Review Article
Curcumin in Inflammatory Diseases

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Abstract

Curcumin (diferuloylmethane), a yellow coloring agent extracted from turmeric is also used as a remedy for the treatment and prevention of inflammatory diseases. Acute and chronic inflammation is a major factor in the progression of obesity, type II diabetes, arthritis, pancreatitis, cardiovascular, neurodegenerative and metabolic diseases, as well as certain types of cancer. Turmeric has a long history of use in Ayurvedic medicine for the treatment of inflammatory disorders. Recent studies on the efficacy and therapeutic applicability of turmeric have suggested that the active ingredient of tumeric is curcumin. Further, compelling evidence has shown that curcumin has the ability to inhibit inflammatory cell proliferation, invasion, and angiogenesis through multiple molecular targets and mechanisms of action. Curcumin is safe, non-toxic, and mediates its anti-inflammatory effects through the down-regulation of inflammatory transcription factors, cytokines, redox status, protein kinases, and enzymes that all promote inflammation. In addition, curcumin induces apoptosis through mitochondrial and receptor-mediated pathways, as well as activation of caspase cascades. In the current study, the anti-inflammatory effects of curcumin were evaluated relative to various chronic inflammatory diseases. Based on the available pharmacological data obtained from *in vitro* and *in vivo* research, as well as clinical trials, an opportunity exists to translate curcumin into clinics for the prevention of inflammatory diseases in the near future. © 2012 BioFactors, 39(1):69–77, 2013

Keywords: *curcumin; inflammation; infection; diseases; prevention*

1. Introduction

Inflammation is an adaptive physiological response induced by deleterious circumstances including infection and tissue injury. Observational studies have revealed that inflammation is the product of a complex series of responses triggered by the immune system. Inflammation also harbors a wide range of physiological and pathological morbidities [1]. Extensive research has shown that inflammation is associated with alteration of signaling pathways, which results in increased levels of inflammatory markers, lipid peroxides, and free radicals. It has also been hypothesized that inflammation plays a central role in the wound healing and combating infection. However, persistent inflammation can activate the immune system for long durations, which stimulates the progression of chronic diseases such as pulmonary, cardiovascular, metabolic, and neurologic diseases, as well as cancers [1,2].

Curcumin is a turmeric polyphenol derived from the rhizomes of *Curcuma Longa*, which belongs to the *Zingiberaceae* family, and it is cultivated in most parts of Southeast Asia. Turmeric contains curcumin, demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (zingiberone, tumerone, and atlantone), sugars, proteins, and resins [3]. Curcumin, first identified in 1910 by Lampe and Milobedzka, is responsible for the vibrant yellow color associated with turmeric. Curcumin is a lipophilic agent that is nearly insoluble in water yet quite stable in the acidic pH of the stomach. Furthermore, it has been prized since ancient times for its various pharmacological benefits associated with its antioxidant and anti-inflammatory properties [4]. Several reports have shown that curcumin induces apoptosis, via deactivation of nuclear factor-kappa B (NF-κB) and its regulated gene products, in addition to suppression of cell proliferation, invasion, and angiogenesis. Curcumin was also found to suppress several inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, -1β, -6, and -8), and cyclooxygenase-2 (COX-2) [4].

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The current study mainly focused on the multiple pharmacological and therapeutic effects of curcumin as well as its application to the prevention of inflammatory diseases. Based on the results of the clinical trials, ample evidence validates the therapeutic use of curcumin for the treatment of inflammatory diseases.

2. Molecular Targets of Curcumin in Combating Inflammation

It has been shown that curcumin regulates diverse molecular targets implicated in inflammation. Specifically, curcumin inhibits inflammatory cytokines such as TNF-α, IL-1, -2, -6, -8, -12, mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK), as well as suppresses the inducible nitric oxide synthase (iNOS), COX-2, and lipoxygenase (LOX) in a variety of cancer cells [5]. Recently, it has been shown that curcumin inhibits NF-κB activation, matrix metalloproteinase (MMP-1, -9, and -13) secretion, COX-2 expression, and anti-apoptotic protein such as Bcl_2, as well as activates Bax and caspase-3. Furthermore, curcumin suppresses IL-1β-induced NF-κB activation and nuclear translocation as well as IL-1β-induced phosphatidylinositol 3-kinase (PI3K/Akt) activation through the decreased phosphorylation and degradation of inhibitory kappa B alpha (IκBα) [6]. Curcumin abrogates the TNF-α-induced expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), disrupts TNF-α-induced secretion of IL-6 and -8, and monocyte chemotactic protein-1 (MCP-1), and inhibits NF-κB activity in endometriotic stromal cells [7]. Curcumin has also been reported to decrease the expression of inflammatory markers such as NF-κB, COX-2, 5-LOX, macrophage inflammatory protein-1α (MIP-1α), adhesion molecules, C-reactive protein, and chemokine receptor type 4 (CXCR-4) [8]. Curcumin decreases inflammation in the adipose liver steatosis through the phosphorylation of the signal transducer and activator of transcription 3 (STAT3), as well as through down-regulation of suppressor of cytokine signaling 3 (SOCS3) and sterol regulatory element-binding protein-1c (SREBP-1c) in livers of obese mice. Curcumin was also found to decrease gene expression of mitochondrial DNA (mtDNA), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (Tfam), as well as reduce hepatic NF-κB activities and the levels of thiobarbituric acid reactive substances (TBARS) [9]. Thus, curcumin suppresses inflammation through multiple pathways which are summarized (Fig. 1).

3. Therapeutic Uses of Curcumin in Treating Inflammatory Diseases

Curcumin has the ability to mediate multiple anti-inflammatory effects for the treatment of various chronic inflammatory diseases including obesity, diabetes, cardiovascular and neurodegenerative diseases, cerebral edema, allergy, bronchial asthma, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), renal ischemia, psoriasis, scleroderma, acquired immunodeficiency syndrome (AIDS), and certain types of cancers (Fig. 1). These inflammatory diseases are discussed in detail under the following headings.

3.1. Obesity

Obesity is a weight-related disorder and serious global epidemic resulting in reduced quality of life, morbidity, and mortality. Inflammation is considered a major risk factor for the development of co-morbidities such as obesity, type II diabetes, cardiovascular disease, hepatic steatosis, and cancer [10]. Curcumin has been shown to mediate a variety of inhibitory effects through suppression of the MAPK and Wnt/β-catenin signaling pathways, which are closely associated with obesity. Curcumin treatment has also been shown to inhibit MAPK (ERK, JNK, and p38) and β-catenin phosphorylation through repression of casein kinase 1α (CK1α), glycogen synthase kinase-3β (GSK-3β), and axin. These components are believed to be associated with the differentiation of 3T3-L1 cells into adipocytes [11]. Additionally, curcumin possesses *in vitro* and *in vivo* activities that ameliorate vascular endothelial growth factor (VEGF) and VEGF receptor 2. Curcumin augments AMP-activated protein kinase (AMPK) phosphorylation and glycerol-3-phosphate acyl transferase-1, as well as mediates carnitine palmitoyltransferase-1 expression. It was also shown to lower the serum cholesterol level and expression of PPARγ and CCAAT/enhancer binding protein alpha (C/EBPα) in adipogenesis and angiogenesis [12]. Several studies have shown that curcumin reduces macrophage infiltration of white adipose tissue, leptin, and leptin receptor (Ob-R) levels, and increases adiponectin expression in inflammation-related obesity. Increased production of adiponectin associated with curcumin might negatively regulate obesity by decreasing the activities of NF-κB, as well as those of obesity-related inflammatory and metabolic markers [10]. Recently, it has been shown that curcumin reduced levels of nuclear factor erythroid-2-related factor-2 (Nrf2) and heme oxygenase-1 (HO-1) in high fat diet (HFD)-induced mice. Curcumin was also found to improve glucose tolerance in HFD-induced mice by mediating oxidative stress through the activation of Nrf2 and its downstream target, HO-1 [13].

3.2. Diabetes

Diabetes is an epidemic and hyperglycemic condition that affects the liver, heart, brain, and kidneys, and inflammation is considered a main cause of the development of type II diabetes. Various inflammatory cytokines, transcription factors, and enzymes play important roles in the initiation and progression of diabetes [14]. Curcumin treatment was shown to suppress blood glucose levels in diabetics by increasing the antioxidant status of pancreatic β-cells and by activating peroxisome proliferator-activated receptor gamma (PPAR-γ) [15]. Furthermore, the anti-diabetic effects of curcumin have been

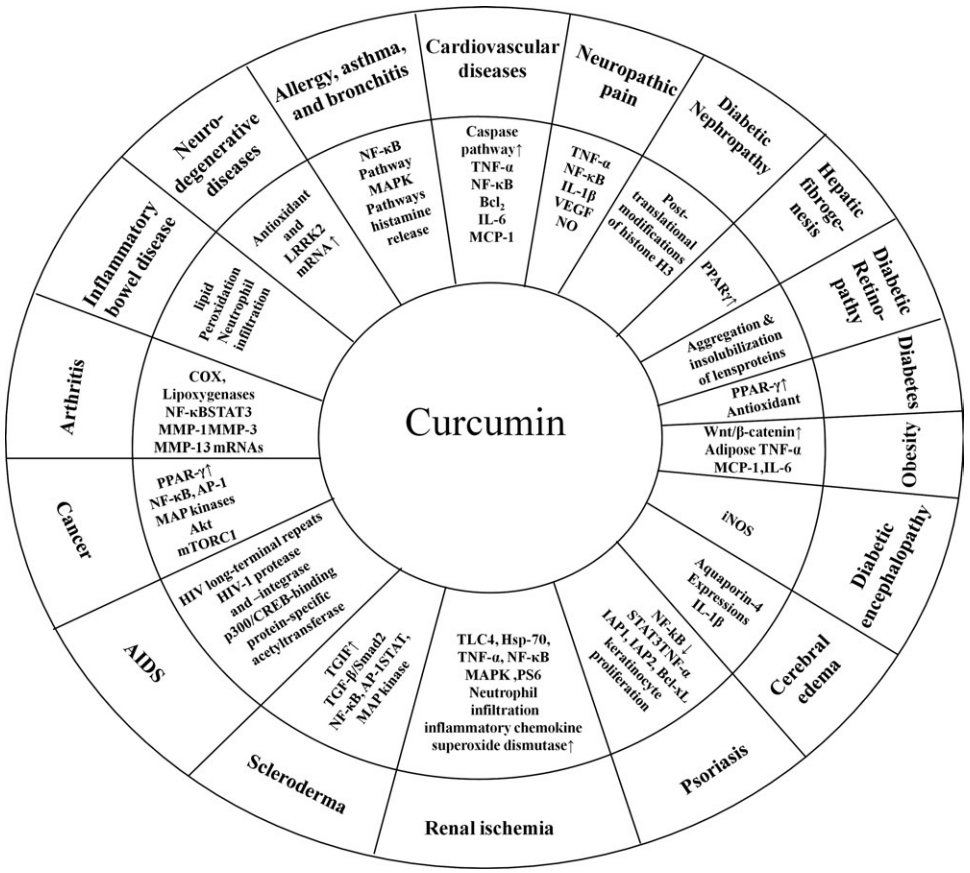

FIG 1 *A model of the multiple molecular targets of curcumin is illustrated. The upward pointing arrows represent up-regulation or activation, and the molecules without arrows represent down-regulation or inhibition by curcumin.*

investigated in HFD-induced obese and leptin-deficient ob/ob male C57BL/6J mice, wherein curcumin improved obesity-associated diabetes condition by decreasing macrophage infiltration of white adipose tissue, inhibited levels of NF-κB related markers of hepatic inflammation, and increased adiponectin expression [16]. Furthermore, curcumin was shown to prevent diabetes-induced reduction of antioxidant capacity, and diabetes-induced increase in IL-1β, VEGF, and NF-κB activity [17,18]. Curcumin was also found to suppress blood glucose levels through the enhancement of PPAR-γ ligand-binding activity in type II diabetic KK-Ay mice [19]. Several studies have evaluated the effect of curcumin in streptozotocin (STZ)-nicotinamide-induced diabetic rats. In these reports, curcumin prevented hyperlipidemia by suppressing the levels of serum and liver cholesterol, triglyceride, free fatty acid and phospholipid, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol, and HMG CoA reductase activity, as well as by normalizing the levels of high-density lipoprotein (HDL) cholesterol [20]. Additionally, curcumin pre-treatment was shown to protect lindane-induced oxidative damage in livers of Wistar rats through augmentation of the anti-oxidant enzyme system, such as lipid peroxidation, and also decreased the levels of glutathione, superoxide dismutase (SOD), catalase, glutathione-S-transferase (GST), glutathione peroxidase (GPx), glutathione reductase, and NADPH [21].

Curcumin has been approved for the treatment of type II diabetes-associated hepatic fibrogenesis. Curcumin treatment abolishes the activating effects of advanced glycation end-products (AGEs) on hepatic stellate cells (HSCs), possibly through induction of AGE receptor-1 (AGE-R1). Curcumin further promotes the induction of AGE-R1 through activation of PPARγ and inhibition of ERK [22]. Furthermore, the effects of curcumin on hyperalgesia in STZ-induced diabetic male SD rats have been investigated. Curcumin dose dependently diminished thermal hyperalgesia and hot-plate latencies by modulating the release of TNF-α and NO [23].

Studies have shown that the diabetic retina over-expresses VEGF in comparison to control retina. Curcumin treatment has been shown to decrease VEGF expression at both the protein and mRNA levels in rats with STZ-induced diabetic retina [24]. Diabetes is also a major cause of nephropathy characterized by increased production of extracellular matrix (ECM)

proteins through transforming growth factor-beta1 (TGF-β1), NF-κB, and p300 in the kidneys. Curcumin decreases the production of ECM proteins through inhibition of p300. Further, it was found to suppress the activation of NF-κB, and decrease the levels of TGF-β1, endothelial nitric oxide synthase, and endothelin-1 as a treatment for diabetic nephropathy [25]. In rats, curcumin has been shown to remarkably decrease the levels of blood urea nitrogen and creatinine, and increased albumin, followed by the inhibition of HSP-27 and p38 expression associated with diabetic nephropathy. Curcumin also inhibits the translational expression of histone H3 [26]. Diabetic encephalopathy is characterized by impaired cognitive functions along with neurochemical structural abnormalities caused by intracellular glucose, and it is directly involved in neuronal damage. In a previous work, curcumin administration (60 mg/kg) extensively attenuated cognitive deficits, cholinergic dysfunction, oxidative stress, and inflammation in diabetic rats [27]. Altogether, these studies revealed that curcumin plays an important role in attenuating diabetes and diabetes-associated symptoms.

3.3. Cardiovascular Diseases

Several reports have pointed out that inflammation plays a large role in the development of cardiovascular diseases (CVDs). In most CVD complications, there are increased production and enhanced release of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-2, -6, -8, -10, -13, -18, and monocyte chemo-attractant protein-1 (MCP-1) [28]. Atherosclerosis is a chronic inflammatory disorder characterized by oxidative damage that affects lipoproteins, and blood vessels walls, as well as promotes the deposition of excess lipids within the arterial internal layer. Excess lipids accumulation in foam cells and oxidation of LDL cholesterols play important roles in the development of atherosclerosis [29].

Extensive research has suggested that curcumin treatment mediates anti-inflammatory effects against CVDs through diverse mechanisms. Curcumin has been shown to induce HO-1 expression by activating Nrf2-dependent antioxidant response element (ARE), and inhibits the proliferation of various cardiovascular cells including vascular endothelial cells, vascular smooth muscle cells, and human aortic smooth muscle cells. Curcumin also inhibits TNF-α and increases p21 expression via HO-1 in vascular and human aortic smooth muscle cells [30,31]. Curcumin has been reported to be an excellent inhibitor of p300 in combating cardiomyocytes hypertrophy. Further, where curcumin suppresses the acetylation of transcription factor GATA binding protein 4 (GATA4), inhibiting the GATA4/p300 complex and its DNA-binding capacity, thereby enhancing nuclear histone acetylation. Curcumin administration (50 mg/kg) has also been shown to improve systolic function and prevent heart failure in salt-sensitive Dahl rats model of hypertensive heart disease as well as in rats surgically induced to present myocardial infarction [32]. The effects of curcumin treatment against myocardial ischemia have been investigated in the rat myocardium. It was found that curcumin treatment improves post-ischemic cardiac function, decreases myocardial infarct size, and lactate dehydrogenase release into the coronary flow, and reduces the number of apoptotic cardiomyocytes through the JAK/STAT3, Bcl_2, and caspase pathways [33]. Furthermore, curcumin reduced cardiac ischemia-reperfusion injury due to augmentation of oxidative stress and inflammation. This effect is mediated by decreasing the expression of toll-like receptor 2 (TLR2), MCP-1, macrophage infiltration (CD68), and fibrosis. Curcumin has also restored the function of connexin 43 and heart contractility and also prevented myocardial infarction [34]. Previous studies have examined the protective role of curcumin in experimental abdominal aortic aneurysms. Specifically, it was shown that curcumin decreases the AP-1 expression and NF-κB-DNA-binding activities as well as suppresses the secretions of IL-1β, IL-6, MCP-1, and MMP-9 in aortic tissue of mice [35]. Furthermore, a microarray study revealed that curcumin mediates the differential expression of 179 genes between sham-operated rats and coronary artery-ligated rats. Finally, curcumin mediates a preventive effect in cardiac hypertrophy, inflammation, and fibrosis through the inhibition of p300 and cytokines that mediate signaling pathways [36,37].

3.4. Cerebral Edema

The main causes of cerebral edema include structural damage and osmotic differences induced by traumatic brain injuries associated with poor prognosis. Currently available drugs are ineffective in preventing cerebral edema. Thus, novel therapeutics are urgently needed to treat this condition. It has been shown that pre- (150 mg/kg) or post-administration (300 mg/kg) of curcumin was effective in reducing brain water content through the inhibition of IL-1β-induced aquaporin-4 expression with moderate controlled cortical impact in mice. Attenuation of aquaporin-4 by curcumin was found to be mediated through suppression of both NF-κB subunit p65 in cultured astrocytes, as well as astrocytic water channel associated with cellular edema following head trauma, *in vivo* [38]. Curcumin was administered and brain edema measured following intra-cerebral hemorrhage and blood–brain barrier disruption. Interestingly, curcumin treatment prevented intra-cerebral hemorrhage, and decreased blood–brain barrier disruption and brain edema through modulation of MMP cells [39]. Additionally, the role of curcumin has been investigated in oxidative stress and inflammatory pathways in a hypoxia-induced cerebral edema model. Hypoxic conditions reduced anti-oxidant enzyme activity followed by increased gene expression of NF-κB and pro-inflammatory cytokines, as well as increased the levels of cell adhesion molecules. Moreover, curcumin pre-treatment (100 mg/kg) decreased the levels of brain NF-κB and markedly attenuated hypoxia-induced cerebral edema [40].

3.5. Neurodegenerative Diseases

Inflammation is a leading cause of neurodegenerative disease which may be triggered by injured neurons and noxious proteins with abnormal regulation properties. Abnormal

development pattern of proteins in neurodegenerative diseases results in gene mutations such as human amyloid precursor protein (*hAPP*) or *presenilins 1 or 2* in Alzheimer's disease (AD), which is characterized by inflammation and oxidative damage [41]. Curcumin treatment was found to repress the gene transcription of early growth response gene-1 (Egr-1), which mediates TNF-α, IL-1β, IL-8, MIP-1β, and MCP-1 in PBM and THP-1 cells through the interaction of amyloid-β-proteins (Aβ). In the AD transgenic Tg2576 mouse brain, curcumin significantly lowered the levels of oxidized proteins and IL-1β, and decreased the levels of insoluble and soluble Aβ and plaque burden without affecting amyloid precursor protein. Curcumin has been evaluated in a clinical trial for the prevention of AD [42]. Curcumin was also proven to be a neuroprotective agent in 6-OHDA model of Parkinson's disease (PD). Specifically, curcumin was shown to protect a number of tyrosine hydroxylase-positive cells in the substantia nigra and maintain dopamine levels in the striatum, possibly through its antioxidant activity and efficient dispersion into the brain [43]. In another study, curcumin was administered orally to pentylenetetrazole (PTZ)-induced kindled epileptic rat, resulting in prevention of seizures, seizure-induced memory impairment, oxidative stress, and cognitive impairment [44]. The potential efficacy of curcumin for the prevention of multiple sclerosis has been well documented. Curcumin also inhibited the differentiation and development of Th17 cells, which are responsible for initiating multiple sclerosis through the down-regulation of NF-κB, IL-6, IL-21, and STAT3-phosphorylation [45]. Curcumin also protected against ischemia-reperfusion injury in the rat forebrain by suppressing xanthine oxidase activity, superoxide anion production, malondialdehyde level, as well as GPx, SOD, and lactate dehydrogenase activities [46]. Chronic administration of haloperidol increases vacuous chewing movements, tongue protrusion, and facial jerking by modulating the antioxidant system in rats. However, pre-treatment with curcumin was shown to dose dependently repress these effects. Curcumin also increased the levels of dopamine, norepinephrine, and serotonin levels in the cortical and subcortical regions, which were reduced as a result of the haloperidol chronic administration [47]. Neurochemical evidence has also demonstrated the protective role of curcumin in spongiform encephalopathies (Creutzfeld–Jakob disease) through binding of prion protein (PrP) [48]. Recently, the antinociceptive effects of curcumin were investigated for treatment of neuropathic pain. It was revealed that the antinociceptive effects curcumin are mediating, at least in part, through inhibition of the monoamine system that is coupled with spinal β2-adrenoceptor and 5-HT1A receptor [49].

3.6. Allergy and Bronchial Asthma

Allergy and asthma are pro-inflammatory diseases mediated through inflammatory cytokines. Curcumin has been reported to provide protection from allergies through the repression of mast cell histamine release [50]. In an allergy and asthma model, it was shown that a hydroxyl group in diferuloylmethane (curcumin) decreased allergic reactions as well as improved constricted airways and antioxidant levels [51]. In another study, a latex allergy model (BALB/c mice) overexpressing Th2 type immune response was treated intragastrically with curcumin. Curcumin inhibited Th2 responses followed by suppression of lung inflammation, peripheral blood eosinophilia, and decreased expression of co-stimulatory molecules (CD80, CD86, and OX40L) on antigen-presenting cells, MMP-9, ornithine amino transferase, and thymic stromal lymphopoietin [52]. Furthermore, the disruption of oxidative stress attributed to resistance to steroid therapy in chronic obstructive pulmonary disease (COPD) and asthma through NF-κB activation and unbalanced acetylation and deacetylation state of histone deacetylase. Curcumin is a powerful antioxidant that scavenges free radicals (O_2 and NO) through decreased activation of NF-κB and MAPK as well as down-regulates pro-inflammatory mediators such as MMPs, adhesion molecules, and growth factor receptor genes in inflammatory lung disease [53]. Curcumin was also found to reduce lung tumor progression in non-typeable hemophilus influenzae (NTHi)-induced by COPD, which increases neutrophil chemoattractant keratinocyte-derived chemokine and neutrophils in bronchoalveolar lavage fluid. An *in vitro* study revealed the anti-tumor effects of curcumin as evidenced by cell viability, colony formation, and apoptosis [54].

3.7. Inflammatory Bowel Disease

IBD is a debilitating immune disorder most commonly involving chronic inflammation of the digestive tract, and it includes Crohn's disease (CD) and ulcerative colitis (UC). Curcumin has been found to reduce colitis in several chemically induced *in vitro* and *in vivo* colitis models [55]. It has been shown that curcumin prevents NF-κB translocation as well as inhibits COX-2, 5-LOX, and iNOS expression in IBD. Curcumin also suppressed TLR4-induced NF-κB activation in experimental colitis [56]. The effects of curcumin treatment were previously investigated in a small, pilot study on five approved patients with UC/proctitis (curcumin dose of 550 mg/kg) and five patients with CD (curcumin dose of 300 mg/kg) for 1 month. The UC/proctitis group showed improvement in the form of reduced CD activity index (CDAI) and erythrocyte sedimentation rate, whereas C-reactive protein was observed in the CD. The curcumin-treated group showed improved bowel movements and reduction of diarrhea, abdominal pain, and cramping [57]. A different randomized, multicenter, double-blinded, placebo-controlled 6-month clinical trial including 89 patients with UC was conducted using curcumin plus sulfasalazine or mesalamine (45 patients), or placebo plus sulfasalazine or mesalamine. Curcumin decreased the relapse rate, suppressed the disease-associated clinical activity index and the endoscopic index in UC [58]. All of these data show that curcumin possesses efficacy for the prevention and treatment of IBD.

3.8. Rheumatoid Arthritis

RA, including osteoarthritis (OA), is an inflammatory disorder that causes body joint distortion, loss of function and

demolition, particularly in cartilage and bone. OA is the most common form of arthropathy and is characterized by degeneration of articular cartilage and subsequent malfunction of cartilage structure due to combination of genetic, physiological, and biochemical processes [59]. In a previous study on patients with RA, curcumin treatment dose-dependently down-regulated Bcl-2 and Bcl-xL, up-regulated Bax, activated caspase-3 and -9, and degraded poly(ADP-ribose) polymerase (PARP) in the synovial fibroblasts. Curcumin also inhibited the inflammatory response in synovial fibroblasts through suppression of COX-2, followed by inhibition of prostaglandin E_2 synthesis [60]. In another study, curcumin inhibited inflammatory processes through suppression of collagenase and stromelysin expression in HIG-82 synoviocytes [61]. Furthermore, the effects of curcumin were investigated in IL-1β- and TNF-α-stimulated human articular chondrocytes. Curcumin suppressed IL-1β-induced NF-κB and AKT activation by decreasing IκBα phosphorylation and degradation correlated with down-regulation of COX-2 and MMP-9. Very similar results were obtained when curcumin was analyzed in TNFα-stimulated chondrocytes [62]. A clinical study (WOMAC) that treated curcumin to 50 OA patients found that curcumin could prevent joint inflammation through the down-regulation of enzymes (COX-2 and LOX), and inflammatory transcription factors (NF-κB and STAT3) [63]. Recently, a randomized pilot study was conducted in order to evaluate the effectiveness of curcumin (500 mg in 14 patients) and curcumin with diclofenac sodium (50 mg in 12 patients) treatment to patients with active RA. The curcumin treated group showed improvement relative to the diclofenac sodium treatment group as indicated by Disease Activity Score (DAS) and American College of Rheumatology (ACR) score [64].

3.9. Renal Ischemia

Renal ischemia/reperfusion injury (IRI) is a complex interconnected outcome of renal transplantation, possibly caused by acute kidney injuries associated with poor prognosis. IRI is characterized by the up-regulation of inflammatory markers in the kidney as a result of oxidative stress and NF-κB activation [65]. The potential roles of curcumin, either alone or in concomitant administration have been investigated in IRI and skin allograft models. It was noted that curcumin increases serum creatinine levels and decreases tubular damage and renal inflammation in IRI, as well as prolongs skin graft survival [66]. The anti-IRI role of curcumin has been well documented in kidney and brain tissue. Recently, curcumin was used to treat IRI in rat skeletal muscles. Curcumin prevented IRI via reduction of pro-inflammatory cytokines and enhancement of anti-oxidant systems such as SOD and GPx, as well as catalase activation followed by up-regulation of malondialdehyde, NO, and carbonyl proteins [67]. In another study, liposomal curcumin was fed to C57/B6 mice with bilateral renal ischemia. Curcumin induced apoptosis through the down-regulation of TLR-4, heat shock protein-70, and TNF-α expression, as well as normalized serum creatinine with improved healing of histological injury. Curcumin also enhanced SOD and reduced superoxide generation through inhibition of NF-κB, MAPK, and phospho-S6 ribosomal protein, and also inhibited neutrophil infiltration and inflammatory chemokine activation in the renal IRI [68]. These studies revealed the protective role of curcumin for the prevention of IRI via its anti-inflammatory activities.

3.10. Psoriasis

Psoriasis is chronic disease characterized by inflammation of the skin through abnormal keratinocyte proliferation and differentiation. Inflammatory markers that mediate psoriasis include NF-κB, survivin, STAT3, and TNF-α [69]. Several lines of evidence suggest that curcumin may provide protection against psoriasis, as it decreases the expression of pro-inflammatory cytokines in psoriatic keratinocytes. Similar to other anti-psoriatic drugs, curcumin also inhibits keratinocyte proliferation [70]. Recently, it has been shown that curcumin treatment induces apoptosis in both TNF-α and TRAIL stimulated HaCaT cells through the down-regulation of anti-apoptotic proteins such as inhibitor of apoptosis protein 1 and 2 (IAP1, IAP2) and Bcl-xL, as well as inhibits activation of NF-κB subunit p65. These results imply that curcumin can be used to cure psoriasis [71]. Furthermore, a phase II, open-label, Simon's two-stage clinical trial using orally administered curcuminoid C3 complex (4.5 g/day) was conducted on patients with plaque psoriasis. Despite the absence of a placebo group, the results suggest that curcumin is successful in suppressing psoriasis [72].

3.11. Scleroderma

Scleroderma is an autoimmune rheumatic disease that typically results in vasculopathy and fibrosis of skin and other organs. In scleroderma, there is abnormal regulation of inflammatory cytokines and NF-κB which are involved in angiogenesis and fibrosis [73]. In scleroderma lung fibroblasts (SLF), curcumin treatment induces apoptosis through the induction of HO-1 and GST P1, which are regulated by epsilon isoform of protein kinase C (PKCε). Curcumin selectively mediates expression of PKCε expression, which regulates phase 2 detoxification enzymes in normal fibroblasts and SLFs as well as in fibrotic lung tissue, *in vivo* [74]. Additionally, curcumin selectively inhibited the TGF-β-induced phosphorylation of Smad2 and induced apoptosis in systemic scleroderma patient cells through up-regulation of TGF-β-induced factor (TGIF). As TGIF is a negative regulator of TGF-β signaling, curcumin may thus decrease ubiquitination of TGIF, which also inhibits TGF-β [75].

3.12. Curcumin Safety

The development of therapeutic strategies of featuring neutraceuticals such as curcumin for the treatment of inflammatory diseases has gained significant attention recently. A very early report by the Food and Agriculture Organization and the World Health Organization demonstrated that the optimal daily intake of curcumin is 0–1 mg/kg body weight [3].

Curcumin is safe and well tolerated in humans for a variety of inflammatory diseases. In 2001, Cheng and coworkers investigated the toxicology, pharmacokinetics, pharmacodynamics, and physiologically effective doses of curcumin in different human inflammatory conditions. In a phase I clinical trial, curcumin was administered at a dose of 500 mg/day, followed by increases to 1, 2, 4, 8, and 12 g/day for 3 months. No dose-limiting toxicity was observed in any subject under any condition [76]. In addition, curcumin (C3 Complextrade mark, Sabinsa Corporation) was administered at doses of 500 mg–12,000 mg to healthy volunteers. This study revealed that only 7 of 24 subjects experienced minimal toxicity, which was not dose-related [77]. Recently, a randomized-pilot study was conducted in order to assess the safety and efficacy of curcumin treatment to patients with RA. Curcumin exhibited potent anti-inflammatory effects and was found to be safe with no adverse effects [64]. Despite its proven efficacy over centuries of use in ancient times and safety demonstrated in several human studies, its application has not yet been translated to clinics for the treatment of inflammation.

4. Conclusion

The current study summarized the definitive association of inflammatory pathways with the initiation and progression of chronic inflammatory diseases, as well as the role that curcumin may perform in managing these diseases. We have clearly shown that curcumin modulates multiple molecular targets and exerts multifaceted pharmacological activities, including anti-inflammation effects for the treatment and prevention of chronic inflammatory diseases. Curcumin is a non-toxic and highly promising natural anti-inflammatory compound with a long history of use and is already being administered in phase II and III clinical trials. Further human studies are required in order to validate the clinical use of curcumin for treating a wide variety of inflammatory diseases. Tailored agents derived from curcumin or its use in combination with other drugs may provide improved anti-inflammatory effects in the near future.

References

[1] Ruslan, M. (2008) Origin and physiological roles of inflammation. Nature 454, 428–435.

[2] Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., and Kelley, K. W. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

[3] Shehzad, A. and Lee, Y. S. (2010) Curcumin: multiple molecular targets mediate multiple pharmacological actions—a review. Drugs Fut. 35, 113–119.

[4] Shehzad, A., Wahid, A., and Lee, Y. S. (2010) Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. Arch. Pharm. (Weinheim) 343, 489–499.

[5] Goel, A., Kunnumakkara, A. B., and Aggarwal, B. B. (2008) Curcumin as "Curecumin": from kitchen to clinic. Biochem. Pharmacol. 75, 787–809.

[6] Buhrmann, C., Mobasheri, A., Busch, F., Aldinger, C., Stahlmann, R., et al. (2011) Curcumin modulates nuclear factor kappaB (NF-κB)-mediated inflammation in human tenocytes in vitro: role of the phosphatidylinositol 3-kinase/Akt pathway. J. Biol. Chem. 286, 28556–28566.

[7] Kim, K. H., Lee, E. N., Park, J. K., Lee, J. R., Kim, J. H., et al. (2012) Curcumin attenuates TNF-α-induced expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and proinflammatory cytokines in human endometriotic stromal cells. Phytother. Res. 26, 1037–1047.

[8] Jurenka, J. S. (2009) Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. Altern. Med. Rev. 14, 141–153.

[9] Kuo, J. J., Chang, H. H., Tsai, T. H., and Lee, T. Y. (2012) Positive effect of curcumin on inflammation and mitochondrial dysfunction in obese mice with liver steatosis. Int. J. Mol. Med. 30, 673–679.

[10] Shehzad, A., Ha, T., Subhan, F., and Lee, Y. S. (2011) New mechanism and anti-inflammatory role of curcumin in obesity and obesity related metabolic disease. Eur. J. Nutr. 50, 151–161.

[11] Ahn, J., Lee, H., Kim, S., and Ha, T. (2010) Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/beta-catenin signaling. Am. J. Physiol. Cell. Physiol. 298, 1510–1516.

[12] Ejaz, A., Wu, D., Kwan, P., and Meydani, M. J. (2009) Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. Nutrition 139, 919–925.

[13] He, H. J., Wang, G. Y., Gao, Y., Ling, W. H., Yu, Z. W., et al. (2012) Curcumin attenuates Nrf2 signaling defect, oxidative stress in muscle and glucose intolerance in high fat diet-fed mice. World J. Diabetes 3, 94–104.

[14] Choudhary, S., Sinha, S., Zhao, Y., Banerjee, S., Sathyanarayana, P., et al. (2011) NF-kappaB-inducing kinase (NIK) mediates skeletal muscle insulin resistance: blockade by adiponectin. Endocrinology 152, 3622–3627.

[15] Hongyu, Z., Christopher, S. B., and Shile, H. (2011) Targets of curcumin. Curr. Drug Targets 12, 332–347.

[16] Weisberg, S. P., Leibel, R., and Tortoriello, D. V. (2008) Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology 149, 3549–3558.

[17] Abolfazl, B. and Moosavi-Movahedi, A. A. (2011) Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin. PLoS One 6, e26012.

[18] Kowluru, R. A. and Kanwar, M. (2007) Effects of curcumin on retinal oxidative stress and inflammation in diabetes. Nutr. Metab. (Lond) 4, 8.

[19] Nishiyama, T., Mae, T., Kishida, H., Tsukagawa, M., Mimaki, Y., et al. (2005) Curcuminoids and sesquiterpenoids in turmeric (*Curcuma longa* L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. J. Agric. Food. Chem. 53, 959–963.

[20] Pari, L. and Murugan, P. (2007) Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. Ren. Fail. 29, 881–889.

[21] Singh, R. and Sharma, P. (2011) Hepatoprotective effect of curcumin on lindane-induced oxidative stress in male Wistar rats. Toxicol. Int. 18, 124–129.

[22] Lin, J., Tang, Y., Kang, Q., and Chen, A. (2012) Curcumin eliminates the inhibitory effect of advanced glycation end-products (AGEs) on gene expression of AGE receptor-1 in hepatic stellate cells in vitro. Lab. Invest. 92, 827–841.

[23] Sharma, S., Kulkarni, S. K., Agrewala, J. N., and Chopra, K. (2006) Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. Eur. J. Pharmacol. 536, 256–261.

[24] Mrudula, T., Suryanarayana, P., Srinivas, P. N., and Reddy, G. B. (2007) Effect of curcumin on hyperglycemia-induced vascular endothelial growth factor expression in streptozotocin-induced diabetic rat retina. Biochem. Biophys. Res. Commun. 361, 528–532.

[25] Soetikno, V., Sari, F. R., Veeraveedu, P. T., Thandavarayan, R. A., Harima, M., et al. (2011) Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. Nutr. Metab. *(Lond)* 8, 35.

[26] Tikoo, K., Meena, R. L., Kabra, D. G., and Gaikwad, A. B. (2008) Change in post-translational modifications of histone H3, heat-shock protein-27 and MAP kinase p38 expression by curcumin in streptozotocin-induced type I diabetic nephropathy. Br. J. Pharmacol. 153, 1225–1231.

[27] Kuhad, A. and Chopra, K. (2007) Curcumin attenuates diabetic encephalopathy in rats: behavioral and biochemical evidences. Eur. J. Pharmacol. 576, 34–42.

[28] Rosner, M. H., Ronco, C., and Okusa, M. D. (2012) The role of inflammation in the cardio-renal syndrome: a focus on cytokines and inflammatory mediators. Semin. Nephrol. 2, 70–78.

[29] Yuan, Y., Li, P., and Ye, J. (2012) Lipid homeostasis and the formation of macrophage-derived foam cells in atherosclerosis. Protein Cell 3, 173–181.
[30] Pae, H. O., Jeong, G. S., Jeong, S. O., Kim, H. S., Kim, S. A., et al. (2007) Roles of heme oxygenase-1 in curcumin-induced growth inhibition in rat smooth muscle cells. Exp. Mol. Med. 39, 267–277.
[31] Wongcharoen, W. and Phrommintikul, A. (2009) The protective role of curcumin in cardiovascular diseases. Int. J. Cardiol. 133, 145–151.
[32] Morimoto, T., Sunagawa, Y., Kawamura, T., Takaya, T., Wada, H., et al. (2008) The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J. Clin. Invest. 118, 868–878.
[33] Duan, W., Yang, Y., Yan, J., Yu, S., Liu, J., et al. (2012) The effects of curcumin post-treatment against myocardial ischemia and reperfusion by activation of the JAK2/STAT3 signaling pathway. Basic Res. Cardiol. 107, 1–12.
[34] Kim, Y. S., Kwon, J. S., Cho, Y. K., Jeong, M. H., Cho, J. G., et al. (2012) Curcumin reduces the cardiac ischemia-reperfusion injury: involvement of the toll-like receptor 2 in cardiomyocytes. J. Nutr. Biochem. 23, 1514–1523.
[35] Parodi, F. E., Mao, D., Ennis, T. L., Pagano, M, B., and Thompson, R. W. (2006) Oral administration of diferuloylmethane (curcumin) suppresses proinflammatory cytokines and destructive connective tissue remodeling in experimental abdominal aortic aneurysms. Ann. Vasc. Surg. 20, 360–368.
[36] Morimoto, T., Sunagawa, Y., Fujita, M., and Hasegawa, K. (2010) Novel heart failure therapy targeting transcriptional pathway in cardiomyocytes by a natural compound, curcumin. Circ. J. 74, 1059–1066.
[37] Hong, D., Zeng, X., Xu, W., Ma, J., Tong, Y., et al. (2010) Altered profiles of gene expression in curcumin-treated rats with experimentally induced myocardial infarction. Pharmacol. Res. 61, 142–148.
[38] Laird, M. D., Sukumari-Ramesh, S., Swift, A. E., Meiler, S. E., Vender, J. R., et al. (2010) Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? J. Neurochem. 113, 637–648.
[39] Sun, Y., Dai, M., Wang, Y., Wang, W., Sun, Q., et al. (2011) Neuroprotection and sensorimotor functional improvement by curcumin after intracerebral hemorrhage in mice. J. Neurotrauma. 28, 2513–2521.
[40] Himadri, P., Kumari, S. S., Chitharanjan, M., and Dhananjay, S. (2010) Role of oxidative stress and inflammation in hypoxia-induced cerebral edema: a molecular approach. High Alt. Med. Biol. 11, 231–244.
[41] Smith, D. G., Cappai, R., and Barnham, K. J. (2007) The redox chemistry of the Alzheimer's disease amyloid beta peptide. Biochim. Biophys. Acta. 1768, 1976–1790.
[42] Hamaguchi, T., Ono, K., and Yamada, M. (2010) Review: curcumin and Alzheimer's disease. CNS Neurosci. Ther. 16, 285–297.
[43] Zbarsky, V., Datla, K. P., Parkar, S., Rai, D. K., Aruoma, O. I., et al. (2005) Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radic. Res. 39, 1119–1125.
[44] Mehla, J., Reeta, K. H., Gupta, P., and Gupta, Y. K. (2010) Protective effect of curcumin against seizures and cognitive impairment in a pentylenetetrazole-kindled epileptic rat model. Life Sci. 87, 596–603.
[45] Xie, L., Li, X. K., and Takahara, S. (2011) Curcumin has bright prospects for the treatment of multiple sclerosis. Int. Immunopharmacol. 11, 323–330.
[46] Ghoneim, A. I., Abdel-Naim, A. B., Khalifa, A. E., and El-Denshary, E. S. (2002) Protective effects of curcumin against ischaemia/reperfusion insult in rat forebrain. Pharmacol. Res. 46, 273–279.
[47] Bishnoi, M., Chopra, K., and Kulkarni, S. K. (2008) Protective effect of curcumin, the active principle of turmeric (*Curcuma longa*) in haloperidol-induced orofacial dyskinesia and associated behavioural, biochemical and neurochemical changes in rat brain. Pharmacol. Biochem. Behav. 88, 511–522.
[48] Hafner-Bratkovic, I., Gaspersic, J., Smid, L. M., Bresjanac, M., and Jerala, R. (2008) Curcumin binds to the alpha-helical intermediate and to the amyloid form of prion protein—a new mechanism for the inhibition of PrP(Sc) accumulation. J. Neurochem. 104, 1553–1564.
[49] Zhao, X., Xu, Y, Zhao, Q., Chen, C. R., Liu, A. M., et al. (2012) Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: descending monoamine system and opioid receptors are differentially involved. Neuropharmacology 62, 843–854.
[50] Yano, S., Terai, M., Shimizu, K. L., Futagami, Y., Sekine, T., et al. (2000) Antiallergic activity of *Curcuma longa.* (II). Features of inhibitory actions on histamine release from mast cells. Nat. Med. 54, 325–329.
[51] Viswanath, P. K. and Christy, S. B. (2008) Immunomodulatory effects of curcumin in allergy. Mol. Nutr. Food Res. 52, 1031–1039.
[52] Viswanath, P. K., Christy, S. B., Raghavan, R., Bryon, D. J., Michael, B. L., et al. (2007) Immune response modulation by curcumin in a latex allergy model. Clin. Mol. Allergy 5, 1.
[53] Biswas, S., and Rahman, I. (2008) Modulation of steroid activity in chronic inflammation: a novel anti-inflammatory role for curcumin. Mol. Nutr. Food Res. 52, 987–994.
[54] Moghaddam, S. J., Barta, P., Mirabolfathinejad, S. G., Ammar-Aouchiche, Z., Garza, N. T., et al. (2009) Curcumin inhibits COPD-like airway inflammation and lung cancer progression in mice. Carcinogenesis 30, 1949–1956.
[55] Ali, T., Shakir, F., and Morton, J. (2012) Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. Digestion 85, 249–255.
[56] Lubbad, A., Oriowo, M. A., and Khan, I. (2009) Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. Mol. Cell. Biochem. 322, 127–135.
[57] Holt, P. R., Katz, S., and Kirshoff, R. (2005) Curcumin therapy in inflammatory bowel disease: a pilot study. Dig. Dis. Sci. 50, 2191–2193.
[58] Hanai, H., Iida, T., Takeuchi, K., Watanabe, F., Maruyama, Y., et al. (2006) Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin. Gastroenterol. Hepatol. 4, 1502–1506.
[59] Shiozawa, S. and Tsumiyama, K. (2009) Pathogenesis of rheumatoid arthritis and c-Fos/AP-1. Cell Cycle 8, 1539–1543.
[60] Park, C., Moon, D. O., Choi, I. W., Choi, B. T., Nam, T. J., et al. (2007) Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis. Int. J. Mol. Med. 20, 365–372.
[61] Jackson, J. K., Higo, T., Hunter, W. L., and Burt, H. M. (2006) The antioxidants curcumin and quercetin inhibit inflammatory processes associated with arthritis. Inflamm. Res. 55, 168–175.
[62] Shakibaei, M., John, T., Schulze-Tanzil, G., Lehmann, I., and Mobasheri, A. (2007) Suppression of NF-kappaB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: implications for the treatment of osteoarthritis. Biochem. Pharmacol. 73, 1434–1445.
[63] Belcaro, G., Cesarone, M. R., Dugall, M., Pellegrini, L., Ledda, A., et al. (2010) Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Altern. Med. Rev. 15, 337–344.
[64] Chandran, B. and Goel, A. (2012) A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother. Res. 26, 1719–1725.
[65] Patschan, D., Patschan, S., and Müller, G. A. (2012) Inflammation and microvasculopathy in renal ischemia reperfusion injury. J. Transplant. 2012, 764154.
[66] Bayrak, O., Uz, E., Bayrak, R., Turgut, F., Atmaca, A. F., et al. (2008) Curcumin protects against ischemia/reperfusion injury in rat kidneys. World J. Urol. 26, 285–291.
[67] Rogers, N. M., Stephenson1, M. D., Kitching, A. R., Horowitz, J. D., and Coates, P. H. (2012) Amelioration of renal ischaemia–reperfusion injury by liposomal delivery of curcumin to renal tubular epithelial and antigen-presenting cells. Br. J. Pharm. 166, 194–209.
[68] Jones, E. A. and Shoskes, D. A. (2000) The effect of mycophenolate mofetil and polyphenolic bioflavonoids on renal ischemia reperfusion injury and repair. J. Urol. 163, 999–1004.
[69] Abdou, A. G. and Hanout, H. M. (2008) Evaluation of survivin and NF-kappaB in psoriasis, an immunohistochemical study. J. Cutan. Pathol. 35, 445–451.

[70] Pol, A., Bergers, M., and Schalkwijk, J. (2003) Comparison of antiproliferative effects of experimental and established antipsoriatic drugs on human keratinocytes, using a simple 96-well-plate assay. In Vitro Cell. Dev. Biol. Anim. 39, 36–42.

[71] Sun, J., Han, J., Zhao, Y., Zhu, Q., and Hu, J. (2012) Curcumin induces apoptosis in tumor necrosis factor-alpha-treated HaCaT cells. Int. Immunopharmacol. 13, 170–174.

[72] Kurd, S. K., Smith, N., VanVoorhees, A., Troxel, A. B., Badmaev, V., et al. (2008) Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: a prospective clinical trial. J. Am. Acad. Dermatol. 58, 625–631.

[73] Yamamoto, T. (2009) Scleroderma—pathophysiology. Eur. J. Dermatol. 19, 14–24.

[74] Tourkina, E., Gooz, P., James, C. O., Ludwicka-Bradley, A., Silver, R. M., et al. (2004) Curcumin-Induced Apoptosis in Scleroderma Lung Fibroblasts Role of Protein kinase Cε. Am. J. Respir. Cell Mol. Biol. 31, 28–35.

[75] Song, K., Peng, S., Sun, Z., Li, H., and Yang, R. (2011) Curcumin suppresses TGF-β signaling by inhibition of TGIF degradation in scleroderma fibroblasts. Biochem. Biophys. Res. Commun. 411, 821–825.

[76] Cheng, A. L., Hsu, C. H., Lin, J. K., Hsu, M. M., Ho, Y. F., et al. (2001) Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 21, 2895–900.

[77] Lao, C. D., Ruffin, M. T., Normolle, D., Heath, D. D., Murray, S. I., et al. (2006) Dose escalation of a curcuminoid formulation. BMC. Complement. Altern. Med. 6, 10.