* downregulating the protein expression of sonic hedgehog ligand, and its most important downstream targets glioma associated oncogene-1 and patched-1 receptor. Furthermore, curcumin reduced the levels of β-catenin, N-myc, C-myc, cyclin D1 and induced apoptosis in DAOY medulloblastoma cells (Elamin et al. 2010).

Other cancer

Curcumin treatment significantly downregulated LRP6, phospho-LRP6, Wnt3a, β-catenin, phospho-β-catenin, surviving and C-myc resulting in inhibition of gastric carcinoma. In addition, curcumin prevents the proliferation of uterine leiomyosarcoma *via* induction of apoptosis, autophagy, ERK 1/2 activity and fragmentation of DNA in gastric carcinoma cells (Imran et al. 2016). Curcumin treatment suppressed JAK-STAT signaling thus reducing tumor cell growth in ovarian (OVCA 420 and OVCA 429) and endometrial (RL95-2 and Ishikawa) cancer cell lines (Saydmohammed, Joseph, and Syed 2010). Curcumin downregulated the expression of IL-6, IL-11 and NF-kB which leads to induce apoptosis of fibrosarcoma cells resulting in anticancer activity against bone cancer (Kondo et al. 2001; Kwak et al. 2006). Curcumin induced cell cycle arrest in G2/M phase, apoptosis and cytotoxicity in squamous carcinoma cells as well as reduced tumor volume in head and neck cancer (Borges et al. 2017). Curcumin treatment reversed the migration and proliferation of hepatic carcinoma by downregulating the expression of HIF-1α. In addition, curcumin reduced the level of MMP-2 and MMP-9 as well as decreased the phosphorylation of p38, which is associated with suppression of cancer invasion and migration in hepatic carcinoma. Additionally, curcumin treatment exhibited anti-proliferative effect in MHCC97H liver cancer cells through generation of ROS, apoptosis and activating toll like receptor -4/MyD-88 pathway (Imran et al. 2016; Liang et al. 2014). Curcumin treatment significantly upregulated the expression of p21/CIP1 and p27/KIP1 CDK, and downregulated the expression of cyclin D1 resulting in decreased proliferation of pancreatic cancer cells. Apart from this, curcumin induced apoptosis *via* downregulating the ratio of Bcl-2/Bax and increasing the activation of caspase-9/3 in pancreatic cancer cells. Curcumin treatment inhibited PI3K/Akt pathway and induced forkhead box O1 in Panc-1 pancreatic cancer cells leading to apoptosis (Zhao et al. 2015). Curcumin suppressed the oral tumor volume, numbers of dysplasic lesions, papillomas and squamous cell carcinoma (Imran et al. 2016). Interestingly, curcumin treatment has potential for many cancer types like esophagus cancer, testicular cancer, sarcoma and lymphoma (Kunnumakkara et al. 2017).

Potential anticancer mechanisms of curcumin

Curcumin inhibits the NF-κB and STAT3 signaling pathways, which play key-roles in the development and progression of cancer. It inhibits a highly expressed transcription factor Sp-1 and its downstream genes, including ephrin type-B receptor 2 precursor, HDAC4, calmodulin and ADEM10 which serve as an important mechanism to prevent metastasis. Curcumin enhances the expression of several extracellular matrix components and inhibits the phosphorylation of focal adhesion kinase (FAK) and CD24 expression, thus prevents cancer formation, migration and invasion (Vallianou et al. 2015; Shi et al. 2001; Zhou et al. 2013). In addition, the potential mechanism of the anti-invasive effect of curcumin includes downregulation of Akt, EGFR, cyclin D1, cMET and upregulation of DNAJ/heat shock protein (HSP) 40 chaperone. Recent studies revealed that ER stress and autophagy might involve in apoptosis process. Mechanistically, autophagy inhibition could increase

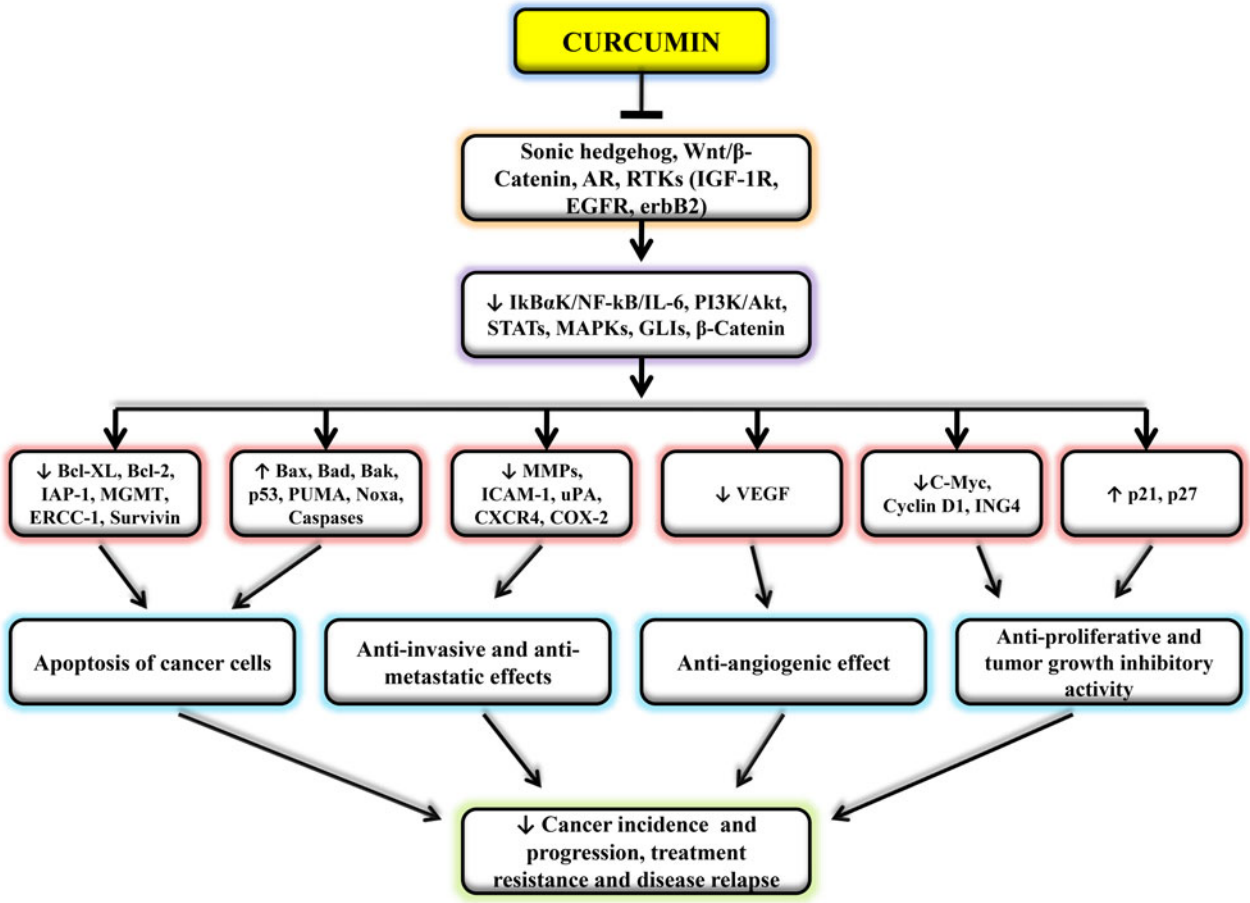

Figure 4. Modulation of growth factor pathways and intracellular signaling components by curcumin in its anticancer effects. Curcumin treatment blocked the effect of Shh-Gli1, Wnt/β-catenin, ATKs and AR pathways as well as its downstream signaling components which lead to reduce cancer incidence, cancer progression, treatment resistance and disease relapse.

curcumin induced apoptosis by inducing ER stress (Vallianou et al. 2015). Further, the anticancer effects induced by phytoconstituent curcumin in malignant cells are mediated *via* the modulation of multiple signaling pathways and its effectors. Curcumin induced anti-carcinogenic effects includes down-regulation of the insulin-like growth factor type-1 receptor (IGF-1R), EGFR/avian erythroblastosis oncogene B1 (erbB1), erbB2/human epidermal growth factor receptor 2 (HER2), Wnt/β-catenin and sonic hedgehog/glioma associated oncogene (SHH/GLIs), and their respective downstream signaling effectors. Curcumin modulates intracellular signal transduction elements such as p21, p27, inhibitor of growth family member 4 (ING4), cyclin D1, c-Myc, VEGF, ICAM-1, MMPS, uPA, COX-2, CXCR-4, Bax, Bad, Bak, Noxa, p53, modulator of apoptosis, caspases etc. resulting in reversal of cancer incidence, progression and relapse (Figure 4) (Jordan et al. 2016; Mimeault and Batra 2011; Kasi et al. 2016).

Kidney diseases

Kidney disease is a condition in which the kidneys lose the ability to balance fluids and eliminate waste. In animal model, curcumin treatment significantly reduced plasma MPO activity, thiobarbituric acid reactive substances (TBARS) level, superoxide anion generation while increased GSH levels in rat ischemia reperfusion model of acute kidney injury. In addition, curcumin reduced plasma potassium level, plasma uric acid level, microproteinuria and blood urea nitrogen along with induced NMDA receptor antagonism during acute kidney injury resulting in nephroprotective effect (Kaur et al. 2016). Curcumin administration (200 mg/kg, p.o.) significantly reduced the level of MPO, IL-1β, IL-6, IL-10, TNF-α, MDA and caspase-3 resulting in protective effect against cisplatin induced renal dysfunction in male Wistar albino rats (Topcu-Tarladacalisir, Sapmaz-Metin, and Karaca 2016). Curcumin administration downregulated the expression of NAD(P)H oxidase subunits (p22phox, p47phox and p67phox), cytochrome P450 2E1 (CYP2E1) and nitrotyrosine renal protein. In addition, curcumin decreased inflammatory cytokine like IFNγ, IL-1β and TNF-α. Besides, the expression of glucose regulated protein 78, MAPKs, p-ERK1/2, p-JNK and C/EBP homologous protein (CHOP) were downregulated. In the same study, curcumin administration reduced apoptosis signaling proteins (cleaved caspase-12 and cleaved caspase-3) in low-dose streptozotocin with high-fat diet induced nonalcoholic steatohepatitis kidney disease in mice (Afrin et al. 2017). Curcumin ameliorated kidney function *via* reducing plasma adiponectin, plasma sclerostin, plasma cystatin C while increasing renal CAT, SOD, Nrf2, GSH in adenine induced chronic kidney

disease in rats (Ali et al. 2018). Moreover, curcumin administration reduced renal mesangial matrix expansion, reduced renal hypertrophy, downregulated fibronectin and collagen IV expressions, decreased the levels of NLRP3 protein, cleaved caspase-1 and IL-1β in the renal cortices of *db/db* mice (Lu et al. 2017). Curcumin treatment reduced fibrosis of kidney by decreasing the methylation of CpG in the klotho promoter, resulting in induction of klotho expression and inhibition of TGF-β signaling in cyclosporine A induced mouse model of kidney disease (Hu et al. 2016). In earlier study, curcumin administration reduced superoxide production, nicotinamide-adenine dinucleotide phosphate oxidase 4 level, carbonylation of protein, nitrotyrosine -protein level, autophagy and mitochondrial fission while increased GSH/GSSG ratio which leads to reversal of nephrotoxicity induced by maleate treatment in rats (Molina-Jijón et al. 2016). Experimental data have conclusively proved that, curcumin treatment reduces fibronectin and collagen IV expressions, suppresses TGF-β signaling and exhibits antioxidant, anti-inflammatory and anti-apoptotic potential thereby ameliorating kidney functions.

Inflammatory diseases

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disease that primarily affects joints, including those in feet and hands. In a randomized, pilot study, curcumin administration (500 mg, b.i.d., p.o., for 8 weeks) reduced Disease Activity Score in rheumatoid arthritis without any adverse events. In addition, the effect of curcumin was better than the patients receiving diclofenac sodium (Chandran and Goel 2012). In animal model, curcumin administration (100 mg/kg orally for two weeks) showed anti-arthritic activity by augmenting the generation of somatostatin in the small intestine of Freund's complete adjuvant induced arthritic rats (Yang et al. 2015). Curcumin (50 mg/kg, i.p.) attenuated the severity and progression of collagen induced arthritis in DBA/1 J mice by decreasing the production of B cell-activating factor belonging to the TNF family in spleen cells and serum as well as reduction of serum IL-6 and IFNγ (Huang et al. 2013). It reduced the pannus formation process that produced through articular cartilage of collagen induced arthritic rats (Kamarudin et al. 2012). In *in vitro* studies, curcumin treatment (2.5–10 µmol for 14 days) inhibited the osteoclastogenic potential of peripheral blood mononuclear cells obtained from patients with rheumatoid arthritis by decreasing stimulation of ERK 1/2, c-Jun N-terminal kinase, p38 and downregulating nuclear factor of activated T cells (NFATc1), receptor activator of NF-κB and c-Fos expression, and reduce bone deterioration during rheumatoid arthritis (Shang et al. 2016b). Curcumin treatment efficiently blocked phorbol 12-myristate 13 acetate and IL-1β-induced upregulation of IL-6 expression in MH7A cells and Fibroblast-like synoviocytes. In addition, it inhibited NF-κB activation, induced ERK1/2 dephosphorylation, exerted strong anti-inflammatory activity and induced apoptosis in fibroblast-like synoviocytes, which might use as a natural remedy for the management of rheumatoid arthritis (Kloesch et al. 2013). Mechanistically, curcumin blocks certain cytokines and enzymes that lead to inflammation, and this sheds light on the possibility of curcumin for the treatment of rheumatoid arthritis.

Osteoarthritis

Osteoarthritis is the most common type of arthritis, which is characterized by pain, tenderness, bone spurs, stiffness, and loss of function in the joints (Farzaei et al. 2015). In a randomized, double-blind, placebo-controlled prospective study, chronic administration of curcumin (180 mg/day, p.o., for 8 weeks) significantly reduced knee pain in osteoarthritic patients as compared to the placebo group (Nakagawa et al. 2014). Curcumin treatment showed protection against osteoarthritis by inhibiting the release of inflammasome NLRP3, followed by downregulation of IL-1β, TNF-α and cleaved caspase-1 in surgical mouse osteoarthritis model (Sun et al. 2017). Experimental evidence revealed that, nanocurcumin (200 mg/kg, for 14 days) significantly prevented the structural changes of articular cartilage in mono-iodoacetate model of osteoarthritis in rats (Niazvand et al. 2017). Mechanistically, curcumin reduced MMP-2, MCP-1, L-selectin, advanced oxidation protein product levels, suppressed the release of proteoglycans, expression of cyclooxygenase, prostaglandin E2 and inflammatory cytokines while increased CD47 levels in chondrocytes (Liu et al. 2016; Chin 2016).

Gingivitis

Gingivitis is an inflammatory gums disease. In a randomized, double-blinded, controlled trial, topical application of curcumin (twice daily for 10 minutes in oral cavity up to 29 days, each gram contained 10 mg *C. longa* extract) significantly reduced the levels of IL-1β and chemokine (C-C motif) ligand 28 in pooled gingival crevicular fluid of healthy selected subjects (Pulikkotil and Nath 2015). In another pilot study, it was reported that curcumin mouthwash reduced the inflammation during chronic gingivitis similar to the topically applied chlorhexidine in patients (Muglikar et al. 2013). Clinically, curcumin application suppressed gingival index scores and plaque formation in patients of periodontal disease (Gottumukkala, Sudarshan, and Mantena 2014).

Mucositis

Mucositis, also called as oral mucositis, mouth sores or esophagitis, is the painful ulceration and inflammation of the mucous membranes. In a pilot study curcumin mouthwash exhibited anti-inflammatory response by reducing inflammatory scores against oral mucositis without any adverse events in pediatrics patients (Meidan et al. 2013). In an *in vitro* oral mucositis model, curcumin treatment reduced the secretion of inflammatory chemokine/cytokine like IL-6 and IL-8 in detroit pharyngeal cells and can be used as oral anti-mucositis agent (Lüer et al. 2014).

Curcumin treatment suppressed activation of inflammation induced by *moraxella catarrhalis via* decreasing the release of IL-8 in human oropharyngeal cells. Further, topical curcumin administration reduced the toxic effects of bacteria on upper respiratory tract on oropharyngeal cells which would be used to manage cancer chemotherapy mediated mucositis (Lüer et al. 2011). In conclusion, anti-inflammatory activity of curcumin is associated with reversal of oral mucositis.

Gastritis

Gastritis is acute or chronic erosion, irritation or inflammation of the lining of the stomach. Clinically, curcumin administration (40 mg orally, three times a day, for four weeks) reduced the production of IL-1β, IL-8, COX-2 and TNF-α in gastric mucosa, and attenuated inflammation in gastritis patients infected with *H. pylori* bacteria (Koosirirat et al. 2010). In a randomized clinical trial, administration of curcumin (Turmeric Tablet-700 mg orally, three times a day, for 4 weeks) reduced the level of MDA, DNA oxidative damage, endoscopic and chronic inflammation scores and glutathione peroxides in gastritis patients (Judaki et al. 2017). In animal model, curcumin treatment downregulated the expression of chemokines such as CXCL1, CCL5, CXCL10, CXCL11, CCL20 and Chemokine (C-C motif) ligand 25 in stomach of mice bearing *Helicobacter pylori* induced gastric inflammation. In addition, curcumin decreased secretion of IL-1β, IL-6 and TNF-α during *H. pylori* infection. Further, curcumin supplementation reduced the macromolecular leakage, MyD88 expression and NF-κB activation in gastric cells (Santos et al. 2015). Study suggested that antimicrobial activity of curcumin against *H. pylori* is responsible for the management of gastritis in mice (De et al. 2009). The biological effect of dietary polyphenol curcumin to reduce chronic gastritis is mainly due to its antioxidant, anti-inflammatory and anti-bacterial activities (Yadav et al. 2013), therefore, it can be recommended as a novel drug for management of gastritis.

Skin diseases

Psoriasis

Psoriasis is a skin disease that causes skin cells to become itchy, scaly and dry patches. Curcumin application (1% alcoholic gel preparation) effectively reduced the level of phosphorylase kinase in the skin of psoriatic subjects. In addition, the effectiveness of curcumin to reduce phosphorylase kinase level was more pronounced than calcipotriol (Thangapazham, Sharma, and Maheshwari 2007). Clinically, oral curcumin administration (20 mg, p.o., b.i.d.) reduced the level of serum IL-22 and alleviated psoriasis vulgaris (Antiga et al. 2015). In animal study, curcumin administration (40 mg/kg, for 20 day) exhibited significant reduction in ear thickness, ear weight, ear redness and lymph node weight in the keratin 14-VEGF transgenic mouse model of psoriasis. Furthermore, curcumin treatment downregulated the serum levels of IL-2, IL-12, IL-22, IL-23, IFN-γ and TNF-α in psoriatic mice. Curcumin administration inhibited Kv1.3 channel and suppressed the cytokines expression and T cells proliferation resulting in reduction of psoriasis phenotype (Kang et al. 2016). Curcumin treatment decreased incrassation and skin inflammation in mouse ear induced by imiquimod. Curcumin application promoted epidermal TCR $\gamma\delta$-cell proliferation and downregulated C-C chemokine receptor type 6 expression in the ear skin of imiquimod-induced psoriasis (Sun, Zhao, and Hu 2013). Curcumin reduces psoriasis-associated inflammation as well as hyperproliferation of keratinocyte that suggest its role in development of antipsoriatic drug (Aggarwal, Surh, and Shishodia 2007).

Wound-healing

In animal models, curcumin treatment exerted the wound healing effects *via* several mechanisms leading to a decrease in the levels of IL-1, IL-6 and TNF-α inflammatory mediators. It is reported to reduce chronic wound by blocking ROS mediated tissue injury, inducing excessive extracellular matrix production, increasing myofibroblast differentiation as well as ameliorating fibroblast proliferation (Shah and Amini-Nik 2017). Curcumin upregulated collagen and fibronectin expressions, ameliorated tissue granulation like neovascularization and induced wound re-epithelialization in diabetics. It was reported that curcumin treatment suppressed the H_2O_2 induced tissue damage in human fibroblasts and keratinocytes through antioxidant mechanism (Maheshwari et al. 2006). The suggested wound-healing mechanisms of curcumin effects are decreasing inflammatory cytokines, blocking the action of ROS, inhibiting NF-kB activation, inducing extracellular matrix production, upregulating collagen and fribronectin expressions etc.

Dermatitis

Dermatitis, also called as eczema, is a group of disease that describes the inflammation of skin. The polyphenol curcumin has been traditionally used by Asian countries to manage dermatitis (Gupta, Kismali, and Aggarwal 2013a). In a randomized, double-blind, placebo-controlled study, curcumin administration (6g/day, p.o., t.i.d, during radiotherapy) was reported to reduce the dermatitis severity in breast cancer patients (Ryan et al. 2013). In animal model, curcumin treatment reduces the inflammation of mouse epidermis by reducing the activity of epidermal COX and lipoxygenase (LOX). Further, topical application of curcumin (200 mg/cm^2, b.i.d. for 35 days) ameliorated survival and recovery of epithelial cell after radiation exposure (Kim et al. 2016c). The biological effect of curcumin to reduce dermatitis is mainly due to inhibition of COX and LOX activities. The mode of action of curcumin against dermatitis is less documented therefore further studies are warranted to prove its potential.

Vitiligo

Vitiligo is a disease in which the melanocytes or cells of skin lose their normal pigment so become white. In clinical

study, application of turmeric cream (GPO curmin, Government Pharmaceutical Organization, Bangkok, Thailand) twice daily with phototherapy significantly reduced symptoms of vitiligo (Vaughn, Branum, and Sivamani 2016). In experimental studies, capsaicin and curcumin pretreatment ameliorated the total antioxidant capacity and reduced ROS formation thus decreasing the apoptosis of keratinocyte and vitiligo disease (Malathi and Thappa 2016). It was further reported that, combining curcumin with phototherapy was safe and effective for management of vitiligo by ameliorating antioxidant mechanism (Daniel and Wittal 2015). Mechanistically, the antioxidant potential of curcumin helps to mitigate the symptoms of vitiligo.

Microbial diseases

Bacterial infections

In roundworm pathogenicity models, curcumin affect quorum sensing, virulence and biofilm initiation resulting in anti-infective activity against *pseudomonas aeruginosa* in *Caenorhabditis elegans* (Rudrappa and Bais 2008). In *in vitro* antimicrobial testing, curcumin treatment reduced the adherence of *Streptococcus* mutants to the tooth surfaces of human and extra cellular matrix protein. Further, curcumin treatment mediated the inhibition of bacterial cell by suppressing the dynamics assembly of FtsZ in the Z ring (Tyagi et al. 2015). A recent study revealed that, curcumin exhibited *in vitro* antibacterial activity against most prevalent organisms like *Enterococcus faecalis*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Actinomyces viscosus*, *Lactobacillus casei*, *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans* (Mandroli and Bhat 2013). Moreover, curcumin demonstrated its effectiveness against *Bacillus subtilis, Mycobacterium tuberculosis*, *Escherichia coli, Helicobacter pylori, Staphylococcus intermedius*, *Sarcina lutea*, *Sarcina lutea* and *Neiserria gonorrhoeae* (Tyagi et al. 2015; Marathe et al. 2011). Curcumin treatment reduced growth of gut microbiota like *Bifidobacterium*, *E. faecalis*, *Bifidobacterium. pseudocatenulatum G4*, *Bifidobacterium. longum BB536*, *E. coli K-12*, *Lactobacillus acidophilus* and *Lactobacillus casei Shirota* thereby inducing the susceptibility to infectious disease (Marathe et al. 2011). Curcumin inhibited the growth of both Gram- negative and Gram-positive bacteria. Curcumin effectively reduced the infectious disease caused by various species of *Staphylococcus aureus* (Tong et al. 2015; Teow et al. 2016). Mechanistically, curcumin interfere with quorum sensing, virulence and biofilm initiation, and inhibits bacterial cell by suppressing its dynamic assembly.

Giardia, trypanosoma and plasmodium infections

Curcumin demonstrated its effectiveness against parasites like *Trypanosoma*, *Plasmodium* and *Giardia*. In parasites culture, curcumin treatment induced DNA damage *via* its prooxidant activity and inhibited histone acetyltransferases in *Plasmodium falciparum* resulted in cytotoxicity, which can be targeted for treatment of malaria (Cui, Miao, and Cui 2007), revealing its therapeutic potential against cerebral malaria as adjunctive therapy (Mimche, Taramelli, and Vivas 2011). Curcumin induced DNA damage and apoptosis and effectively inhibited the growth of *Giardia lamblia* (Perez-Arriaga et al. 2006). Moreover, curcumin administration mediates anti-parasitic activity against Trypanosoma, a parasite which is responsible for African sleeping sickness and Chagas disease (Marathe et al. 2011). The biological effect of curcumin to reduce these infections is mainly due to its pro-oxidant and apoptotic activities, therefore, it can be recommended as a novel drug for management of giardia, trypanosoma and plasmodium infections.

Fungal infections

In animal model, curcumin treatment upregulated the transcription of chitin synthase-1, chitin synthase-3 and PKC in *Sporothrix schenckii* thus reduced virulence in infected mice (Huang et al. 2016a). Curcumin induced photodynamic inactivation of the fungus *Candida albicans* in murine mouse model of oral candidiasis (Dovigo et al. 2013). Also, curcumin exhibited therapeutic potential against *oropharyngeal candidiasis* in a mouse model (Karaman et al. 2011). In fungal cell cultures, curcumin inhibited the growth of wide range of pathogenic fungus that includes *Aspergillus clavatus*, *Aspergillus terreus*, *Aspergillus tamarii*, *Aspergillus fumigatus*, *Aspergillus flavus* IMI190443, *Aspergillus nomius* ATCC 15546, *Aspergillus fumigatus* ATCC 16913, *Paracoccidioides brasiliensis* B339, *Paracoccidioides brasiliensis* MG04, *Paracoccidioides brasiliensis* 17, *Paracoccidioides brasiliensis* 608, *Paracoccidioides brasiliensis* Pb18, *Paracoccidioides brasiliensis* Pb01, *Paracoccidioides brasiliensis* MG05, *Sporothrix schenckii* ATCC 10212, *Cryptococcus neoformans* ATCC 32608, *Candida dubliniensis* (Cd28), *Candida dubliniensis* (Cd22), *Candida glabrata* ATCC 2001, *Candida parapsilosis* ATCC 20019, *Candida krusei* ATCC 20298, *Candida tropicalis* ATCC 750 and *Candida albicans* ATCC 18804 (Martins et al. 2008). Curcumin (500 mg/L) also exhibited antifungal effects against *Phytophthora infestans*, *Pu. Recondite* and *Rhizoctonia solani* (Kim, Choi, and Lee 2003). Curcumin demonstrated fungicidal activity against the clinical isolates of Candida species like *Candida tropicalis*, *Candida kefyr*, *Candida krusei*, *Candida guilliermondii*, *Candida glabrata*, *Candida parapsilosis* and *Candida albicans* at MIC value of 32–128 µg/mL (Zorofchian Moghadamtousi et al. 2014). The suggested anti-fungal mechanisms of curcumin includes the leakage of intracellular component through the flappy membrane, disruption of fungal plasma membrane, generation of oxidative stress, induction of early apoptosis, inhibition hyphae development, upregulation of chitin synthase and PKC etc (Lee and Lee 2014; Sharma et al. 2010). These evidences on the mechanistic action of curcumin could be employed in improving the treatment strategies for fungal infections.

Viral infections

A recent study has shown that the anti-inflammatory and anti-oxidant effects conferred by curcumin protect from human cytomegalovirus infection in Balb/c mice (Lv et al. 2014). Among various phytochemicals evaluated for antiviral activity against norovirus, curcumin exhibited most potent anti-noroviral effects. In a cell culture infection model, curcumin exposure for 3 days was found to reduce norovirus infectivity by 91%. Thus, curcumin might be a promising anti-noroviral candidate to prevent foodborne illness (Yang et al. 2016). In tissue culture infectious dose assay, curcumin modified silver nanoparticles (cAgNPs) efficiently inhibited respiratory syncytial virus (RSV) infection, by inactivating the virus directly without affecting human laryngeal epithelial type 2 cells (Yang, Li, and Huang 2016). Curcumin and its analogs demonstrated promising anti-influenza activity against influenza viruses PR8, H1N1 and H6N1 by interfering with viral hemagglutination activity (Chen et al. 2010; Dao et al. 2012; Ou et al. 2013). In dengue infected BHK-21 cells, curcumin administration reduced the number of plaques produced, intracellular accumulation of viral proteins and increased the level of Lys48 ubiquitin-conjugated proteins in dengue virus (Padilla-S et al. 2014). In *in vitro* assays, curcumin demonstrated potent antiviral effect against Human enterovirus 71 (EV71). Curcumin inhibited viral RNA synthesis and expression of viral protein, thereby decreasing production of viral progeny (Qin et al. 2014). Proteomics analysis indicated that curcumin (15–240 μM) pretreatment exert antiviral activity by downregulating heat shock cognate 71 and inhibited the replication of viral hemorrhagic septicemia virus (Jeong et al. 2015). On the other hand, curcumin exhibited remarkable antiviral effects against herpes simplex virus type 1 (HSV-1) by blocking the recruitment of RNA polymerase II and expression of viral immediate-early genes (Kutluay et al. 2008). In another study, curcumin and its metallo derivatives, *viz.* gallium-curcumin and Cu-curcumin also exhibited remarkable anti-HSV-1 activity *in vitro* (Zandi et al. 2010). Moreover, curcumin administration conferred significant protection against intravaginal HSV-2 infection (Bourne et al. 1999). Curcumin inhibited both HIV-1 (IC_{50}-100μM) and HIV-2 protease (IC_{50}-250μM) thereby suppressed the replication of viral genes and prevent multiplicity of HIV (Sui et al. 1993). Curcumin mediated inhibition of HIV protease and integrase (IC_{50} 40 μM) resulted in anti-retroviral activity (Mazumder et al. 1997; Mazumder et al. 1995). Curcumin induced anti-HIV activity can be attributed to degradation of Tat *via* proteosomal pathway and inhibition of Tat protein acetylation by p300/CREB-binding protein thereby suppressed HIV-1 multiplication (Ali and Banerjea 2016; Balasubramanyam et al. 2004). Curcumin demonstrated strong anti-HPV activity in cervical and oral cancer cells through downregulation of HPV oncogene expression (E6 and E7) of highly oncogenic HPV, HPV-16 and HPV-18 (Divya and Pillai 2006; Mishra and Das 2015; Prusty and Das 2005). Curcumin downregulated the transcription factor, AP-1 in HeLa cells which is critical for transcription of HPV-16 and HPV-18 (Prusty and Das 2005). Curcumin mediated downregulation of viral oncogenes is attributed to its ability to modulate apoptosis and prevent NFkB and AP-1 translocation thereby suppressing the transcription of HPVs (Divya and Pillai 2006; Prusty and Das 2005). Curcumin exhibited potent antiviral effect against coxsackie virus by inhibiting viral replication, RNA expression and protein synthesis *via* ubiquitin-proteasome system mediated protein modification or degradation (Si et al. 2005; Si et al. 2007). Mechanistically, curcumin treatment downregulated JunD protein, reduced production of infective viral particles, downregulated genomic transcription and translation, inhibited viral oncoproteins E6 and E7 expressions, suppressed the Akt/sterol regulatory element-binding proteins (SREBP)-1 pathway, increased p53 level, inhibited hemagglutination, inhibited proteases, integrase and Tat protein acetylation (Zorofchian Moghadamtousi et al. 2014; Mazumder et al. 1995; Balasubramanyam et al. 2004; Dutta, Ghosh, and Basu 2009). The extensive research on antiviral activities of curcumin against different viral pathogens nominates this compound as a potent antiviral drug candidate.

Helminths infections

In *in vitro* studies, curcumin exerted anthelmintic activity against *Schistosoma mansoni* and *Schistosoma japonicum* at the concentration of 50 and 100 μM (Magalhães et al. 2009; Chen et al. 2012). Curcumin treatment is reported to inhibit *Wuchereriai, B. malayi* and *Setaria digitata* helminths (Rana and Misra-Bhattacharya 2013).

Other disease

Clinically, chronic curcumin administration (375 mg, t.i.d., p.o., for 6–22 months) reduced the symptoms associated with idiopathic inflammatory orbital pseudo-tumors in patients (Lal et al. 2000). It is also known to reduce the irritation symptoms in patients with benign prostatic hyperplasia. It decreased the post-operative pain in patients (Cosentino, Fratter, and Cosentino 2016). Norflo tablets (curcumin-phosphatidylcholine complex, 600 mg, b.i.d., p.o., 1 year) administration attenuated the degenerative and inflammatory conditions associated with eye like recurrent uveitis, dry eye, glaucoma, maculopathy and diabetic retinopathy in patients (Allegri, Mastromarino, and Neri 2010). Clinical studies revealed the effectiveness of curcumin against wide range of conditions like ulcerative proctitis, diabetic nephropathy, biliary dyskinesia, chronic periodontitis, β-thalassemia, Dejerine-Sottas disease, lupus nephritis, human immunodeficiency virus infection and acquired immune deficiency syndrome (Kunnumakkara et al. 2017; Prasad and Tyagi 2015).

Clinical trials

In clinical trials, curcumin ameliorated skin health, reduced psoriasis, reduced depressive symptoms as well as effective in inflammatory bowel disease. It reduced the serum levels of TNF-α, lipid peroxides, total cholesterol while increased

HDL cholesterol (Aggarwal, Surh, and Shishodia 2007; Kunnumakkara et al. 2017; Heng et al. 2000). Topical application of curcumin remarkably relieved the symptoms like lesion, itching and pain (Kuttan, Sudheeran, and Josph 1987). Curcumin treatment alone or in combination with other drugs showed potential against oral cancer, lung cancer, multiple myeloma, prostate cancer, breast cancer, pancreatic cancer, colorectal cancer and head and neck squamous cell carcinoma (Gupta, Patchva, and Aggarwal 2013b). Clinically, curcumin administration is reported to reduce irritable bowel syndrome (Bundy et al. 2004), osteoarthritis (Belcaro et al. 2010), anterior uveitis (Lal et al. 1999), inflammation (Satoskar, Shah, and Shenoy 1986), peptic ulcers (Prucksunand et al. 2001), Dejerine-Sottas Disease (Burns et al. 2009), Alzheimer's Disease (Baum et al. 2008), acute coronary syndrome (Alwi et al. 2008), atherosclerosis (Soni and Kuttan 1992), diabetes (Chuengsamarn et al. 2012), type 2 diabetic nephropathy (Khajehdehi et al. 2011), diabetic microangiopathy (Appendino et al. 2011), lupus nephritis (Khajehdehi et al. 2012), β-thalassemia (Fibach and Rachmilewitz 2008), biliary dyskinesia (Niederau and Göpfert 1999), respiratory tract infections (Zuccotti et al. 2008), hepatotoxicity (Adhvaryu, Reddy, and Vakharia 2008), alcohol intoxication (Gupta, Patchva, and Aggarwal 2013b; Sasaki et al. 2011), bronchial asthma (Abidi et al. 2014), chronic periodontitis (Gottumukkala et al. 2013), gingivitis (Waghmare et al. 2011), oral mucositis (Meidan et al. 2013), oral lichen planus (Chainani-Wu, Collins, and Silverman 2012), chronic pulmonary complications, Crohn's disease and arsenic toxicity (Kunnumakkara et al. 2017). Many clinical trials are ongoing to evaluate the potential of curcumin against glioblastoma, breast cancer, cervical intraepithelial neoplasia, colon cancer, head and neck cancer, non-small cell lung cancer, lymphoma, prostate cancer, rectal cancer, osteosarcoma, pancreatic cancer, cardiovascular disease, rheumatoid arthritis, metabolic syndrome, diabetes, Crohn's disease, familial adenomatous polyposis, bowel syndrome, chronic periodontitis, oral submucous fibrosis, ulcerative colitis, mucositis, orthodontis, osteoarthritis, Alzheimer's disease, psoriasis, inflammation, erectile dysfunction, abdominal aortic aneurysm, autosomal dominant polycystic kidney disease, hyperprolactinoma, bipolar disorder, end-stage kidney disease, fibromyalgia, *H. Pylori* infection, kidney disease, kidney allografts, proteinuria, nonalcoholic fatty liver disease, multiple sclerosis, migraine, prostatectomy, vascular reactivity, vascular aging and vascular stiffness (Kunnumakkara et al. 2017).

Drug interactions

Numerous studies have shown the potential of curcumin and its combination with various drugs or nutraceuticals. For instance, chronic administration of oral curcumin along with piperine attenuated lipid peroxidation in tropical pancreatitis patients, while did not reduced the pain (Durgaprasad, Pai, and Alvres 2005). In a cohort study, curcumin treatment along with chlorogenic acid, inulin and rosemary bud essential oil relived the functional dyspepsia symptoms in outpatients (Sannia 2010). The combined treatment of curcumin with quercetin decreased the number and size of familial adenomatous polyposis in patients with negligible side effects (Cruz-Correa et al. 2006). It was reported that combined curcumin and emodin treatment synergistically attenuated the proliferation and invasion of breast cancer cells. In addition, curcumin and emodin combination upregulated miR-34a expression, which helps to mediate its anti-cancer effect *via* downregulation of Bcl-2 and Bmi-1 in MDA-MB-231 and MDA-MB-435 human breast cancer cells (Guo et al. 2013a). Further, combined curcumin and emodin treatment significantly downregulated the expression of P-Smad3, Smad4, TGF-β Receptor II, cyclinD1, p21 and mesenchymal markers (Snail and Slug), and reduced the migration and invasion of HeLa and SiHa human cervical cancer cells (Thacker and Karunagaran 2015). Curcumin treatment is reported to potentiate the cytotoxic effect of temozolomide and etoposide in U-87MG and D283 brain tumor cells *via* increasing Bax/Bcl-2 ratio and downregulating the mRNA expression of p10 and p53 (Ramachandran et al. 2012). A recent study demonstrated that combined treatment using turmeric ethanolic extract (with absorbable curcumin) and bevacizumab significantly inhibited the tumor growth and showed beneficial efficacy in mice bearing colon cancer (Yue et al. 2016). Moreover, numerous studies demonstrated the interaction of curcumin with various drugs and/or nutraceuticals for management of various ailments (Table 2). In addition, curcumin is known to induce pharmacokinetic alterations like changes in maximum plasma concentration (Cmax) and area under the plasma concentration time curve (AUC) when concomitantly administered with antidepressants, antihistaminics, cardiovascular drugs, anticoagulants, antibiotics and chemotherapeutic agents. The underlying mechanisms of these pharmacokinetic interactions involve the inhibition of P-glycoprotein and cytochrome (CYP) isoenzymes (Table 3) (Bahramsoltani, Rahimi, and Farzaei 2017). Although, *in vivo* and *in vitro* studies do not provide any significant evidence to judge the clinical drug interactions of curcumin that could lead to serious adverse reaction, nevertheless physician must remain cautious prior to prescribe (Bahramsoltani, Rahimi, and Farzaei 2017).

Pharmacokinetics of curcumin

Clinically, oral administration of curcumin 12 g/day was relatively well tolerated and the absorption of curcumin was insignificant (<1%). Neither curcumin nor its metabolites were detected in urine or blood, however curcumin was recovered from feces, which reflected its low systemic bioavailability (Aggarwal, Surh, and Shishodia 2007). Low water solubility and poor intestinal permeability generally hiders the bioavailability of curcumin. Several studies have been conducted to improve the bioavailability of curcumin through various formulations. The lipid nanoparticle and dispersions system shown improvement in the absorption and bioavailability of curcumin (Siviero et al. 2015). Several studies have reported the variations in the distribution of

Table 2. Interaction of curcumin with various drugs and/or nutraceuticals.

Interaction	Subject	Mechanisms	Clinical/pre-clinical outcome	Reference
5-Fluorouracil + curcumin	Gastric adenocarcinoma cells	↓survivin level, ↓STAT3 level and ↑cell death	Synergistic anticancer effect on gastric malignancies	Pandey et al. 2015
ABT-737 + curcumin	HepG2 human HCC cell	↑caspase-3 activity, ↑poly(ADP ribose) polymerase 1, ↑ROS, induce death of HCC cells and activate apoptosis signal-regulating kinase 1/c-Jun N-terminal kinase pathway	Antitumor effect of ABT-737 was enhanced by curcumin	Zheng et al. 2016
Arabinogalactan + curcumin	MDA-MB-231 human breast cancer cell	↓cell growth, ↑cell population in sub-G1 phase, ↑apoptosis, ↑Bax/Bcl-2 ratio, ↑caspase-3, ↑ROS level, ↓glutathione and ↑p53	Enhanced potential to induce apoptosis in breast cancer	Moghtaderi, Sepehri, and Attari 2017
Arsenic trioxide + curcumin	KG1a cells	↓Bcl-2 and PARP, ↑Bax protein expression, ↓cell proliferation and ↑apoptosis	Synergistic killing effect on leukemia stem/progenitor cells	Fan et al. 2014
Arsenic trioxide + curcumin	KG1a and SKM-1 cells	↑growth inhibition in MTT assays, ↑caspase-3 and cleaved-PARP, ↑apoptosis and ↓survivin protein expression	Curcumin enhanced arsenic trioxide-induced apoptosis in leukemia stem and myelodysplastic cells	Zeng et al. 2016
Aspirin or rofecoxib + curcumin	Rat	↓TNF-α level and ↑COX enzyme inhibition	Curcumin enhanced the anti-inflammatory effect of aspirin or rofecoxib in the cotton pellet granuloma pouch model	Nandal et al. 2009
Benznidazole + curcumin	Mice	↓parasitemia, ↓parasite load, ↓anti-T. cruzi IgG reactivity, ↓IFN-γ, ↓IL-4 and MIP1-α, ↓myocardial inflammation, ↓cardiac injury and ↓mortality	Better tolerated combination for chagas disease against *Trypanosoma cruzi* infection	Novaes et al. 2016
Berberine + curcumin	MDA-MB-231 and MCF-7 cells	↑beclin1 and JNK phosphorylation, ↓Bcl-2 phosphorylation, ↑autophagic and apoptosis-induced cell death	Synergistic chemopreventive effects on breast cancer cell	Wang et al. 2016b
Celecoxib + curcumin	HT-29, SW-480, and Caco-2 colorectal cancer cells	↓proliferation, ↑apoptosis, ↓PGE2 synthesis and ↓COX-2 expression	Synergistic antineoplastic effect on colorectal cancer cells	Lev-Ari et al. 2005
Celecoxib + curcumin	Male Sprague–Dawley rats	↓MPO and leukocyte infiltration in colonic samples	Enhanced effectiveness against hapten reagent 2,4,6-trinitrobenzene sulfonic acid induced ulcerative colitis	Gugulothu et al. 2014
Chlorogenic acid- + inulin + curcumin + rosemary bud essential oil	Human	↓total cholesterol, ↓LDL, ↓triglyceride levels, ↓AST, ↓ALT, ↓gamma-glutamyl transferase in blood	Symptomatic relief from functional dyspepsia in patients	Sannia2010
Citral + curcumin	MCF 7 cells	↑activation of p53 as well as poly (ADP-ribose) polymerase-1, ↑apoptosis, ↑DNA damage, ↑cell cycle arrest at G0/G1 phase and ↑generation of ROS	Enhanced anticancer effect against breast cancer	Patel, Thakkar, and Patel 2015
Copper supplementation + curcumin	Human oral cancer cells	↑intracellular ROS, ↑Nrf2 level, ↑ E-cadherin level, ↑vimentin and ↑apoptosis	Copper potentiate anticancer effect of curcumin	Lee et al. 2016
Cucurbitacin B + curcumin	Human hepatoma cells	↑caspase-3, ↑cell cycle arrest, ↓tumor growth and ↓multidrug resistance	Enhanced induction of apoptosis and reversed multidrug resistance	Sun et al. 2015
Cyclosporine + curcumin	Rats	↓granzyme B, ↓IFN-γ and IL-2 in rat cardiac allografts	Enhanced immunosuppressive activity and mean survival time in rat heterotopic cardiac transplant models	Chueh et al. 2003
Cytarabine + curcumin	Acute myeloid leukemia bone marrow	↓BCRP, ↓LRP, ↓MDR1genes and ↑anti-proliferative effect	Downregulation of genes involved in acute myeloid leukemia	Shah et al. 2016b
D942 + curcumin	Mouse neonatal cardiomyocytes	↑cell survival after oxygen glucose deprivation, activate AMPK pathway, ↓mTOR signaling and ↑autophagy induction	Enhanced cardioprotective effects	Yang et al. 2013
Diclofenac + curcumin	Female Wistar rats	↑anti-nociception in formalin test	Synergistic effect on inflammatory pain management	De Paz-Campos et al. 2014
Diclofenac + curcumin	Rats	↓telomerase activity, ↓telomerase reverse transcriptase catalytic subunit, ↓CDK4, ↓CDK2, ↓cyclin D1 and ↓cyclin E expression, ↑tumor suppressor proteins Rb, ↑p21, ↑p51 expression and ↑apoptosis	Enhanced anticancer activity in 1, 2-dimethylhydrazine dihydrochloride-induced colorectal cancer	Rana et al. 2015

(*continued*)

Table 2. Continued.

Interaction	Subject	Mechanisms	Clinical/pre-clinical outcome	Reference
Docetaxel + curcumin	PCa cell lines DU145 and PC3	↓proliferation, ↑apoptosis, ↑cytotoxicity, ↓Bcl-2, ↓Bcl-XL and ↓MCL-1, ↓NF-κB activation, ↓PI3K, ↓phospho-AKT, ↓EGFR, ↓HER2 and ↑p53	Curcumin enhanced the anticancer efficacy of docetaxel in prostate cancer	Banerjee et al. 2017
Donepezil + curcumin	Adult male albino Wistar rats	↑spatial working memory, ↓adenosine deaminase, ↓AChE, ↓butyrylcholinesterase, ↑NO, ↓MDA, ↑SOD, ↑GSH, ↑CAT	Synergistic anti-amnestic effect in scopolamine-induced memory impairment	Akinyemi et al. 2017
Doxorubicin + curcumin	4T1 tumor-bearing mice	↓tumor volume, ↓tumor weight, ↓creatine kinase MB, ↓creatine kinase, ↓LDH and AST in serum, ↑tumor cell apoptosis in liver, spleen, lungs, kidney and heart	Co-administration of curcumin and doxorubicin in hyaluronic acid-vitamin E succinate polymer enhanced antitumor effect with minimal side effects	Ma et al. 2017
Ellagic acid + curcumin	HeLa cervical carcinoma cells	↑DNA damage, ↑ROS formation, ↑cytotoxicity, ↑stabilization of p53, ↓oncogene E6, ↑Bax and ↑apoptosis	Synergistic anti-cancer activity against cervical cancer	Kumar et al. 2016
Etoposide + curcumin	SGC7901 cells/ gastric tumor bearing BALB/c nude mice	↑cytotoxicity	Impressive anti-tumor activity in gastric carcinoma	Jiang et al. 2016
Etoposide + curcumin	LT12 cell line	↑DNA damage, ↑cell cycle arrest in G2/M phase and ↑annexin-V-positive cells	Enhanced antileukemic potential	Papiez 2013
Fennel essential oil + curcumin	Human	↓symptom severity score in irritable bowel syndrome (IBS) after 30 days of treatment	Improved symptoms and quality of life in IBS patients over 30 days	Portincasa et al. 2016
Fenretinide + curcumin	Mouse Lewis lung carcinoma cells	↑cytotoxicity	Synergistic effect in treatment of lung cancer	Chen et al. 2016
Fluconazole + curcumin	Mice	↓fungal burden in the brain, ↓pulmonary damage and ↓ fungal colonies in brain	Enhances activity against *Cryptococcus gattii*-induced cryptococcosis	da Silva et al. 2016
Folic acid + curcumin	Male Wistar rats	↓aortic collagen, ↑SOD, ↓MDA, ↑GSH, ↑serum nitrite and ↑aortic relaxation	Abrogated vascular side effects induced by methotrexate	Sankrityayan and Majumdar 2016
Gliclazide + curcumin	Rats	↑tail-flick and hot-plate latencies, ↓TNF-α, ↓peroxynitrite and ↓LPO	Increased protection against streptozotocin induced diabetic neuropathy in rats	Attia et al. 2012
Glyburide + curcumin	Human	↓triglycerides, ↓VLDL, ↓LDL, ↑HDL and better glycaemic control	Enhanced lipid lowering and antidiabetic properties without hypoglycemia in patients with type-2 diabetes mellitus	Neerati, Devde, and Gangi 2014
Hemopressin + curcumin	Rats	↓COX-2, ↓ALT, ↓AST, ↓total bilirubin, ↓liver hydroxyproline, ↓CB1 receptor expression, ↑Bcl-2, ↑GSH, ↓LPO, ↓MDA and ↓NF-κB	Attenuated liver fibrosis induced by cholestasis in rats	El Swefy et al. 2016
Hyaluronic acid + chondroitin sulfate + quercetin + curcumin	Human	↓recurrent urinary tract infections, reduction rate was significantly higher in women receiving vaginal estrogen therapy	Effectively reduced urinary tract infections in postmenopausal women	Torella et al. 2016
Imatinib + curcumin	Human	↓NF-κB pathways and ↓c-kit expression in the metastatic specimens	Successful for the treatment of metastatic adenoid cystic carcinoma	Demiray et al. 2016
Insulin + curcumin	Mice	↓serum TNF-α and NO, ↓hot-plate latencies and thermal hyperalgesia	Enhanced protection against neuropathic pain in streptozotocin induced diabetic mice	Sharma, Chopra, and Kulkarni 2007
Irinotecan + curcumin	LoVo and HT-29 colorectal cancer cells	↓cell viability, ↑apoptosis, ↑cell cycle arrest, ↑ROS and ↑activation of ER stress pathway	Curcumin ameliorate the effects of irinotecan against colorectal cancer	Huang et al. 2017
Mesalamine + curcumin	Human	↓Simple Clinical Colitis Activity Index, ↑endoscopic and clinical remission	Superior to placebo for inducing remission in mild-to-moderate ulcerative colitis	Lang et al. 2015
Metformin + curcumin	Mice	↓tumor volume, ↑survival of the animals and ↓cancer stem cell markers	Ameliorative chemopreventive effect against 4-nitro quinoline-1-oxide induced oral carcinogenesis in mice	Siddappa et al. 2017
Methotrexate + curcumin	KG-1 cells	↑folate receptor β expression and ↑cytotoxicity		Dhanasekaran et al. 2013

			Therapeutic intervention for leukemia's	
Methylseleninic acid + curcumin	MDA-MB-231 breast cancer cells	↑suppression of focal adhesion kinase activity and ↑apoptosis	Improved efficacy against breast cancer	Guo et al. 2013b
N-acetyl cysteine + curcumin	Rats	↓creatinine, ↓blood urea nitrogen, ↓AST and ↓ALT in blood, ↑CAT, ↑GPx and ↓MDA in liver and kidney	Enhanced protection against paracetamol-induced hepato-renal damage	Kheradpezhouh et al. 2010
Nebivolol + curcumin	Rat	↑survival rate, ↑body weight, improve heart index, improved electrocardiogram, ↓troponin I, ↓creatine phosphokinase, ↓creatine kinase MB, ↓MDA, ↑GPx, ↑SOD and ↓NO	Enhanced cardioprotective effects against doxorubicin-induced cardiac toxicity	Imbaby et al. 2014
Oxaliplatin + curcumin	Xenografted LoVo human colorectal cancer cells in nu/nu mice	↓growth of colorectal cancer, ↑apoptosis, ↑S and G2/M phases arrest in cell cycle, ↑Bax, ↑caspase-3 and ↑poly (ADP-ribose) polymerase (PARP) expression, ↓survivin, ↓Bcl-2, ↓pro-caspase-3, ↓HSP70 and ↓pro-PARP	Effectively reduced colorectal carcinoma	Guo et al. 2015
Paclitaxel + curcumin	Mice	↑cell cycle arrest and ↑apoptosis induction	Synergistically inhibited brain tumor growth in orthotopic glioma model	Cui, Li, and Zhu 2016
Paclitaxel + curcumin	MCF-7 cell line	↓Rho-A, ↓c-Ha-Ras, ↓Bcl-xL p53, ↓NF-κB and ↓Bcl-2 expression	Synergistic effect against breast cancer	Quispe-Soto and Calaf 2016
Paclitaxel + curcumin	MCF-7/ADR and MCF-7 cell lines	↑cytotoxicity in cell lines, selective and enhanced drug concentration in tumor as compared to other organ, ↑tumor growth inhibition	Potentiation of antitumor activity of paclitaxel in cell lines. Enhanced antitumor efficacy *in vivo*.	Anwar et al. 2016
Paclitaxel + curcumin	Hep3B cells	↓Lin28 and NF-κB activation, ↓proliferation and ↑apoptosis	Synergistic anti-cancer effect on hepatoma cells	Zhou et al. 2015
Paclitaxel + curcumin	Human brain tumor cells, U138MG and LN18 cells	↓invasion of cells, ↓network formation of cells, ↑caspase-8, ↑Bid and tBid, ↓Bcl-2, ↑p-Bcl-2, ↓mitochondrial cytochrome c, ↑cytosolic cytochrome c, ↑calpain, ↑caspase-3 and ↑PARP (cleaved) expressions	Synergistically blocked cell proliferation, angiogenesis and invasion while induced apoptosis in brain tumor stem and glioblastoma cells	Hossain, Banik, and Ray 2012
Piperine + curcumin	Rats	↑locomotor activity, ↑motor function, ↓MDA and nitrite levels, ↑reduced GSH, ↓TNF-α, ↓IL-1β and ↓IL-6 levels in striatum, ↑nor-adrenaline, ↑dopamine, ↑serotonin, ↑GABA and adenosine while ↓DOPAC and HVA levels in the brain	Enhanced neuroprotective effect in quinolinic acid induced neurological and behavioral dysfunctions	Singh and Kumar 2016
Piperine + curcumin	C57BL6 mice	↓blood lipids, ↓cholesterol in bile, ↓Niemann-Pick C1-like 1 and sterol response element-binding protein 2 expression	Reduced cholesterol gallstones formation induced by high fat diet	Li et al. 2015b
Piperine + curcumin	Rat	↓total cholesterol, ↓triglyceride, ↑HDL and ↓LDL, ↑lecithin, ↑cholesterol acyltransferase, ↑cholesterol 7α-hydroxylase in serum; ↑apolipoprotein A1 (apoA-1), cholesterol 7α-hydroxylase, lecithin cholesterol acyltransferase and LDL receptor expressions in liver	Potentiation of hypocholesterolemic effect against high fat diet administration	Tu et al. 2014
Piperine + curcumin	Rats	↑sucrose preference, ↓immobility period, ↓LPO, ↑GSH, ↓nitrite, ↑CAT level, ↓serum corticosterone, ↓TNF-α, ↓caspase 3 activity, ↑BDNF level, ↓cerebral cortex and hippocampal damage	Piperine enhanced the radical scavenging, anti-apoptotic, anti-inflammatory and antidepressant activity of curcumin in olfactory bulbectomized rats	Rinwa, Kumar, and Garg 2013
Piperine + curcumin	Rats	↑grip strength, ↑locomotor activity, ↓fall off time in rota rod, ↓MDA, ↓nitrite and ↑GSH level in striatum, ↓TNF-α, ↓IL-1β and ↓IL-6 in striatum; ↑norepinephrine, ↑dopamine, ↑serotonin, ↑GABA and ↓glutamate in brain homogenate	Enhanced locomotor activity and motor co-ordination against 6-hydroxy dopamine induced motor deficit	Singh and Kumar 2017
Piperine + curcumin	Mice	↓anxiety, ↑exploratory behavior, ↓depression, ↓MDA, ↓nitrite, ↑GSH level in hippocampus; ↓IL-1β, ↓TNF-	Enhanced anxiolytic and antidepressant effect against	Jangra et al. 2016

(*continued*)

Table 2. Continued.

Interaction	Subject	Mechanisms	Clinical/pre-clinical outcome	Reference
		α and ↑BDNF level in the hippocampus, ↓plasma corticosterone level	lipopolysaccharide-induced behavioral dysfunctions	
Piperine + curcumin	Rats	↓TBARS, ↓superoxide anion, ↑non-protein thiols, ↓NO, ↓TNF-α, ↓caspase activity, ↓p65, ↑norepinephrine, ↑dopamine and ↑serotonin in brain homogenate	Enhanced neuroprotection in haloperidol intoxicated rats	Bishnoi et al. 2011
Piperine + curcumin	Rats	↑heart rate, ↓QRS interval, ↓QT interval, ↓RR interval, ↓PR interval, ↓AST, ↓ALT, ↓ALP, ↓creatine kinase-MB, ↓creatine kinase-NAC, ↓LDH, ↓cholesterol, ↓triglycerides, ↓TBARS, ↑SOD and ↑CAT	Profound cardioprotective activity against cyclophosphamide-induced cardiotoxicity	Chakraborty, Bhattacharjee, and Kamath 2017
Quercetin + curcumin	Human	↓number and size of polyps after six months' treatment	Synergistic effect against colorectal neoplasia	Cruz-Correa et al. 2006
Quercetin + curcumin	Human	↓serum creatinine and ↑HO-1 induction	Ameliorated outcomes in cadaveric renal transplantation and neurotoxicity in patients	Shoskes et al. 2005
Quercetin + curcumin	MGC-803 cells	↓cell proliferation, ↓release of cytochrome c, ↓mitochondrial membrane potential, ↓AKT and ERK phosphorylation, ↑apoptosis	Enhance anti-gastric cancer activity	Zhang et al. 2015a
Quercetin + curcumin	Male laka mice	↑caspase 3 and 9, ↑apoptosis and ↑post-translational modifications of p53	Prophylactic treatment for lung carcinogenesis induced by benzo(a)pyrene	Zhang and Zhang 2018
Quercetin + piperine + curcumin	Rats	↑HDL, ↓plasma glucose, ↓post prandial blood glucose, ↑SOD, ↑CAT and ↑GPx	Enhanced hypolipidemic and antihyperglycemic effects against high-fat diet and low-dose streptozotocin-induced diabetes	Kaur and Meena 2012
Resveratrol + curcumin	Rats	↓sperm cell count and motility, ↑serum testosterone level, ↓tBid, ↓FasL, ↓Apaf1, ↓caspase 3, 8 and 9, and ↓cleaved PARP expression in testis, ↓p38, ↓MAPK, ↓ERK 1/2 and ↓JNK 1/2 activation	Alleviated benzo(a)pyrene induced male germ cell apoptosis	Banerjee et al. 2016
Resveratrol + curcumin	Cardiomyocytes (H9C2)	↓caspase 3/7 activity and ↓ROS	Enhanced protection against doxorubicin-induced cardiotoxicity	Carlson et al. 2014
Resveratrol + curcumin	Rats	↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑GST, ↓AChE, ↓BASE-1, ↓APP, ↑presenilin-1, ↑PS2, ↓IL-1, ↓IL-1β and ↓TNF-α	Synergistic effect against aluminum chloride-induced neuroinflammation	Zaky et al. 2017
Resveratrol + curcumin	Rats	↓alveolar bone loss, ↓IL-1β, ↓IL-4 and ↓TNF-α	Curcumin and resveratrol reduced alveolar bone loss during periodontitis induced by tying a silk suture, as a ligature, around one of the first molars	Corrêa et al. 2017
Saffron + curcumin	Major depressive patients	↑65% response rate in people with atypical depression, improvements in STAI-state and STAI-trait scores	Greater improvements in depressive and anxiety symptoms	Lopresti and Drummond 2017
Sertraline + curcumin	Rat	↓loss of spines, ↑surface area and ↑dendrite length of the cortical neurons	Enhanced protection against stress induced morphological alterations of neurons and dendrites	Noorafshan et al. 2015
Sildenafil + curcumin	Rat	↓hyperalgesia, ↓paw heat allodynia, ↓cold hyperalgesia, ↓MDA, ↑GSH, ↓swelling of nerve fiber, ↓fiber derangement and ↑regeneration of fiber	Synergistically attenuated the alcohol induced neuropathy	Kaur et al. 2017
Silymarin + curcumin	Colon cancer cells (DLD-1)	↓cell proliferation, ↑caspase3/7 activity and ↑apoptosis	Synergistic anticancer effect in colon cancer	Montgomery et al. 2016
Sorafenib + curcumin	Human hepatocellular carcinoma cells	↓MMP 9 *via* NF-κB/p65 signaling pathway, ↑apoptosis and ↑cell cycle arrest	Synergistically prevents tumor growth and metastasis	Hu et al. 2015a
Tacrolimus + curcumin	Human glioblastoma cells A172	↓IL-17, ↓IL-22 and ↓TNF-α	Synergistic effect in management of psoriasis	Jain et al. 2016

Taurine + curcumin	Rat	↓malignant changes in liver, ↓α-fetoprotein, ↓α-L-fucosidase, ↑IL-2 and ↑IFN-γ	Novel prophylactic agent for treatment of hepatic carcinoma induced by diethylnitroseamine	El-Houseini et al. 2017
Tetramethylpyrazine + resveratrol + curcumin	Mice/rat	↓NF-κB p65, ↓TNF-α, ↓IL-1β, ↓IL-6 and ↓inflammation	Improved protection against inflammation in acute paw swelling and collagen-induced arthritis models	Chen et al. 2017
Thymoquinone + curcumin	Birds	↑antibody titer against avian influenza virus and ↑immunomodulation	Synergistic anti-viral activity against H9N2	Umar et al. 2016)
Tolfenamic acid + curcumin	Human pancreatic cancer cells (L3.6pl, MIA PaCa-2)	↑cell growth inhibition, ↓Sp proteins, ↓survivin, ↑c-PARP expression, ↑caspase-3, ↑caspase-7 activity, ↑apoptosis, ↑ROS level and ↓NF-kB translocation	Enhanced antiproliferative activity against pancreatic cancer	Basha et al. 2016
Valproic acid + curcumin	Human leukemia cells (HL-60 cells)	↑histone H3 and H4 acetylation of bax, ↑increases Sp1 binding, ↑bax expression, ↓cell proliferation, ↑apoptosis	Enhanced anticancer activity of valproic acid in HL-60 cells	Chen et al. 2010
Valproic acid + curcumin	Rats	↓neuroinflammation, ↓oxidative stress in brain tissue, ↓BACE-1, ↓APP, ↓iNOS, ↓COX-2 in brain tissue	Valproic acid potentiated the neuroprotective effect of curcumin in lipopolysaccharide treated rats	Zaky et al. 2014
α-tomatine + curcumin	Prostate cancer PC-3 cells; SCID mice	↓NF-κB activity, ↓Bcl-2 expression, ↓phospho-ERK1/2 and phospho-Akt levels in cells, ↑inhibition of tumor growth in mice with PC-3 xenograft	Synergistically induced apoptosis and inhibited the growth of human prostate cancer cells	Huang et al. 2015a

curcumin across tissues. These variations are due to the extraction, formulation, preparation of dose and specificity of the assay. It was reported that oral curcumin administration (500 mg/kg) showed its maximum concentration in intestine at 1 h, while in liver, blood and kidney the maximum curcumin levels were detected at 1–24 h (Suresh and Srinivasan 2010). Body has a high potential to metabolize absorbed curcumin through both phase I and phase II biotransformation's. In phase I metabolism, curcumin undergoes successive reduction of the double bonds in heptadiene-3, 5-dione system. Study revealed that, hexahydrocurcumin, tetrahydrocurcumin, hexahydrocurcuminol, dihydrocurcumin and octahydrocurcumin are the metabolites of curcumin. Further, the enzyme alcohol dehydrogenase is mainly responsible for the reduction of curcumin in the intestine and cytosol of liver (Ravindranath and Chandrasekhara 1981; Hoehle et al. 2006; Ireson et al. 2002; Hassaninasab et al. 2011). In phase II metabolism, the glucuronidation of reduced curcumin leads to the formation of dihydro-C-glucuronide, C-glucuronide, tetrahydrocurcumin-glucuronide and C-sulfate (Siviero et al. 2015; Pan, Huang, and Lin 1999). Most of curcumin administered by oral route is excreted primary in the feces, while very little is measured in urine (Suresh and Srinivasan 2010). In animal study, administration of curcumin suspension in water (100 mg/kg, p.o.) showed the volume of distribution (4.793 L), clearance (1.351 L/h), AUC (7.942 μg/mL/h), T_{max} (3.0 h), C_{max} (1.016 μg/mL), Ka (1.245 h^{-1}), absorption half-life (0.557 h), Ke (0.282 h^{-1}) and elimination half-life (2.457 h) (Madhavi, Madhavi, and Jithan 2012).

Safety and tolerability of curcumin

Several preclinical and clinical studies indicate that curcumin is well tolerated and generally recognized as safe by FDA (Cheng et al. 2001; Prasad et al. 2014; Shankar et al. 1980). The overwhelming safety profile of curcumin is evident from the fact that up to 12 g/kg curcumin did not exhibit any harmful effects on healthy individuals (Lao et al. 2006). Moreover, according to JECFA, an average 70 kg healthy individual can consume 4–10 g turmeric safely (Kocaadam and Şanlier 2017). Also, EFSA recommends 0–3 mg/kg curcumin is generally regarded as safe accepted daily intake in healthy humans (Kocaadam and Şanlier 2017). A Phase I clinical trial of curcumin is well tolerated when administered in patients with high risk conditions or pre-malignant lesions of the bladder, skin, cervix, stomach or oral mucosa as a single daily oral dose ranging from 500 to 8000 mg/day for 3 months (Cheng et al. 2001). Phase I trials of Sharma and coworkers reported that curcumin extract in doses between 440 and 2200 mg/day, equivalent to 36–180 mg of curcumin, for up to 4 months was well tolerated and is devoid of dose limiting toxicity in patients with advanced colorectal cancer substantiating the safety of curcumin (Sharma et al. 2001). On the contrary, another study reported that curcumin at doses ranging from 0.45 to 3.6 g/day for a period of 1 to 4 months in humans, minor elevation in serum alkaline phosphatase, lactate dehydrogenase

Table 3. Pharmacokinetic alterations of conventional drugs in concomitant use with curcumin.

Compound/preparation	Drug	Pharmacokinetic model	Duration	Outcome	Mechanism
Curcumin (500 mg/kg, p.o., suspended in tween 80 or as nanoparticles)	Phospho-sulindac (200 mg/ kg, p.o.)	Mouse xenograft model of human lung cancer	Single dose	↑C_{max} (40% with nanoparticles-70% with tween 80) and total $AUC_{0-24\,h}$ (1.5 fold with nanoparticles-2.4 fold with tween 80)	—
Curcumin (500 mg/kg, p.o. in rats and 100 mg/kg in dogs)	Rosuvastatin (5 mg/kg, p.o. in both rats and dogs)	Sprague-Dawley rats, Beagle dogs	Single dose	Rats: ↑C_{max} (1.3 fold), ↑Total $AUC_{0-\infty}$ (2.2 fold), ↑Total AUC_{0-24} (2 fold) Dogs: ↑C_{max} (1.4 fold), ↑Total $AUC_{0-\infty}$ (1.7 fold), ↑Total AUC_{0-24} (1.6 fold)	↓OATP activity by curcumin-O glucuronide and curcumin-O-sulfate.
Curcumin (200 mg/kg, p.o.)	Buspirone (10 mg/kg, i.v.)	Sprague-Dawley rats	Single dose	No significant change in AUC, CL, $V_{d,}$ MRT, and $t_{1/2}$ of buspirone	—
Curcumin (0.5–10 mg/kg, p.o. and i.v.)	Tamoxifen (9 mg/kg p.o. and 2 mg/kg i.v.)	Sprague-Dawley rats	Single dose	↓Metabolite-parent AUC ratio, ↑C_{max} (38.9–70.6%) and total $AUC_{0-\infty}$ (33.1–64.0%) for p.o. tamoxifen	↓CYP3A4 activity (IC_{50} = 2.7μM), ↓P-gp activity
Curcumin (50 mg/kg, p.o.)	Paclitaxel (20 mg/kg, p.o.)	SKOV3 human ovarian adenocarcinoma bearing female nu/nu mice	3 days	↑Total $AUC_{0-\infty}$ (4.1 fold), ↑Paclitaxel accumulation in tumor tissue (3.2 fold), ↑Bioavailability (5.2 fold)	↓P-gp and CYP3A2 protein level,
Curcumin (0.4–8 mg/kg, p.o.)	Etoposide (2 mg/kg, p.o. and 6 mg/kg, i.v.)	Sprague-Dawley rats	Single dose	↑C_{max} (32.2%–35.9%) and total $AUC_{0-\infty}$ (35.1%-50.8%) for p.o. etoposide, ↑Bioavailability (36.0%-52.0%)	↓CYP3A4 activity (IC_{50} = 2.7μM), ↓P-gp activity
Curcumin (0.5–8 mg/kg, p.o.)	Loratadine (40 mg/kg, p.o. and 1 mg/kg, i.v.)	Sprague–Dawley rats	Single dose	↑C_{max} (34.2–61.5%) and total $AUC_{0-\infty}$ (39.4–66.7%)	↓CYP3A4 activity (IC_{50} = 2.71μM), ↓P-gp activity
Curcumin (100 mg/kg, p.o.)	Losartan (10 mg/kg, p.o.)	Wistar rats	7 days	↑C_{max} (3.5 fold) and total AUC_{0-t} (1.7 fold) of losartan, ↑C_{max} (3.2 fold) and total AUC_{0-t} (1.9 fold) of EXP3174 (losartan metabolite)	—
Curcumin (25 mg/kg, 50 mg/kg, and 100 mg/kg, p.o.)	Warfarin (0.2 mg/kg, p.o.)	Wistar rats	7 days	↑Total $AUC_{0-\infty}$ (1.6 fold), ↑C_{max} (1.5 fold), ↓CL (57.14%), No significant change with 25 and 50 mg/kg doses	—
Curcumin (25 mg/kg, 50 mg/kg, and 100 mg/kg, p.o.)	Clopidogrel (30 mg/kg, p.o.)	Wistar rats	7 days	↑Total $AUC_{0-\infty}$ (1.61 fold), ↑C_{max} (1.81 fold), ↓CL (58.33%), No significant change with 25 and 50 mg/kg doses	—
Curcumin (20 mg/kg, i.p.)	Fluoxetine (5 and 20 mg/kg, i.p.)	Albino mice	3 doses in 14 h	No significant change in serum or brain levels of fluoxetine.	—
Curcumin (60 mg/kg, p.o.)	Norfloxacin (100 g/kg, p.o.)	New Zealand white rabbits	3 days	↑Total AUC_{0-t} (1.5 fold), ↑AUMC (1.7), ↑K_a (1.4 fold), ↑MRT (1.1 fold), ↑$V_{d(area)}$ (1.3 fold), ↓Overall elimination rate constant (0.8 fold)	—
Curcuminoid/piperine preparation (4 g curcuminoids plus 24 mg piperine), QID	Midazolam (3 mg) or, Flurbiprofen (100 mg), or paracetamol (325 mg)	Randomized placebo-controlled six way crossover trial in healthy volunteers	2 days	No significant change in C_{max}, $t_{1/2}$, $AUC_{0-\infty}$, CL, and metabolite levels of test drugs	—
Curcumin (100 mg/kg, p.o.)	Docetaxel (30 mg/kg, p.o.)	Sprague–Dawley rats	4 days	↑C_{max} (10 fold), total AUC (8 fold) and bioavailability (7.9 fold)	—
Curcumin (0–30 μM)	Docetaxel (0.2–10 μM)	Sprague-Dawley rats	Single dose	↑Total AUC_{0-8} (1.86 fold), ↑$t_{1/2}$ (1.55 fold), ↓CL (52.1%)	Inhibition of OATP1B1 and OATP1B3-mediated uptake of Docetaxel.
Curcumin (300 mg/day, p.o.)	Talinolol (50 mg, p.o.)	Self-controlled, two-period experiment with a randomized, open-labeled design in healthy volunteers	6 days	↓C_{max} (0.7 fold) and total $AUC_{0-\infty}$ (0.7 fold), ↑Total clearance (1.5 fold)	—

Turmeric extract (480 mg, curcuminoids, p.o.)	Nifedipine (10 mg, p.o.)	Open-labeled and randomized crossover study in healthy volunteers	Single dose	No significant change in Cmax, t1/2, AUC0-∞, and MRT.	—
Curcumin (50 and 100 mg/kg, p.o.)	Everolimus (0.5 mg/kg, p.o.)	Sprague–Dawley rats	Single dose	↓AUC_{0-540} (70.6% with 50 mg/kg and 71.5% with 100 mg/kg), ↓C_{max} (76.7%), ↑Mean residence time	↑CYP3A4 activity, ↓P-gp activity
Curcumin (60 mg/kg, p.o.)	Celiprolol (30 mg/kg)	Sprague–Dawley rats	4 days	↑C_{max} (1.9 fold), AUC_{0-8} (1.6 fold) and total AUC (1.3 fold) ↓CL (22%)	↓P-gp level
Curcumin (60 mg/kg, p.o.)	Midazolam (20 mg/ kg	Sprague–Dawley rats	4 days	↑AUC_{0-4} (2.6 fold) and total AUC (3.8 fold), but no change in C_{max}, ↓CL (75%)	↓CYP3A in small intestine, ↑CYP3A in liver and kidney

AUC, area under the plasma concentration-time curve; AUMC, area under first moment of plasma drug concentration-time curve; MRT, mean residence time; Vd (area), apparent volume of distribution; CL, clearance; CYP, cytochrome; P-gp, Pglycoprotein; Cmax, maximum plasma concentration; ka, absorption rate constant; OATP, organic anion transporting polypeptide.
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contents and minor gastrointestinal adverse events like nausea and diarrhea were observed (Sharma et al. 2004). Curcumin at a dose of 8 g/day in combination with gemcitabine in advanced pancreatic cancer patients reported intractable abdominal pain after a few days to 2 weeks of curcumin intake (Epelbaum et al. 2010). Curcumin when administered to patients with premalignant lesions or patients with advanced colorectal cancers at a dose of 3600–8000 mg daily for 4 months did not result in any noticeable toxicities except mild and easily manageable gastrointestinal events (Hsu and Cheng 2007). Further, a double blind cross over study in rheumatoid arthritis patients compare the anti-rheumatic activity of curcumin and phenylbutazone reported that curcumin at a dose of 1200 mg/day for 2 weeks was well tolerated and had no evidence of side effects (Dcodhar, Sethi, and Srimal 1980). Satoskar and coworkers evaluated the anti-inflammatory effects of curcumin in post-operative patients in a controlled trial for 5 days exhibited safe and better anti-inflammatory effects compared to placebo (Satoskar, Shah, and Shenoy 1986). Other clinical studies using doses of 375 mg thrice a day for 12 weeks did not show any untoward effects in humans (Lal et al. 2000; Lal et al. 1999). Recent, phase II trial demonstrates that 8 g/day curcumin for 2 months is well tolerated and exhibit biological effects in patients with advanced pancreatic cancer (Dhillon et al. 2008). Curcumin at a dose of 2 g/day for 6 months, as oral maintenance therapy proved to be safe in patients with ulcerative colitis except minor gastrointestinal disturbances (Hanai et al. 2006). Further, another 6 months randomized, placebo controlled, double blind pilot trial of 1 or 4 g/day curcumin in Alzheimer's patients were found to be tolerated well (Baum et al. 2008). Regular oral intake of 1 g/day of curcumin for 3 months in osteoarthritic patients shows no sign of toxicity (Pinsornsak and Niempoog 2012). A recent study reported that oral administration of 1500 mg/day of curcuminoids and 1.5 g/day of curcumin to osteoarthritic patients for 6 weeks are well tolerated and safe (Panahi et al. 2014; Rahimnia et al. 2015). Another study revealed that 6 months curcumin administration at a dose of 1.5 g/day orally to type 2 diabetes mellitus patients was well tolerated with minor side effects like constipation and nausea in few patients. Oral curcumin, 6 g/day for 4–7 weeks during radiotherapy, reduced the severity of radiation dermatitis without any toxicity in breast cancer patients (Ryan et al. 2013). In patients with nonalcoholic fatty liver disease, the intake of 500 mg amorphous dispersion curcumin formulation, containing 70 mg curcumin daily for 8 weeks was safe and well tolerated during the trial (Rahmani et al. 2016). Curcumin when administered to healthy females orally at a dose of 200 mg/day during 3rd cycles of premenstrual syndrome did not report any side effects (Fanaei et al. 2016). In another study, 500 mg curcumin given to anxiety and fatigue patients twice a day for 30 days was well tolerated (Sudheeran et al. 2016). Also, 3.6 g/day oral curcumin for 6 months was well tolerated and safe in leucoplakia patients demonstrating significant clinical response (Kuriakose et al. 2016). Considering the safety profile of curcumin and its lower cost, it is been widely used in treating various

diseases. Based on the numerous experimental and clinical evidences, curcumin is well tolerated in humans without significant side effects (Soleimani, Sahebkar, and Hosseinzadeh 2018). Although few studies reported minor adverse effects of curcumin particularly in large doses for longer duration, further studies are warranted to evaluate the long-term toxicity associated with curcumin use.

Conclusion

Numerous clinical and preclinical studies of curcumin revealed its potential against various pathologies. Curcumin mediates its effects by modulation of various molecular targets including transcription factors, enzymes, cell cycle proteins, receptors, cell surface adhesion molecules, neurotransmitters etc. Curcumin exhibits antioxidant, anti-inflammatory and anti-apoptotic potential thereby reduce neurodegenerative, cardiovascular, metabolic, gastrointestinal, respiratory and inflammatory diseases. Clinical and preclinical data have conclusively proved that curcumin modulates neurotransmitter levels and reduces neurodegeneration thereby ameliorate neuronal and behavioral dysfunctions. In CNS, curcumin reduce Alzheimer's pathology by reducing Aβ plaques and tau phosphorylation. The antidepressant and anxiolytic mechanism of curcumin includes inhibition of brain MAO activity, modulation of serotonin receptor and amelioration of neurotrophic factors. Curcumin reduces drug addiction and withdrawal symptoms, possibly through modulation of HAT, DNA methyl transferases, CREB, BDNF and CaMKIIα levels. Curcumin administration reduced Huntington's disease by reducing huntingtin aggregates. Based on the findings detailed above, additional large-scale trials/studies are warranted to determine the effectiveness of curcumin in prevention and treatment of neurological disorders. In cardiovascular disease, the anti-atherosclerotic mechanism of curcumin includes the inhibition of platelet aggregation and modulation of cholesterol homeostasis. Curcumin effectively reduce hypertension by blocking angiotensin I receptor, reducing circulating angiotensin-converting enzyme and inducing vasodilation. The antiarrhythmic mechanisms of curcumin are due to modulation of Ca^{2+} homeostasis and blockade of potassium channels. Curcumin administration reduces cerebral infracts size and volume during stroke. Clinical studies on the protective effect of curcumin against cardiovascular diseases are limited and therefore required comprehensive assessment to prove its therapeutic potential. During metabolic diseases, curcumin treatment ameliorates β-cell dysfunction, insulin signaling and GLP-1 secretion while reduces glucose intolerance, hyperglycemia, hyperinsulinemia and hyperlipidemia. Curcumin administration inhibits NF-κB activation and macrophage infiltration, reduces PAI-1, MCP-1 and leptin alongside induced HO-1, fatty acid oxidation, APO-A1 and adiponectin level. More extensive studies regarding the therapeutic potential of curcumin on the metabolic diseases in both animals and humans are warranted. Curcumin reduces the risk of osteoporosis *via* amelioration of mitochondrial membrane function, PKB phosphorylation, microRNA-365 activation, osteoblasts proliferation etc. It reduced ulcerative colitis by inhibiting neutrophil chemotaxis. The gastroprotective effect is due to inhibition of acid release, amelioration of blood flow, angiogenesis and collagenization of gastric tissue. Curcumin shows hepatoprotective action due to inhibitory activity against NF-κB. Additionally, curcumin reduced liver marker enzymes, cholesterol levels and replication of hepatitis B and C viruses. Curcumin treatment reduces asthma and allergy symptoms mainly due to inhibition of histamine release, attenuation of IgE, inhibition of COX-2 enzyme, suppression of JNK54/56, ERK 42/44 and p38 MAPK, stimulation of Nrf-2/HO-1 pathway, upregulation of Notch1, Notch2 receptors, GATA3 etc. Based on these findings, additional large-scale trials are necessary to determine the effectiveness of the curcumin in the management of endocrine, gastrointestinal and respiratory diseases. Curcumin blocks certain cytokines and enzymes, inhibits ROS generation, downregulate NF-kB activation, induce extracellular matrix production, upregulate collagen and fibronectin expressions thereby reduce inflammatory diseases. Curcumin treatment reduces fibronectin and collagen IV expressions, suppresses TGF-β signaling and exhibits antioxidant, anti-inflammatory and anti-apoptotic potential thereby ameliorates kidney functions. Clinical investigations are required for successful application of curcumin in treatment of kidney dysfunction.

Curcumin inhibits the NF-κB and STAT3 pathways, transcription factor Sp-1 and its downstream genes, phosphorylation FAK and CD24 expression, downregulates Akt, EGFR, cyclin D1, cMET expressions while enhance extracellular matrix components and upregulate DNAJ/HSP40 chaperone resulting in anti-cancer effects. In addition, curcumin induced downregulation of IGF-1R, EGFR/erbB1, erbB2/HER2, Wnt/β-catenin and Shh/Gli, and their respective downstream signaling effectors resulting in reversal of cancer incidence, progression and relapse. Studies have indicated the anticancer effects of curcumin by evaluating its effect on a variety of biological pathways involved in cell cycle regulation, apoptosis, tumorigenesis, mutagenesis and metastasis. Due to lack of clinical studies, majority of literature discussed in the current review are from preclinical studies. Therefore, clinical trials of this nutraceutical may be useful in the treatment of tumors and eliminating the use of anticancer drugs that have known side effects.

Curcumin interfere with quorum sensing, virulence and biofilm initiation thus inhibits bacterial cells. The anti-fungal mechanisms of curcumin includes the leakage of intracellular component, disruption of plasma membrane, generation of oxidative stress, induction of apoptosis, inhibition hyphae development, upregulation of chitin synthase and PKC etc. Curcumin treatment downregulated genomic transcription and translation, inhibited viral oncoproteins, suppressed the Akt/SREBP-1 pathway, inhibited hemagglutination, proteases, integrase and Tat protein acetylation resulting in antiviral effects. In spite of this, there are no clinical studies against microbial infections have been reported for this compound, therefore clinical studies are warranted to prove the potential of curcumin against infectious diseases.

Low water solubility and poor intestinal permeability generally hiders the bioavailability of curcumin, novel drug delivery system is in preclinical phase to overcome this barrier. To counter the solubility and bioavailability of curcumin, the use of adjuvant like bioavailability enhancer, and the development of delivery systems based on exosomes, liposomes, nanoparticles, micelles and dendrimers needs to be study in detail. The pharmacokinetic study of curcumin will help in designing drug regimen for clinical trials. Clinical evaluation of curcumin might help to access its safety, efficacy and tolerability against numerous diseases. In drug interaction studies, curcumin exerted enhanced bioavailability or increase the action or reduced the undesirable effects of another drug. Further studies are warranted to enhance the bioavailability, efficacy and tolerability of curcumin for the treatment and prevention of various human ailments.

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Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

3-NT	neurotrophin-3
5-HT	5-hydroxytryptamine
AAPK	acid activated protein kinase C
ABCA1	ATP-binding cassette transporter
AChE	acetylcholinesterase
AD	Alzheimer's disease
ALP	alkaline phosphatase
ALT	alanine transaminase
AMPK	AMP-activated protein kinase
AP-1	activator protein 1
apoA-1	apolipoprotein A1
AST	aspartase transaminase
ATPase	adenosine triphosphatase
Aβ	Amyloid beta
Aβ	androgen receptor
BACE-1	beta-secretase 1
Bcl-2	B-cell lymphoma 2
BDNF	brain-derived neurotrophic factor
BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
CAT	catalase
CD31	cluster of differentiation 31
CDC27	cell division cycle 27
CDKs	cyclin-dependent kinases
CHOP	C/EBP homologous protein
COX	cyclooxygenase
CREB-BP	CREB-binding protein
CTGF	connective tissue growth factor
CXCL	chemokine (C-X-C motif) ligand
CXCR4	C-X-C chemokine receptor type 4
DOPAC	3, 4-dihydroxyphenylacetic acid
EGF	epidermal growth factor
EGFRK	epidermal growth factor receptor-kinase
Egr-1	early growth response-1
eIF2α	eukaryotic initiation factor 2α
ER	endoplasmic reticulum
erbB1	avian erythroblastosis oncogene B1
ERK	extracellular receptor kinase
ER-α	estrogen receptor-alpha
FAK	focal adhesion kinase
Fas-R	Fas receptor
FGF	fibroblast growth factor
FtsZ	filamenting temperature-sensitive mutant Z
GABA	gamma-aminobutyric acid
GLI	glioma associated oncogene
GLUT	glucose transporter
GPx	glutathione peroxidase
GSH	glutathione
GSK-3	glycogen synthase kinase 3
GST	glutathione S-transferase
H2R	histamine (2)-receptor
HAT	histone acetyltransferase
HDAC2	histone deacetylase
HDL	high density lipoprotein
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HGF	hepatocyte growth factor
HIF-1	hypoxia-inducible factor-1
HIV	human immunodeficiency virus
HO-1	haeme oxygenase-1
HOMA	homeostasis model assessment
HPA axis	hypothalamic-pituitary-adrenal axis
HSP	heat shock protein
hTERT	telomerase
HVA	homovanillic acid
ICAM-1	intracellular adhesion molecule-1
IFN	interferon
IGF	insulin-like growth factor
IkB	inhibitor of NF-kB
IKK	IkB kinase
IL	interleukin
ING4	inhibitor of growth family member 4
iNOS	inducible nitric oxide synthase
IR	integrin receptor
IRF	interferon regulatory transcription factor
IRS-1	insulin receptor substrate-1
JAK	janus kinase
JAK2/STAT3	janus kinase 2/signal transducer and activator 3 of transcription
JNK	c-Jun N-terminal kinase
LDH	lactate dehydrogenase
LDL-R	low density lipoprotein-receptor
LOX	lipoxygenase
LPO	lipid peroxidation
LXR-β	liver X receptor-β
MAO	monoamine oxidase
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MDA	malondialdehyde
MIP	macrophage inflammatory protein
MMPs	matrix metalloproteinases
MPO	myeloperoxidase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	mammalian target of rapamycin
MyD88	myeloid differentiation primary response gene 88
NF-kB	nuclear factor kappa B
NGF	nerve growth factor
NLRP3	nucleotide-binding oligomerization domain (NOD)-like receptor protein 3
NMDAR	N-methyl-D-aspartate receptor
NO	nitric oxide
NQO1	NAD(P)H dehydrogenase [quinone] 1
Nrf-2	nuclear factor 2-related factor
PAK	p21-activated kinase
PARP	poly-ADP-ribose polymerase
p-CaMKII	p-calcium/calmodulin-dependent kinase II

PDGF	platelet-derived growth factor
PG	prostaglandin
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	phosphoinositide 3-kinase
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PPAR-γ	peroxisome proliferator-activated receptor-gamma
PSD-95	postsynaptic density-95
PTEN	phosphatase and tensin homolog
PTK	protein tyrosine kinase
RANK	receptor activator of NF-kB
RNS	reactive nitrogen species
ROS	reactive oxygen species
RXR	retinoid X receptor
SERCA-2	Ca2+-ATPase pump
SIRT	NAD-dependent deacetylase sirtuin
SOCS	suppressor of cytokine signaling
SOD	superoxide dismutase
SREBP	sterol regulatory element-binding proteins
STAT	signal transducers and activators of transcription
TBARS	thiobarbituric acid reactive substances
TGF-β1	transforming growth factor-β1
Th17	T helper 17
TIMP	tissue inhibitor of metalloproteinase
TLR	Toll-like receptor
TNF-α	tumor necrosis factor alpha
Treg	T regulator
TrkB	tropomyosin receptor kinase B
uPA	urokinase-type plasminogen activator
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
VLDL	very low density lipoprotein
WT-1	Wilms' tumor gene 1

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