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A Review of Therapeutic Effects of Curcumin

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Abstract: There is a growing interest in herbal medicine. Scientific studies have demonstrated the beneficial pharmacological effects of curcumin. Curcumin is a bright yellow spice, derived from the rhizome of Curcuma longa Linn. It has been proven that curcumin is a highly pleiotropic molecule which can be a modulator of intracellular signaling pathways that control cell growth, inflammation, and apoptosis. Curcumin might be a potential candidate for the prevention and/or treatment of some diseases due to its anti-oxidant, anti-inflammatory activities and an excellent safety profile. We present an updated concise review of currently available animal and clinical studies demonstrating the therapeutic effect of curcumin.

Keywords: Curcumin, therapeutic effects, review.

INTRODUCTION

Curcumin, a bright yellow spice, derived from the rhizome of Curcuma longa Linn, was primarily isolated by Vogel (1842), and was structurally characterized by Milobedeska and colleagues (1910); it was synthesized and confirmed in 1913 by Lampe and colleagues [1, 2]. Curcumin is the active ingredient in the herbal remedy and dietary spice turmeric [1, 2]. Curcumin has a long history of administration in traditional medicine of China, India and Iran, and it has been used in different folks for the treatment of many diseases such as diabetes, liver disease, rheumatoid diseases, atherosclerosis, infectious diseases and cancers [3]. The powder of turmeric rhizome is used in cookery, medicine, fabric dying and also cosmetics for many centuries [3, 4]. This important spice was introduced to the Western world in the 14th century [5] and up to now it is still in use. In the ancient Indian medicine, Ayurveda, a topical agent made of turmeric paste has been applied to treat common ocular infections and inflammations; it has also been used in wound dressing in conditions such as bites, burns, and some other skin diseases [6]; a curcumin poultice has been applied to the perineal area to improve the healing process of any birth canal lacerations [7]. Powdered turmeric has been consumed with hot milk for cure of cough and related respiratory problems [6, 7]. Roasted turmeric has been also administered as an anti-dysenteric agent [6, 7]. This ancient medicine has been also used for treatment of other digestive disorders such as indigestion, dyspepsia, flatulence, gastric and duodenal ulcers [7]. It has also been used for alleviating the hallucination states induced by some opioids and psychotropic drugs [4].

Structural Description, Bioavailability, and Safety of Curcumin

Curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione, is a lipophilic molecule that rapidly permeates cell membrane [8]. It affects the function and structure of the cell membrane and mimics typical events happening during the apoptosis process; however, the cellular response to curcumin contrasts with the typical apoptosis process as curcumin induces immediate and partly reversible loss of membrane integrity, of which cells could recover in a relatively short time [8]. It was also mentioned that membranous alterations evoked by curcumin might underlie some of its influences (ex. by changing access to phosphatidylserine, curcumin may modulate the activity of protein kinase C) [8, 9].

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Fig. (1). Curcumin I, II, and III (curcumin, demethoxycurcumin, bisdemethoxycurcumin), and curcumin keto-enol tautomers.
methoxycurcumin, demonstrated in (Fig. 1), of which I is the most common (Fig. 2) [12, 13]. There is a controversy as to whether I or III is the most potent antioxidant, anti-inflammatory, and anti-tumor agent [12, 14]. Since curcumin was demonstrated to have poor bioavailability and selectivity [15, 16], numerous analogues of this material have been introduced and tested in order to evaluate their activities against known biological targets, and also to improve upon the pharmacological profile of the natural product (improve their bioavailability, selectivity, and stability) [17-21]; moreover, Saladin et al. reported improved solubility by modifying the structure by covalent linking of a sugar to curcumin, and studied its potential as an agent for treating iron-overload disease [22]. Researchers introduced numerous approaches to improve the bioavailability of curcumin, to provide longer circulation, and to increase cellular permeability and resistance to metabolic processes. These approaches include the use of adjuvants such as Piperine that interferes with glucuronidation in liver, and some adjuvants that can block rapid metabolism of curcumin, the use of liposomal curcumin, making curcumin nanoparticles, the use of curcumin-phospholipid complexes, and the use of structural analogues of curcumin. The structural analogues of curcumin have been reported to enhance the rate of absorption with a peak plasma half-life [23-25]. Recent investigations have considered curcumin a lead compound for the design of new chemotherapeutic agents for treatment of cancers including colon cancers [26], prostate cancers [27], and other conditions with indication of chemotherapies [28-30]. In a study on curcumin, it was stated that by replacing the diketone group by an a,b-unsaturated ketone and asymmetrical replacing the phenolic groups by substituted phenyls and other aromatics, curcumin mimics various antiangiogenic activities [31]. Curcumin targets many modulatory molecules which are summarized in table 1 and some of them will be discussed further in this review.

**Curcumin as a Potent Anti-inflammatory Agent**

For thousands of years curcumin has been known to possess anti-inflammatory ability. Many of the activities associated with curcumin are related to its ability to suppress acute and chronic inflammations [43]. Nuclear factor kappa-B (NF-kB) plays a critical role in signal transduction pathways that are involved in inflammatory diseases and various cancers [44]. The NF-kB proteins reside in the cellular cytoplasm inactively, but following their activation, which requires activation of various kinases and the phosphorylation and degradation of activation inhibitors such as IKB, they are translocated to the nucleus; curcumin was shown to inhibit TNF-dependent NF-kB activation, as well as other activation pathways induced by various agents of which some were used to produce reactive oxygen intermediates that were also shown to be put out by curcumin [45]. COX-2, the inducible form of cyclooxygenases, predominates at inflammatory sites, and a great number of papers indicated a critical role of COX-2 in tumor promotion [45-48]. Curcumin down-regulates the expression of COX-2 enzyme and inhibits the expression of pro-inflammatory enzyme 5-LOX; It also induces down-regulation of various inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, interferon γ and some other chemokines [49, 50]. In vivo studies on both human and animals also revealed the anti-inflammatory effects of curcumin. A number of clinical trials revealed the efficacy of curcumin in inflammatory diseases such as inflammatory bowel disease (IBD) in human through its modulatory impact on inflammatory factors [51]. In an animal study on anti-inflammatory activity of curcumin, two oral treatments of 92 mg/g of body weight showed anti-inflammatory effect through reducing iNOS mRNA expression in the livers of lipopolysaccharide-injected mice by 50-70% [52].

**Antioxidative Activity of Curcumin**

Oxidative stress plays a major role in the pathogenesis of various diseases including cancer, diabetes, cardiovascular diseases, neuronal cell injury, and hypoxia and many experimental models, particularly in the field of injuries to nervous system, have been introduced to investigate the therapeutic effects of different materials as well as curcumin in this issue [53]. The most common experimental studies on curcumin, aside from providing new derivatives, are those of its antioxidant potentials. The biological classification of curcumin as both pro-oxidant and antioxidant, is well supported by studies showing curcumin as a free radical scavenger, a reducing agent, and a DNA damage inhibitor, especially in the presence of Cu or Fe ions. Curcumin is able to bind to Fe, Mn and Cu that was reported to modulate the antioxidant properties [54-56].
and radical scavenging effects [57, 58] of this agent. In vitro studies have shown that curcumin inhibits nitric oxide and reactive oxygen species (ROS) production in macrophages [59, 60]; it also inhibits lipoxygenase as well as cyclooxygenase in fibroblast cells of rats [61]. Oxidative stimulation of G-proteins in human brain membranes by metabolic prooxidants, homocysteine, and hydrogen peroxide was shown to be significantly depressed by this material [62]. Cyclophosphamide-induced lung injury caused by antioxidant defense mechanisms was increased by curcumin administration; curcumin administration also inhibited lipid peroxidation in liver microsomes as well as in brain homogenates of laboratory rats [45].

### Anti-tumoral Properties of Curcumin Through Apoptosis Induction, Anti Angiogenesis and Anti Migratory Effects

Extensive researches have been done on anti-tumoral properties of curcumin and several papers including many review articles were published in this field; most authors suggested that the anti-inflammatory, antioxidative, apoptosis inducing, and anti-angiogenic abilities of curcumin are the main characteristics which are involved in its anti tumoral activity [63-69]; for example, curcumin has been found to inhibit growth of gastrointestinal and liver cancers, and head and neck tumors; curcumin was able to target breast stem/progenitor cells, as evidenced by suppressed mammosphere formation along serial passages and by a decrease in the percent of ALDH-positive cells [70, 71].

Down-regulation of NF-κB leads to suppression of Bcl-2 and Bcl-XL, which are the anti-apoptotic genes leading to apoptosis induction [72]. Inhibition of COX-2 was reported as another mechanism which is involved in anti-tumoral activity of curcumin which was considered for being studied for treatment of colonic tumors by this agent [45].Inhibition of Akt, a protein kinase that promotes cell survival and inhibits apoptosis, is also enhanced by curcumin [73]. P53 gene, which mediates apoptosis under stressful situations, and its downstream targets, were overexpressed in human basal cell carcinoma [74], human hepatoblastoma [75], and human breast cancer cells [76, 77] after curcumin administration.

In another study on colorectal carcinoma cell, however, p53, a tumor suppressor gene, was decreased, while the heat-shock protein 70 had an increase concomitantly, after curcumin treatment [78]. Hence, the role of p53 in curcumin induced apoptosis was revealed to be tissue-specific [79].

Tumors are dependent upon angiogenesis and providing the blood supply to continue growth and to allow cancerous cells to enter the circulation for metastasis; curcumin, other than apoptosis inducing effect, was shown to interfere with many of the processes involved in angiogenesis [80] including inhibition of fibroblast growth factor (FGF)-induced neovascularization [80-82], ligands of vascular endothelial growth factor (VEGF), and angiopoietin 1 and 2 [82]. Other than the factors which directly affect the angiogenesis process, curcumin has the ability to regulate cell adhesion molecules such as endothelial leukocyte adhesion molecule-1 (ELAM-1), intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), and cell surface proteins involved in tumor metastasis [83].

### Therapeutic Effects of Curcumin; Developments in the Last Decades

Many researchers have worked on curcumin due to its various therapeutic effects on different diseases. Shortly, curcumin has received attention mostly due to its antioxidant, anti-inflammatory, anti-tumoral, apoptosis-inducing, and anti-angiogenesis effects, which were reported in many investigations. Curcumin acts on multiple targets in cellular pathways making this agent able to perform multiple actions (Fig. 3) [84]. These therapeutic influences of curcumin have been evaluated in many experiments for several diseases. Some examples are briefly mentioned here with more emphasizing on brain and neurological effects, cardiovascular effects, and influences on the reproductive system which consist most of our laboratory experiments and trials (Table 1).

### Curcumin and the Nervous System

Curcumin has been extensively under investigations for its therapeutic effects on nervous system, especially the brain and the diseases related to this vital organ. We have recently attained some good results on the protective activities of curcumin against neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases in animal models which are pending to be published. Reviewing previous literature led to more expectation to receive positive responses from curcumin administration in inflammatory brain diseases as well as brain tumors. Purkayastha et al. (2009) showed that curcumin effectively blocks brain tumor formation and also removes brain tumors; They observed that the solubilized curcumin causes activation of pro-apoptotic enzymes caspase 3/7 in human oligodendroglialoma, and mouse tumor cells N18 (neuroblastoma), GL261 (glioma), and B16F10 *In vitro*: A simultaneous decrease in cell viability was also revealed by MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assays; curcumin effectively suppressed Cyclin D1, NF-κB, Bcl-XL, Akt, and VEGF, which explains its efficacy in blocking proliferation, survival, and invasion of the B16F10 cells in the brain [85]. Curcumin has been also used to treat medulloblastoma and glioblastoma cells [86]; the reduction in viable cell mass was associated with a combination of G2/M phase change arrest and apoptotic induction. Curcumin also considerably decreased anchorage-independent clonogenic growth and reduced the CD133-positive stem-like populations. Downregulation of the insulin-like growth factor pathways in DAOY medulloblastoma cells was observed, levels of STAT3 were also attenuated; conclusively, curcumin could inhibit malignant brain tumor growth via the modulation of cell proliferation, survival and stem cell phenotype alterations[86]. Glioblastoma, the most aggressive form of brain and central nervous system tumors, is characterized by high rates of cell proliferation, migration and invasion. It has been demonstrated that curcumin-loaded glyceral monoleate (GMO) nanoparticles (NP) inhibit cellular proliferation, migration and invasion along with a higher percentage of cell cycle arrest and telomerase inhibition, thus result in a greater percentage of apoptotic cell death in glioma cells compared with native curcumin; the study of Kundu et al. also illustrated enhanced bioavailability of curcumin in blood serum and brain tissue when delivered by curcumin-loaded GMO NPs compared with native curcumin in a rat model[87].

Traumatic brain injury (TBI) is followed by an energy crisis of the brain and often decrease in cognitive abilities[88]. The goal of a study conducted by Sharma *et al.* was to determine the influence of curcumin on molecular systems involved in the monitoring, balance, and transduction of cellular energy, in the hippocampus of animals exposed to mild fluid percussion injury (FPI). The results demonstrated that curcumin diet countered with the effects of FPI and elevated the levels of AMP-activated protein kinase, ubiquitous mitochondrial creatine kinase, cytochrome-c oxidease 2 in curcumin treated group as compared to normal diet rats [89]. Aluminum, a well recognized neurotoxicant, is reported to be involved in the etiology of Alzheimer’s disease due to its easy admittance and collection in central nervous system, so Kakkar et al. (2011) evaluated the therapeutic effects of curcumin loaded solid lipid nanoparticles(C-SLNs) in aluminum induced behavioural, biochemical and histopathological alterations in mice brain; treatment with curcumin demonstrated recovery in membrane lipid oxide (LPO) and acetylcholine-esterase (AChE); histopathology of the brain sections also pointed out significant improvements [90].

Cholesterol is critical to brain growth, but high levels of cholesterol have been associated with neurodegenerative diseases. The liver X receptor-{beta} retinoid X receptor-α (LXR/RXR)-regulated gene, ABCA1, effluxes cellular cholesterol to apolipoprotein A1
The Therapeutic Effects of Curcumin


2035

(apoA1), which plays an important role in reverse cholesterol transport. In a study done by Tian et al. it was disclosed that curcumin may act as a LXR agonist and then activate the ABCA1 promoter and increase ABCA1 protein levels and apoA1 dependent cellular cholesterol efflux from the brain [91], which in fact facilitates cholesterol transportation and prevent its harmful effects on the brain. The efficacy of curcumin on senile brain plaques and cerebral amyloid angiopathy (CAA) was determined in the aged brain of various animal species and a patients with Alzheimer’s disease [92]. Findings indicated that curcumin particularly binds to the aggregated Aβ molecules in various animals, and further to phosphorylated tau protein, most likely according to its conformational nature[92]; thus, it helps amelioration of senile brain alterations and neurodegeneration.

Oxidative stress plays an important part in neuronal damages and cognitive dysfunction made by chronic cerebral ischemia. UCP2 (Uncoupling protein 2), which was shown to be increased as a result of curcumin administration [93], have a central role in inhibiting oxidative stress [93]. Another study was conducted to examine the effect of curcumin on memory functions, brain insulin receptors (IRs), AChE activity, and oxidative stress in intracerebroventricular (ICV) area in Streptozotocin (STZ)-induced dementia in rats. Results suggested that in addition to the anticholinesterase and antioxidant activity, effect on brain IR may also be

Fig. (3). Molecular targets of curcumin. Abbreviations: NF-κB, nuclear factor-kappa B; AP-1, activating protein1; STAT, signal transducers and activators of transcription; Nrf-2, nuclear factor 2-related factor; Egr-1, early growth response gene-1; PPAR-γ, peroxisome proliferator-activated receptor-gamma; CBP, CREB-binding protein; EpRE, CTGF, connective tissue growth factor; EGF, epidermal growth factor; EGFRK, epidermal growth factor receptor-kinase; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; AR, androgen receptor; Ah-R, aryl hydrocarbon receptor; DR-5, death receptor-5; EGF-R, epidermal growth factor receptor; EPCR, endothelial protein C-receptor; ERα, estrogen receptor-alpha; Ras-R, Ras receptor; H2-R, histamine (2) receptor; InsP3-R, inositol 1,4,5-triphosphate receptor; IR, integrin receptor; IL-8-R, interleukin 8 receptor; LDL-R, low density lipoprotein receptor; MMP, matrix metalloprotease; TIMP, tissue inhibitor of metalloproteinase-3; INOS, inducible nitric oxide oxidase; COX-2, cyclooxygenase-2; LOX, lipoygenase; Gcl, glutamate-cysteine ligase; NAT, arylamine N-acetyltransferases; IAP, inhibitory apoptosis protein; TNF-α, tumor necrosis factor alpha; IL, interleukin; MCP, monocyte chemoattractant protein; MIF, migration inhibition protein; MIP, macrophage inflammatory protein; ERK, extracellular receptor kinase; JAK, Janus kinase; NFKβ, nuclear factor kappa B; N-terminal kinase; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; PKC, protein kinase C; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; FAK, focal adhesion kinase; PhK, phosphorylase kinase; pp60src, pp60src tyrosine kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; FPTase, farnesyl protein transferase; GST, glutathione S-transferase; HO, hemeoxygenase; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ELAM-1, endothelial leukocyte adhesion molecule-1; SHP-2, Src homology 2 domain-containing tyrosine phosphatase 2; uPA, urokinase-type plasminogen activator. (obtained from Aggarwal B.B. et al., 2008).
Table 1. Diseases of Different Body Systems Taking Effects from Curcumin

| Nervous system | • Alzheimer’s disease  
|               | • Parkinson’s disease  
|               | • Brain tumor  
|               | • Multiple sclerosis  
|               | • Neurodegenerative diseases  
|               | • Neuromflammatory diseases  
|               | • Traumatic brain injury  
|               | • Ischemia  
|               | • Depression  
|               | • Encephalopathy (hepatic and/or uremic)  
| Respiratory system | • Lung cancer  
|                   | • Inflammatory lung diseases  
|                   | • Pneumonia (anti-bacterial effect)  
| Cardiovascular system | • Cardiomyopathy (ex. Diabetic cardiomyopathy)  
|                    | • Oxidative heart injury  
|                    | • Cardiac hypertrophy  
|                    | • Myocardial infarction  
| Urinary system | • Renal tubular fibrosis  
|              | • Inflammatory kidney diseases  
|              | • Oxidative kidney injury  
|              | • Ischemic kidney damage  
|              | • Cancers of urinary system (Kidney, prostate, bladder)  
| Reproductive system | • Toxin induced oxidative damage (ex. Metronidazol, Aflatoxin, etc.)  
|                    | • Tumors of reproductive system  
|                    | • Dysmenorrhea  
| Digestive and hepato-biliary system | • Tumors  
|                        | • GI ulcers  
|                        | • Inflammatory bowel disease (Crohn’s, Ulcerative colitis)  
|                        | • Pancreatitis  
|                        | • Hepatitis  
|                        | • Cirrhosis  
|                        | • Jaundice  
|                        | • Hepatic injuries (ex. Drug induced)  
|                        | • Oxidative damage  
| Musculoskeletal system and Skin diseases | • Inflammatory diseases (ex. Osteoarthritis)  
|                           | • Oxidative stress  
|                           | • Ischemic damage  
|                           | • Insulin resistance  
|                           | • Tumors (ex. Osteosarcoma)  
|                           | • Osteoporosis  
|                           | • Skin wound  
|                           | • Psoriasis  
|                           | • Oxidative skin injury  
| Endocrine system | • Diabetes  
|                | • Hypothyroidism  
|                | • Endocrine tumors  

an important factor for protective effect of curcumin against STZ-induced dementia [94].

Neuroprotective impacts of curcumin was also examined in rat’s middle cerebral artery occlusion (MCAO) model [95]. Treatment with curcumin could significantly improve neurobehavioral performance compared to untreated ischemic rats as judged by its effect on rota-rod performance and grid walking. An important inhibition in lipid peroxidation and an increase in superoxide dismutase (SOD) activity in corpus striatum and cerebral cortex were observed following treatment with curcumin. Histologically, a decrease in the infarct area from 33% to 24% was observed in MCAO rats treated with this agent [95].

A different study aimed to investigate the antidepressant-like effect and the possible mechanisms of curcumin in a CORT-induced depression model in rats [96]. The results suggest that curcumin makes an antidepressant-like effect in CORT-treated rats, which is probably mediated by increasing brain-derived neurotrophic factors expression in the hippocampus and frontal cortex [96].

In our laboratory experiments we have been working on curcumin and its therapeutic effects on hepatic encephalopathy. We have observed positive therapeutic influences of curcumin on behavioral examinations as well as histopathological investigations in thioacetamide-induced hepatic encephalopathy in laboratory rats. To sum up, curcumin, according to literature and our investigations, is a potent neuroprotective agent with uncertain adverse effects.

Curcumin and the Respiratory system

Pillai and his group investigated the cellular and molecular changes induced by curcumin leading to the reduction of apoptosis in human lung cancer cell lines in a concentration dependent pattern. A reduction in expression of p53, Bcl-2, and Bcl-X<sub>L</sub> was detected after 12 h exposure of 40 μM curcumin. Bak and Caspase genes remained unaffected up to 60 μM curcumin but displayed diminution in expression levels at 80-160 μM [97]. It’s also been hypothesized that more bioavailable curcuminoid complex may adjust lung carcinogenesis, mostly by inhibiting STAT3 activation by Alexandrow et al. (2011) in vitro and in vivo. These reports pointed out that the activity of the STAT3 pathway can be suppressed by curcumin treatment, associated with a reduction in cell proliferation, supporting the hypothesis that inhibition of the STAT3 pathway characterizes at least one important means by which curcumin brings out its effects on the broncho-epithelium [98]. It is well known that matrix metalloproteinases (MMPs) play an important role in the invasion, metastasis and angiogenesis of cancer cells [99], so substances suppressing the MMPs could prevent the cancer cells migration and invasion. In one study the anti-tumor invasion and migration effects of lung cancer cells induced by curcumin were examined. Their findings suggested that curcumin has anti-metastatic ability by reducing invasiveness of cancer cells through inhibition of MMP-2 and MMP-9 in human lung cancer[100]. Effect of dietary curcumin in radiation-induced lung diseases and lung tumor suppression was also examined in a murine model. In vitro, curcumin improved antioxidant defenses by increasing heme oxygenase 1 (HO-1) levels in primary lung endothelial and fibroblast cells and prevented radiation-induced production of ROS [101]. Curcumin, in clinically appropriate concentrations for topical administration, demonstrated powerful antibacterial effect against a facultative upper respiratory tract pathogen by blocking bacterial growth, adherence, invasion, and pro-inflammatory activation of upper respiratory tract epithelial cells (by strongly suppressing IL-8 release) in vitro [102].

Curcumin and the Cardiovascular System

Many studies have pointed out that immune or inducible (iNOS), and endothelial (eNOS) nitric oxide synthase play a crucial part in the pathogenesis of cardiovascular disorders, such as cardiomyopathy, due to diabetes [103]. Since curcumin was shown to
downregulate NOS and decrease NO oxidation, it may have inhibitory effect on the development of cardiovascular disorders in hyper oxidative diseases such as diabetes [104]. Farhangkhoee et al. (2006) demonstrated that the myocardial tissue of rats with diabetes revealed elevated levels of eNOS mRNA and iNOS mRNA versus control rats, and curcumin treatment blocked eNOS mRNA and iNOS mRNA upregulation showing a reduction in the oxidative DNA impairment. Curcumin downregulates NOS by activation of the NF-κB and protein-1 (AP-1) [105].

A study in rats has revealed that adriamycin causes a rise in heart rate, ST segment elevation, reduced myocardial glutathione content and glutathione peroxidase activity, increased serum lipid peroxide, and increased cardiac catalase activity[106]. In a study, phenylbutyrate, a histone acetyl-transferase inhibitor, was demonstrated to have a protective effect against adriamycin-induced cardiac injury by increasing the level and the activity of cardiac manganese superoxide dismutase enzyme[107].

Previous studies have revealed that p300 transcriptional activity was increased during agonist-induced cardiac hypertrophy and after blocking the p300-HAT activity, the agonist-mediated cardiac growth was inhibited [108, 109]. Curcumin also revealed positive effects in the prevention of cardiac hypertrophy and heart failure [110, 111] since it has been reported to be an inhibitor of p300-HAT[112]. Morimoto et al. (2008) have also evaluated these effects in two various heart failure models: hypertensive heart disease in salt-sensitive Dahl rats and surgically induced myocardial infarction in rats. After the administration of curcumin for 7 weeks in salt-sensitive hypertensive Dahl rats a considerable and valuable preservation of the systolic function in the curcumin-treated group was observed; In surgically-induced myocardial infarction rats, the systolic function was ameliorated in the curcumin-treated group, and the hypertrophy of the non-infarcted myocardium was decreased [111]. Li et al. demonstrated that rodents treated with oral curcumin were noticeably resistant to cardiac hypertrophy caused by bundling of the aorta and the progression of heart failure was decreased through reduction of the NF-κB activation and inflammatory markers, including MCP-1, IL-6, IL-1, and TNF-α mRNA and protein expression induced by aortic bundling [110]. The parameters of inflammatory process play an essential part in the pathogenesis of many cardiovascular complications, like atherosclerotic process, acute coronary syndrome[113], and atrial arrhythmias[114]. Therefore, the anti-inflammatory effect of curcumin via down regulating the NF-κB, leading to a decrease in the expression of tumor necrotic factor-α (TNF-α), IL-1 and IL-6 [115], and blocking the independent mitogen activated protein kinase (MAPK) pathways [116], may prevent these complications. Curcumin also exhibited anti-proliferative effect which is remarkably associated to its power to induce HO-1[117]. It is well known that the HO-1 owns important antioxidative and anti-inflammatory functions and effects in concert with other fundamental enzymes in the preservation of cellular homeostasis expression[118].

Curcumin and the Urinary System

Reviewing the literature about effects of curcumin on urinary system revealed that curcumin prevents renal tubular fibrosis by attenuation of TGF-b1-induced epithelial mesenchymal transition in renal tubular cells through the downregulation of transcription factor, snail-1, and also affecting different ILs and MMPs[119]. Epithelial mesenchymal transition not only is an essential phase of kidney development during embryogenesis, but also is involved in several adult pathologies, especially cancer and fibrosis. Epithelial mesenchymal transition of tubular epithelial cells is known to play an important part in renal fibrosis process. [119]. Paracetamol is an agent which is introduced to impose a significant renal impairment, characterized by the increase in blood urea nitrogen and creatinine, in animal models. Moreover, paracetamol has been found to affect renal function by decreasing renal blood supply, glomerular filtration rate, and exerting acute and chronic nephrotoxicity which is characterized by necrosis and damage to proximal tubule [120]. In a study by Yousef et al. (2010) it was concluded that curcumin, according to its antioxidative and anti-inflammatory activities, has a protective effect against paracetamol-induced oxidative kidney damage [121]. Shahed et al. (2001) also reported the protective influence of curcumin against ischemic kidney damage by upregulation of antioxidant gene expression, particularly the antioxidant enzyme Mn-superoxide dismutase, located on the mitochondrial matrix [122].

Curcumin and male Reproductive System

The male reproductive system is consisted of the gonads and the androgen hormones, the epididymides, the ductus or vasa deferens, the seminal vesicles, the ejaculatory ducts, penis, and also certain accessory structures, such as prostate and the bulbourethral glands. This system is of the main targets affected by curcumin.

Metronidazole, an anti-parasitic drug, acts as a testosterone biosynthesis inhibitor which makes negative effects on the testis [123]. Our laboratory investigations demonstrated that curcumin can ameliorate the unfavorable effects of metronidazol such as decrease in tubule volume, length, diameter and height of germinal epithelium, and also leydig cell hyperplasia in the testis. This ameliorative effect of curcumin on the above-mentioned parameters could be due to its ability to scavenge the free radicals and acting as an antioxidant agent, and also might be due to enhancement of serum level of testosterone [124]. Another study was carried out to evaluate the therapeutic effects of curcumin on the di-n- butylphthalate (DBP)-induced testicular damage in rats [125]. Benzenedicarboxylic acid dibutyl ester, also known as butylphthalate or di-n-butylphthalate (DBP), is extensively used as a plasticizer in cellulose plastics, as a solvent for dye, and for a variety of other products[126]. Curcumin may stop peroxide alteration in the sperm and the testicular membrane which leads to enhancement of sperm motility and decrease in spermatozoa defects[125]. Administration of curcumin could also relieve the inhibition of the antioxidant enzymes, G6PD and γ-GT, and/or may have triggered their synthesis that in turn attenuates the oxidative damage caused by DBP or its metabolites [125]. Histopathologically, DBP-treated testes demonstrated marked necrosis of testicular epidermal cells and degeneration of seminiferous tubules[125]. Maintenance of the structural and functional activity of seminiferous tubules by curcumin was somewhat similar to that of the control group, showing its protective effect on the testes[125]. Mathuria et al. investigated the influences of curcumin on aflatoxin-induced toxicity in mice spermatozoa. Aflatoxin noticeably reduced sperm count, viability, and motility; different morphologic defects were encountered; thus, treatment with curcumin improved aflatoxin-induced sperm decrease, immobilization, and viability, and enhanced the morphological characteristics of the sperm [127]. In a study conducted by Giannessi et al., it was showed that curcumin protects Leydig cells of mice from the damage caused by chronic alcohol consumption [128]. It was seen that alcohol consumption inhibited testosterone production and caused testicular atrophy and enhanced mitochondrial diameter by more than three folds. In curcumin-treated alcohol-fed mice the necrosis of Leydig cells was decreased in comparison to alcohol-fed mice; the diameters of the mitochondria were considerably decreased even though testosterone plasma levels were not considerably different from those of the controls[129].

Based on previously published reports, Cisplatin administration caused irregularity of seminiferous tubules, reduction of seminiferous epithelial layers, sperm maturation arrest, and perivascular fibrosis; curcumin administration in cisplatin-treated rats considerably prevented these histopathological changes. Curcumin affected the rats by a major increase in plasma testosterone levels, GSH levels and GSH-glutathione peroxidase activity, and a de-
crease in Malondialdehyde and nitric oxide levels in testicular tissue[130].

Hong et al. evaluated the effects of curcumin on prostate cancer cells invasion in both in vitro and in vivo. Curcumin was shown to markedly reduce the tumor volume, MMP-2 activity, and MMP-9 activity in the tumor-bearing site. In the curcumin-treated group the metastatic nodules were considerably fewer than the untreated group, in vivo. Therefore, curcumin seemed to constitute a potential agent for the prevention of cancer progression, or at least of the initial phase of metastasis, in prostate cancer[131]. Chendil et al. investigated the radio-sensitizing outcomes of curcumin in p53 mutant prostate cancer cell line PC-3 [132]. They strongly suggested curcumin as a potent radio-sensitizer; it acts by overcoming the impacts of radiation-induced prosurvival gene expression in prostate cancer. Another study showed direct anti-inflammatory activity of MKP5 in prostate cells and suggested that upregulation of MKP5 by curcumin may contribute to their chemopreventive actions by reducing prostatic inflammation [133]. Curcumin Analogues also had been studied as novel androgen receptor antagonists with the potential to act as an anti-prostate cancer agent. Results of an experimental study implied that the curcumin analogues may function as a 17α-substituted dehydrotestosterone, thus, some of these compounds have been identified as a new class of anti-androgen agents [134].

Curcumin and the Female Reproductive System

The female reproductive system consists of the paired ovaries and oviducts, the uterus, the vagina, the external genitalia, and the mammary glands. All of these structures have evolved structurally and physiologically for the primary functions of ovulation, fertilization of an ovum by a sperm, and process of pregnancy [135]. In this field, Chlorpyrifos (CPF), an organophosphate pesticide, was evaluated by Madhavi et al. for its potential to produce toxicity in the reproductive system of mice following oral exposure. It was concluded that CPF administration leads to increased levels of lipid peroxidation and decreased levels of FSH hormone in mice which caused inappropriate ovulation leading to infertility of mice, while curcumin restored FSH levels and lactoperoxidase levels to greater amount causing restored fertility in mice. CPF also brings about histopathological alteration through degeneration of germinal epithelium and graffian follicle, while curcumin treatment caused normal architecture of graffian follicle and germinal epithelium in mice [136].

A study was planned by El-Sayed to investigate the effects of curcumin on the uterine contractility of non-pregnant rats in vitro. Curcumin exhibited potential tocolytic effects in the rat uterus possibly through antagonizing receptor-dependent procedure (oxytocin-induced contraction), an effect that could be beneficial in women with dysmenorrhea or in premature labor[137]. The results achieved from another study enclosed that curcumin produces a smooth muscle relaxation effect on rat’s uterus by receptor-dependent and independent mechanisms [138]. The growth-inhibitory effect of curcumin on human ovary cancer was also investigated by Liduan and his colleagues [139]; after being treated by various concentrations of curcumin, the growth of cancerous masses was inhibited considerably in ovary. Some cancer cells presented characteristic morphological changes of apoptosis. The induction of apoptosis by down-regulating the expression of Bcl-2 and p53 was possibly one of its molecular mechanisms[139]. These results were in agreement with those achieved by Xiaofen et al. (2005) that reported the apoptosis-inducing effect of curcumin on human ovary cancer [140]. Estradiol has been established as a risk factor for cervical cancer and has been shown to play a synergistic role with viral oncoproteins. One study conducted by Singh et al. [141] showed that curcumin counteracts with the proliferative effects of estradiol and induces apoptosis in cervical cancer cells through inhibition of the pathways which were improved by estradiol [141].

Curcumin and Hepato-biliary and Digestive System

Paracetamol-induced hepatocellular necrosis is characterized by increased liver enzymes and LDH activities. Paracetamol also showed to cause decrease in plasma total protein, albumin and globulin, while increased plasma bilirubin. The liver is the major source of the serum proteins, in which the parenchymal cells are responsible for synthesis of fibrinogen, albumin, many coagulation factors and most of the globulins [142]. Researchers showed that curcumin administration offered significant protection against hepatic necrosis induced by paracetamol [121]. Another study also exhibited curcumin’s hepatoprotective effect against arsenic-induced liver damage [143]; Messner and colleagues also revealed the antioxidative potential of curcumin in iron loading hepatotoxicity and oxidative stress in rat’s liver without making any alteration in iron uptake [144]. These papers highly suggested the responsibility of antioxidative activity of curcumin for the demonstrated outcomes.

Paraoxonase-1 is an enzyme which is mainly synthesised in the liver and protects low density lipids (LDL) from oxidation, thereby exhibiting antiatherogenic activities. In a experimental study curcumin was introduced as a potent Paraoxonase-1 inducer in vitro, but not in vivo, which could be due to its low bioavailability and absorption in curcumin-fed mice [145]. Curcumin inhibits cell cycle progression during normal liver regeneration in rats predominantly at the level of the G2/M transition point in the cell cycle; this was reported by Seehofer et al. (2009) who administered curcumin to male Sprague-Dawley rats which underwent sham operation with 70% partial hepatectomy. They have seen that liver mass and function was not significantly changed. Nevertheless, they suggested that application of curcumin should be performed with caution in such conditions (high physiological cell proliferation)[146].

There are several studies on hepatoprotective properties of curcumin suggesting different mechanisms of action for this agent to impose its protection against oxidative, inflammatory and even tumor producing states [147-150].

Reviewing articles on various therapeutic effects of curcumin on gastro-intestinal (GI) system showed finite data of clinical trials. It is expected to see positive effects from this medicine in GI diseases related to inflammatory and oxidative states, particularly chronic diseases of GI system which are among the common and still under investigation diseases for diagnosis and treatment [151]. Many researches were done on palliative and healing effects of curcumin on inflammatory bowel diseases, Crohn’s and ulcerative colitis, which all reported positive therapeutic impacts of this agent [152]. Clinical trials also indicated the fact that curcumin, according to its safety for administration, can be used at least as an adjuvant therapy for chronic diseases of GI system involving the inflammatory response of the body; however, almost all of the published studies suggested that larger-scale, double-blind trials are needed to be conducted to establish a role for curcumin in the treatment of inflammatory bowel diseases such as ulcerative colitis. In addition to improving results when curcumin is used in conjunction with conventional medications, it may pose a cost-beneficial alternative [153].

Tumors of digestive system have also been investigated whether they take positive effects from curcumin [154], and it was obvious that curcumin, due to its multiple targets, and activities against inflammation, angiogenesis, and metastasis of tumors (as described above), possesses anti tumor ability in GI tract as well as liver (ex. Hepatocellular carcinoma) [155].

Curcumin and Musculoskeletal System

Considering the anti-inflammatory and antioxidative abilities of curcumin, receiving positive response from its administration in such problems in skeletal system was anticipated [156]. For in-
stance. Lev-Ari et al. suggested COX-2 inhibition as the main mechanism of curcumin action against the inflammatory and apoptotic state in osteoarthritis. They have also recommended that combination therapy of both Celecoxib and curcumin may bring about positive results in treatment of osteoarthritis [157]. The effects of curcumin on skeletal muscle were evaluated during ischemia-reperfusion condition by Avci et al. (2012); Plasma TNF-α and IL-1β levels were decreased significantly in curcumin-treated group of ischemic reperfusion muscular injury. Levels of antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase) activities, Malondialdehyde, and NO in muscle also revealed significant reductions in the curcumin treated group compared with the untreated group. They implied that curcumin had more potent antioxidative activity than vitamin E in the skeletal muscle ischemic damage [158].

Immobilization is characterized by activation of the ubiquitin-proteasome-dependent proteolytic system and turning on the mitochondrial apoptotic pathway. Increased oxidative stress and inflammatory response are resulted from immobilized skeletal muscles; In a study it was demonstrated that curcumin reduces the muscular atrophy and improves muscle reloading by normalizing the proteasome chymotrypsin-like activity, ubiquitin-conjugate levels and caspase-3 activity [159]. Poulin et al. showed that curcumin can prevent muscle atrophy induced by sepsis through its inhibitory effect on NF-κB [160]. Curcumin was also shown to improve muscular insulin resistance by increasing oxidation of fatty acid and glucose, through up-regulating the expression of phosphorylated AMP-activated protein kinase, CD36, and carnitine palmitoyltransferase 1, and down-regulating the expression of pyruvate-dehydrogenase-4 and phosphorylated-glycogen-synthase in vivo and in vitro [161]. There are many published documents on therapeutic effects of curcumin on muscular tissue which mainly point to the protective effects of this agent against muscular injuries of different origins through different pathways [162, 163].

Curcumin and Skin

Wound healing [164], and Psoriasis [165], were some examples of the diseases which demonstrated to receive therapeutic effects from curcumin. In psoriasis, the response rate was low, possibly caused by a placebo effect or the natural history of psoriasis; hence, large placebo-controlled studies are still needed before introducing curcumin as a psoriasis treatment. Of the main mechanisms involved in the wound healing activity of different agents are their antioxidant and anti-inflammatory effects as well as induction of collagen synthesis and vascularization [166, 167]. Curcumin was also proved to have healing effects on skin wound caused by fractionated irradiation [168], and carbon dioxide laserizing[169].

Curcumin and Diabetes

Curcumin demonstrated anti-hyperglycemic and hypoholes-terolemic effects in type 2 diabetes [170-172] as well as protective effect against pancreatic injury (mostly on β cells which secrete insulin) by its antioxidant and anti-inflammatory impact in a model of STZ-induced pancreatic damage [173]. Some studies revealed that curcumin not only attenuates the complications that are directly made by diabetes, but also ameliorates the indirect complications caused by this disease. For instance, diabetic neuropathy, a microvascular problem which occurs mostly due to oxidative damage and inflammation, was shown to be improved after curcumin administration [35]. Diabetic retinopathy [174], nephropathy [175], and cardiomyopathy [176, 177], of the common complications of long-lasting diabetes, were also ameliorated after curcumin consumption. 

Curcumin and Cancer

Curcumin has exhibited therapeutic effects against different types of cancer.

- Breast Cancer: Many studies have described the anticarcinogenic effects of curcumin in various breast cancer cell lines through several mechanisms. For example, curcumin revealed anti breast cancer impact via inhibiting the cytochrome P450 [178], inhibition of COX-1 and COX-2 enzymes, down-regulation of Bax expression, inhibiting VEGF and b-FGF [179, 180], inhibiting telomerase activity through human telomerase reverse transcriptase [181], downregulating the expression of MMP-2, upregulating tissue inhibitor of metalloproteinase-1 (TIMP-1) [182], blocking NF-kB [183], and downregulating the insulin-like growth factor-1 (IGF-1) [184]. In an animal study curcumin usage partially reversed the tumor exosome-mediated inhibition of NK cell that may account for the anticancer properties of this substance [185]. Curcumin also exhibited anti-metastatic activity in breast cancer according to previous in vivo investigations [178, 186].

- Gastrointestinal cancers: Curcumin was shown to inhibit the cytokine-induced activation of iNOS, VCAM, and NF-kB in human esophageal microvascular endothelial cells from normal human esophageal tissues [187]. Since these inflammatory molecules are overexpressed in several cancerous tissues, curcumin was supposed to indirectly affect the esophageal cancers. A study in rats revealed the anti esophageal carcinogenesis effect of dietary curcumin (500 ppm) during initiation and post-initiation stages by 27% and 33%, respectively [186]. Another study on rats also showed the efficacy of curcumin as a chemopreventive agent by modulating the incidence of neoplastic changes in the esophagus [188].

On the effects of curcumin in gastric tumors several in vivo studies demonstrated the positive impacts of this agent against fore-stomach cancers in animal models. In these investigations, dietary curcumin inhibited the incidence and multiplicity of the tumor and also played as a chemopreventive agent [178]. Curcumin also showed chemopreventive and anti metastatic effects as well as apoptosis inducing impact on intestinal cancers in animal models [178]. In a phase I clinical trial including six cases with intestinal metaplasia of the stomach, one out of the six patients showed histological improvement in pre-cancerous lesions after receiving 0.5-12 g/day curcumin for 3 months [186].

Curcumin was shown to interrupt adhesion pathways, and induce apoptosis through PARP cleavage, Caspase 3 and Bcl-X, reduction, and increasing Caspase 8 activity, and also inhibiting the tumoral cell proliferation in colorectal cancers [178, 189]. Moreover, curcumin administration leads to cell shrinkage, chromatin condensation, and fragmentation of DNA in colonocytes [178, 190]. Curcumin-induced apoptosis regulated by Bax suggested that the targeting of Bcl-X, can be taken into account to treat Bax-deficient, chemotherapy-resistant cancers [178, 191]. Curcumin together with celecoxib downregulate COX-2 expression by inhibition of prostaglandin formation [192], it can also induce apoptosis through a parallel ceramide-associated pathway and ROS associated mechanism [193]. In vivo studies demonstrated the chemopreventive and anti-cancerous activities of curcumin in rodents [186, 194, 195] and human [178, 186]. Curcumin induced apoptosis, inhibited the formation of carcinogen-induced colorectal tumors, and induced apoptosis via mitochondrial pathways, in rats [194, 195]. In addition, Liposomal curcumin exhibited noticeable anti-tumoral activity by inhibiting angiogenesis as well as increasing the apoptosis and inhibition the tumor growth in mice [196]. There were numerous clinical studies on anti-tumoral effects of curcumin of which some positive results were obtained such as anti-inflammatory impact in advanced colorectal cancers as well as apoptosis induction; however, literatures revealed that according to extensive intestinal metabolism of curcumin leading to low bioavailability, obtaining a sufficient blood concentration in human is still a concern in clinical studies [178, 186].

- Hepato-biliary and pancreatic cancers: Curcumin was reported as a potent inhibitor of phenol sulfotransferase in human
liver and extrahepatic tissues [197]. Curcumin inhibited the IL-6 production, histone acetyl transferase activity, and AP-1 activation and also hypoxia-inducible factor-1 by degrading the aryl hydrocarbon receptor nuclear translocator [198, 199]. In an in vitro study using hepatic cancer cell lines, a combination of curcumin-cisplatin as well as curcumin-doxorubicin had synergistic anti-tumor effects [178]. A number of investigations have also described curcumin in hepato-cellular carcinoma in vivo. For instance, curcumin reduced the number of gammaglutamyl transferase-positive foci and induced glutathione-linked detoxification enzymes in rat livers in the name of its anti-tumoral activity. This agent also showed anti-inflammatory and carcinogen detoxifying effects; it also demonstrated anti-metastatic and anti-developmental influences in rat liver tumors [200]. The anti-tumorigenic activity of curcumin in hepato-cellular carcinoma cells was found to be mediated through the reduction of COX-2 and VEGF in mice model [200]. In a pilot clinical trial on twelve patients with hepatic metastases from colorectal cancer the curcumin concentration in normal and malignant liver tissue after receiving 450-3600 mg of curcumin daily for 1 week before the surgery were not enough to elicit pharmacologic activity, which might be due to the extensive metabolizability of curcumin in the intestine [178].

Curcumin was also shown to have anticarcinogenic effects in various pancreatic tumors through numerous mechanisms; for example, NF-κB suppression in human pancreatic tumoral tissues and cell lines [22, 201-203], down-regulation of COX-2, ERK1/2 [204], and Notch-1 [205]. When coupled with gemcitabine, curcumin showed synergistic anti-proliferative effects in pancreatic cancers [206]. In vivo studies also showed anti-cancerous impacts of curcumin such as chemosensitization, anti-angiogenic, anti-inflammatory, and anti-proliferative effects [24, 186]. In a clinical trial on 25 patients, the anti pancreatic tumor activity of curcumin was examined; despite the poor bioavailability of this agent in most of the cases, those who demonstrated sufficient biological activity revealed down-regulation of NF-κB, COX-2 and phosphorylated STAT3 in favor of anti tumoral activity of curcumin [207].

- Cancers of Urinary and reproductive systems: Curcumin was assumed to be effective against bladder cancer both in vitro, for example by suppression of NF-κB [208], down regulation of cyclin A and up-regulation of p21, and in vivo, by inhibiting implantation and growth of the tumoral masses [178]. A clinical study revealed that oral curcumin administration led to histological improvement in precancerous lesions in 1 out of 2 patients [186]. Tharakan et al. showed that curcumin alone has anti tumoral effects against human bladder cancer; it further potentiated the gemcitabine effects, possibly through modulation of NF-κB signaling pathway [209].

Curcumin showed apoptosis-inducing impact as well as anti-proliferative effect against renal cell carcinoma in vitro and in vivo, through up-regulation of TRAIL-induced apoptosis and ROS production [210], inhibition of micromosomal lipid peroxidation and DNA damage, COX 1 and 2 inhibition [211], and downregulation of Bcl-2, Bcl-XL, and IAP proteins [212]. An experimental study revealed that curcumin also possesses anti metastasis and tumor preventive effects in rats [213]. Efficacy of curcumin by modulating NF-κB expression, AP-1, cyclin D1, and etc. were also demonstrated in treatment of prostate cancer [178]. Curcumin showed preventive effect in PC-3 prostatic tumor xenograft in mice [214], and also led to reduction of MMP-2 and MMP-9 activity on the tumor bearing site as well as metastasis prevention in vivo [215].

Curcumin was reported to have anti cancerous activity by almost the same mechanisms as other types of cancers against malignancies of cervix, ovaries and uterus both in vivo and in vitro [186].

- Brain tumors: Curcumin was reported to block brain tumor formation [216]. The efficacy of curcumin in various human malignant glioblastoma cells, for example by inhibiting NF-κB signaling pathways, has been established [217, 218]. Numerous other mechanisms, such as the inhibition of MMP transcriptions [219], the induction of histone hypoacetylation leading to apoptosis in a PARP and caspase 3-mediated manner [220], TRAIL-induced apoptosis [221], and the induction of non-apoptotic autophagic cell death [222, 223] have also been suggested. In rats, curcumin significantly decreased the incidence of radiation-induced pituitary tumors [178]. Curcumin inhibited tumor growth by three folds and induced autophagy in the subcutaneous xenograft model of glioblastoma multiforme [223].

- Cancers of respiratory system: Previous studies showed the anti-tumoral activity of curcumin against lung cancer [186] for example by inhibiting AP-1 transcription and lymph node metastasis and also by modulating the NF-κB DNA binding, IkB kinase activation, and COX-2 downregulation [178, 186, 224]. Apoptosis induction via Bcl-XL, Bax and Bcl-2 as well as ROS production were also reported as mechanisms of anti tumoral activity of curcumin [225]. In an animal study, dietary curcumin was found to inhibit the lung metastasis of melanoma and increased the life span of the subjects [178]. Moreover, inhibiting the signal transducer and activator of transcription 3 (Stat3), which was seen to be activated in nearly half of lung cancers, was reported as another mechanism of chemopreventive activity of curcumin in lung cancer [226].

- Bone tumors: Curcumin was reported to induce apoptosis by inhibiting NF-κB, IL-6, IL-11, MMP-9 and VEGF [227, 228]in fibrosarcoma. Further, in human osteosarcoma, curcumin was found to inhibit the ERK gene expression and to induce apoptosis by down-regulating the Bcl-2 expression [178, 186, 229, 230].

CONCLUSION

The wisdom and scientific knowledge of curcumin, a highly pleiotropic agent, which were used for its therapeutic effects particularly in Chinese, Iranian and Ayurvedic traditional medicine, have been corroborated by numerous investigations conducted in the last thirty years, especially the last decade. Of the most noticeable therapeutic influences of curcumin, researchers mostly pointed at the anti-oxidant potential, anti-inflammatory, and anti-tumoral activities through its regulatory impacts on molecular targets involved in development of cancerous cells as well as anti-angiogenic, anti-proliferative, and chemopreventive effects on the cancerous cell lines. Curcumin, due to its ability to affect a wide range of molecular targets and an excellent safety profile, was demonstrated to be a potential candidate for the prevention and/or treatment of a number of diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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