ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES OF CURCUMIN

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Abstract: Curcumin, a yellow pigment from *Curcuma longa*, is a major component of turmeric and is commonly used as a spice and food-coloring agent. It is also used as a cosmetic and in some medical preparations. The desirable preventive or putative therapeutic properties of curcumin have also been considered to be associated with its antioxidant and anti-inflammatory properties. Because free-radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are believed to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis, and neurodegenerative diseases, curcumin is thought to play a vital role against these pathological conditions. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). COX-2, LOX, and iNOS are important enzymes that mediate inflammatory processes. Improper upregulation of COX-2 and/or iNOS has been associated with the pathophysiology of certain types of human cancer as well as inflammatory disorders. Because inflammation is closely linked to tumor promotion, curcumin with its potent anti-inflammatory property is anticipated to exert chemopreventive effects on carcinogenesis. Hence, the past few decades have witnessed intense research devoted to the antioxidant and anti-inflammatory properties of curcumin. In this review, we describe both antioxidant and anti-inflammatory properties of curcumin, the mode of action of curcumin, and its therapeutic usage against different pathological conditions.

1. CURCUMIN: THE SPICE OF LIFE–UNLOCKING THE SECRETS OF CURCUMIN

–*"Imagine if the key to disease prevention was as close as your kitchen shelf. It's not the product of someone's imagination, but the product of years of medical research. Scientists are beginning to take notice of a well-known spice as a potent new preventive therapy against disease, especially cancer—John C. Martin,* LE Magazine*, September 2001"*

More than one billion people consume curcumin regularly in their diets. Curcumin has long been used in Eastern medicine and is gaining attention in Western medicine, not only as a nonsteroidal anti-inflammatory drug (NSAID) but also

for its chemopreventive properties. Essentially, curcumin is believed to possess generalized protective properties.

Curcumin, a yellow pigment from *Curcuma longa*, is a major component of turmeric and is commonly used as a spice and food-coloring material. It exhibits anti-inflammatory,[1] antitumor, and antioxidant[2] properties. Curcumin is a low-molecular-weight polyphenol, first chemically characterized in 1910, with the molecular formula of $C_{21}H_{20}O_6$. It is generally regarded as the most active constituent of and comprises 2–8% of most turmeric preparations. It has long been used as the yellow spice in Indian food and as a naturally occurring medicine for the treatment of inflammatory diseases.[3]

The desirable preventive or putative therapeutic properties of curcumin have also been considered to be associated with its antioxidant property.[4] Because free radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are believed to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis, neurodegenerative diseases, and aging,[5] curcumin is thought to play a vital role against oxidative-stress-mediated pathological conditions. Hence, the past few decades have witnessed intense research devoted to the antioxidant activity of curcumin. Before pointing out the potential antioxidant property of curcumin, it is worthwhile to outline the role of free radicals and antioxidants in health and disease.

2. ROLE OF FREE RADICALS IN HEALTH AND DISEASE

It has been nearly 50 years since Denham Harman[6] suggested that free radicals produced during aerobic respiration cause cumulative oxygen damage, resulting in aging and death.

Oxygen is an essential molecule for all aerobic forms; however, oxygen plays univalent roles. Although oxygen is indispensable for all cells for chemical energy production (ATP), it is also often transformed into highly reactive forms: reactive oxygen species (ROS), which are often very toxic to the cells.[7,8] Approximately 2% of the oxygen reduced by the mitochondria then forms superoxide ($O_2^{-\cdot}$) or the dismutation product H_2O_2. Superoxide and peroxide reacts with metal ions (Heiber-Weiss and Fenton's reactions) to promote additional radical generation, particularly with the generation of hydroxyl radicals. The hydroxyl radical reacts with all components of the cell, including lipid membrane, DNA and proteins.[9]

Nitric oxide (NO) has an unpaired electron and is therefore a free-radical species. It is a short-lived, lipophilic molecule generated from L-arginine by NO synthase (NOS). NO is involved physiologically in vasorelaxation, neurotransmission, inhibition of platelet aggregation, immune defense, and intracellular signaling. However, NO reacts with $O_2^{-\cdot}$ to form peroxynitrite ($ONOO^-$), which is a powerful oxidant. NO bioactivity is related to the production of many reactive intermediates, but many of these reactive nitrogen species (RNS) are capable of damaging DNA or hindering DNA repair.[10] It is now beyond doubt that oxidants are generated *in vivo* and can cause significant damage to cells.

When an imbalance occurs between oxidants and defense systems, in favor of oxidants, oxidative stress occurs. This oxidative stress in cells results in severe metabolic dysfunctions, including loss of cell integrity, enzyme function, genomic stability, and so forth, which ultimately lead to pathogenesis of many human diseases (e.g., inflammation, ischemia, atherosclerosis, arthritis, cancer, Parkinson's disease, Alzheimer's disease, and so forth).

3. ANTIOXIDANTS: WHY ARE THEY NEEDED?

To deal with the threat of oxidant-induced damage, biological antioxidants were evolved. Cells are equipped with an impressive repertoire of antioxidant enzymes, as well as small antioxidant molecules, the later being mostly ingested from fruits and vegetables. The antioxidant defenses include the following:

1. Superoxide dismutase (SOD), which hastens the dismutation of $O_2^{\cdot -}$ to H_2O_2, catalase, and glutathione peroxidase (GPx), which converts H_2O_2 to water
2. Hydrophilic radical scavengers such as ascorbate, urate, and glutathione (GSH)
3. Lipophilic radical scavengers such as tocopherols, flavonoids, carotenoids, and ubiquinol
4. Enzymes involved in the reduction of oxidized form of small-molecule antioxidants (GSH reductase and ascorbate reductase) or responsible for the maintenance of protein thiols (thioredoxin reductase)

Antioxidant systems are complex and act in concert to decrease ROS load. It also helps to divert ROS to other reaction pathways that form less reactive products, to selectively inactivate (in redox terms) transition metal ions, and, when all of these fails, to provide sacrificial molecules that act as a replicable or recyclable "buffer" to absorb oxidative hits and excess energy.[11]

Human antioxidant defenses are effective, but they are not infallible and oxidative damage to key biological sites occurs, accumulates with age, and contributes to senescence and age-related disease. This means that oxidative stress, which is an oxidant:antioxidant imbalance in favor of oxidation, remains a real and constant threat.

The evolution of our endogenous antioxidant system has not progressed beyond the breakeven point of cost-effectiveness. This has led to the attention of dietary antioxidants. Wood and Brooks[12] suggested that "we are what we ate," and although many geographical and environmental factors undoubtedly determined the evolutionary development of our species, our future health as individuals might well depend on what we eat today.

4. CURCUMIN: ANTIOXIDANT MECHANISM

The antioxidant mechanisms of curcumin have recently been the focus of interest of free-radical chemists and biologists.

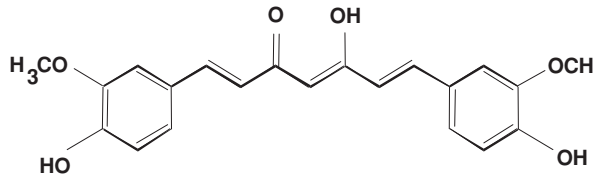

Figure 1. Curcumin.

Curcumin is known to protect biomembranes against peroxidative damage. Peroxidation of lipids is known to be a free-radical-mediated chain reaction, leading to the damage of the cell membranes, and the inhibition of peroxidation by curcumin is mainly attributed to the scavenging of the reactive free radicals involved in the peroxidation. Most of the antioxidants have either a phenolic functional group or a β-diketone group. Curcumin is an unique antioxidant, which contains a variety of functional groups, including the B-diketo group, carbon–carbon double bonds, and phenyl rings containing varying amounts of hydroxyl and methoxy substituents (Figure 1).[13]

The central argument is whether the phenolic or the central methylenic hydrogen in the heptadienone moiety is responsible for its antioxidant activity. Jovanovic and collaborators[14] concluded that curcumin is a superb H-atom donor by donating the H-atom from the central methylenic group rather than from the phenolic group in acidic and neutral aqueous and acetonitrile solutions. On the other hand, Barclay et al.[15] proposed that curcumin is a classical phenolic chain-breaking antioxidant, donating H-atoms from the phenolic group. Priyadarsini et al.[16] have also claimed that the phenolic group is essential for the free-radical-scavenging activity and that the presence of the methoxy group further increased the activity.

Theoretical calculations by the density functional theory (DFT) demonstrated that the enol form of curcumin is significantly more stable than the diketo form and that the bond dissociation enthalpy (BDE) of the phenolic O:H bond is significantly lower than the BDE of the central O:H bond, suggesting that the hydrogen atom abstraction takes place in the phenolic group.[13,16,17] It was also pointed out that the relative contribution of the phenolic group and the central methylenic group on the antioxidant activity depends on the activity of attacking radical and the reaction medium.[13,18] Litwinienko and Ingold[19] recently compared the rate constants of the reaction of 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical with curcumin in ionizing solvents and nonionizing solvents and resolved the curcumin antioxidant controversy by the mechanism of sequential proton loss electron transfer (SPLET); that is, in solvents that support ionization, curcumin reacts with electrophilic radicals initially at ionized keto-enol moiety and the resulting neutral radicals lose a phenolic photon, thus yielding the same phenoxyl radical, as would have been formed by H-atom transfer (HAT) from the phenolic hydroxyl group of the curcumin anion to the radicals. However, in nonionizing solvent, the SPLET mechanism cannot occur and the reactions involve only HAT from a phenolic hydroxyl group of the neutral curcumin to the radical.[19]

Another important mechanism is that curcumin can degrade into trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexanal, ferulic acid, ferruloylmethane, and vanillin at basic pH within 30 min.[3] Among these, ferrulic acid and vannilin are well-established antioxidants.

5. ANTI-INFLAMMATORY PROPERTY OF CURCUMIN

Curcumin was found to have a miraculous power in anti-inflammatory response. The natural anti-inflammatory activity of curcumin is on a par with steroidal drugs and nonsteroidal drugs as indomethacin and phenylbutazone, which have dangerous side effects. Its anti-inflammatory property appears to be mediated through the inhibition of induction of COX-2, LOX, iNOS and production of cytokines such as interferon-γ and tumor necrosis factor, and activation of transcription factors like NF-κB, and AP-1.

5.1. Effect of Curcumin on Cyclooxygenases and Lipoxygenases

The anti-inflammatory properties of curcumin have been attributed, at least in part, to suppression of prostaglandins (PGs) synthesis.[20] The involvement of PGs and other eicosanoids in the development of human cancer has been known for over two decades. Importantly, an increase in PG synthesis might influence tumor growth in human beings and experimental animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen metabolism, tumor cell proliferation, and metastatic potential.[21] Cyclooxygenase (COX) is a key enzyme responsible for the conversion of arachidonic acid to PGs. It consists of two different isoforms, designated COX-1 and COX-2. COX-1 is a constitutive isoform present in most tissues and is generally regarded as a "housekeeping" enzyme[22] and its inhibition results in serious effects such as peptic ulceration or impairment of renal blood flow. In contrast, COX-2 is constitutively expressed only in brain and spinal cord tissue and it can also be induced in a wide variety of normal tissues by the hormones of ovulation and pregnancy, cytokines, growth factors, oncogenes, and tumor promoters.[23] COX-2 overexpression has been implicated in the carcinogenesis of tumors of the colon, rectum, breast, head and neck, lung, pancreas, stomach, and prostate.[24] There is growing evidence that inhibitors of COX-2 activity are useful for treating inflammation and preventing or treating cancer.[25] Therefore, agents that interfere with the signaling mechanisms governing the transcription of COX-2 should also inhibit inflammation and tumorigenesis. Further investigations suggest that arachidonic acid (AA) metabolites derived from lipoxygenase (LOX) pathways play an important role in growth-related signal transduction, implying that intervention through these pathways should be useful for arresting cancer progression.

An expanding body of evidence suggests that curcumin inhibits the expression of COX-2. Kawamori et al.[26] have demonstrated that dietary curcumin significantly inhibits phospholipase A2 in colonic mucosa and tumors, leading to the release of arachidonic acid from phospholipids, alters COX and LOX activities, and modifies

PGE_2 levels. Unlike selective COX-2 inhibitors, which inhibit the catalytic activity of the COX enzyme, curcumin decreases COX-2 expression at the transcriptional level.[27] Several lines of evidence also indicate that the mechanism of action of curcumin is not limited to PG inhibition. They have also observed that dietary curcumin inhibits LOX activity and the production of the LOX metabolites in the colonic mucosa and in tumors. LOX metabolites have also been shown to promote tumor cell adhesion, stimulate the spreading of tumor cells, and augment metastatic potential.[28]

In one study, Zhang and colleagues[27] from the Cornell University campus in New York City, exposed gastrointestinal cells to two known tumor promoters: bile acids (BA) and phorbol esters (PMA). The team found COX-2 to be induced in several of the cell lines, accompanied by a 10-fold increase in the synthesis of inflammatory-causing PGE_2. However, dose-dependent treatment of the cells with curcumin suppressed both BA- and PMA-mediated induction of COX-2 protein, genetic COX-2 expression (as measured by mRNA), and the synthesis of PGE_2. Most impressive, however, was the discovery that curcumin directly inhibited the enzymatic activity of COX-2.

An additional study presented at the 1999 American Association for Cancer Research (AACR) conference also examined the pain-relieving properties of curcumin. Researchers at the University of California, San Diego and the Veterans Administration Medical Center, San Diego[29] investigated whether curcumin could suppress COX-2 expression in human colon cancer cells. After exposing such cells to curcumin, the researchers found the compound not only inhibited cell growth but also reduced the expression of COX-2 mRNA in a time- and dose-dependent manner.

Therefore, curcumin would appear to be a safe, natural COX-2 inhibitor in humans, given its safety profiles and demonstrated anti-inflammatory activity.

5.2. Effect of Curcumin on Inducible Nitric Oxide Synthase

Another enzyme that plays a pivotal role in mediating inflammation is inducible nitric oxide synthase (iNOS). iNOS catalyzes the oxidative deamination of L-arginine to produce NO, a potent pro-inflammatory mediator. NO has multifaceted roles in mutagenesis and carcinogenesis.[30] In addition to acting as an initiator of carcinogenesis, NO is involved in the promotional stage of tumorigenesis or neoplastic transformation. NO is also known to affect tumor progression by regulating the angiogenesis, possibly by stimulating the production of vascular endothelial growth factor (VEGF).[31] NO reacts rapidly with superoxide anion to produce the extremely powerful oxidant peroxynitrite ($ONOO^-$).[32] Peroxynitrite can cause various DNA modifications and other types of cellular injury, contributing to genotoxicity or initiation of multistage carcinogenesis. One of the secondary processes that might follow DNA damage by NO or peroxynitrite includes activation of the tumor suppressor gene *p*53 or the DNA repair enzyme poly(ADP-ribose)polymerase (PARP).[33] It is known that activation of *p*53 or PARP is often associated with apoptotic cell death. There are numerous reports on the NO- or peroxynitrite-induced

apoptosis.[34] Increased expression of iNOS and/or its catalytic activity has been observed in several human tumor tissues and also in chemically induced animal tumors as well as in inflammatory disorders.[35–37] Human breast tumor biopsies in higher grades exhibited elevated levels of iNOS, compared with those in lower-grade ones.[38] Thus, aberrant or excessive expression of iNOS, as in the case of COX-2, is considered to be implicated in the pathogenesis of cancer, and compounds that can selectively inhibit abnormal expression of iNOS can act as a potential candidate for chemoprevention. iNOS has been shown to be involved in the regulation of COX-2 and, hence, the subsequent production of pro-inflammatory PGs.[39]

In addition to COX-2, iNOS also appears to be a target for the anti-inflammatory effect of curcumin. Curcumin is reported to inhibit the NO production and expression of iNOS protein and mRNA in RAW 264.7 cells stimulated with lipopolysaccharides (LPSs) or interferon-γ.[40] Downregulation of the iNOS gene by curcumin in RAW 264.7 cells might be attributed to suppression of c-Jun/AP-1 activation, because it is a known fact that the consensus AP-1-binding sequence is present in the promoter region of the iNOS gene and it can be attenuated by curcumin.[40] Chan et al.[41] have reported that curcumin can inhibit the iNOS gene expression in isolated BALB/c mouse peritoneal macrophages and in the livers of LPS-injected mice.

5.3. Effect of Curcumin on Nuclear Factor-κB

One of the most ubiquitous eukaryotic transcription factors that regulate expression of genes involved in controlling cellular proliferation/growth, inflammatory responses, cell adhesion, and so forth is nuclear factor-κB (NF-κB).[42,43] The functionally active NF-κB exists mainly as a heterodimer consisting of subunits of the Rel family (e.g., Rel A or p65, p50, p52, c-Rel, v-Rel, and Rel B), which is normally sequestered in an inactive cytoplasmic complex by binding to an inhibitory protein, IκB. Exposure of cells to such external stimuli as mitogens, inflammatory cytokines, ultraviolet radiation, ionizing radiation, viral proteins, bacterial LPSs, and ROS causes rapid phosphorylation of IκB with subsequent degradation by proteosomes. Dissociation of IκB from NF-κB allows the activated free dimer to translocate to the nucleus, where it induces, through binding the cis-acting κB element, the transcription of a large variety of target genes that normally encode cytokines, cell adhesion molecules, growth factors, and so forth. The transcriptional activity of NF-κB is regulated via an elaborate series of intracellular signal transduction events in response to external stimuli.[30] In addition to its central roles in mediating inflammation, NF-κB is important in control via cell proliferation, oncogenesis, and cell transformation.[44] Thus, aberrant constitutive activation of NF-κB/Rel has been observed in an array of human and experimentally induced tumors and transformed cells in culture. There is increasing evidence that constitutive activation of this transcription factor is associated with the proliferation and survival of certain tumor cells and causes resistance to apoptosis.[45]

The data from experimental studies have demonstrated that curcumin inhibits the activation of NF-κB in different cancer cell lines.[46] It has been found that oxidative stress activates NF-κB DNA-binding activity. Because curcumin has been known as an antioxidant, its inhibitory effects on oxidative stress might be mediated through the suppression of NF-κB DNA-binding activity. It has been reported that curcumin inhibited IKB kinase (IKK), suppressed both constitutive and inducible NF-κB activation and potentiated tumor necrosis factor (TNF)-induced apoptosis. Curcumin treatment reduced the amount of phosphorylated IKK, which ultimately prevents the translocation of NF-κB to the nucleus. Curcumin also showed strong antioxidant and anticancer properties through regulating the expression of genes that require the activation of activator protein (AP1) and NF-κB.[47]

5.4. Effect of Curcumin on Tumor Necrosis Factor

Tumor necrosis factor (TNF) has been shown to mediate tumor initiation, promotion, and metastasis.[48] Moore et al.[49] have reported that TNF-deficient mice have been shown to be resistant to skin carcinogenesis. The induction of pro-inflammatory genes by TNF has been linked to most diseases. The pro-inflammatory effects of TNF are primarily due to its ability to activate NF-κB. Almost all cell types, when exposed to TNF, activate NF-κB, leading to the expression of inflammatory genes. These include COX-2, LOX-2, cell adhesion molecules, inflammatory cytokines, chemokines, and iNOS. TNF has been found to be a growth factor for most tumor cells.[50]

Because of the critical role of TNF in mediating tumorigenesis, agents that can suppress TNF activity have the potential for therapy of TNF-linked diseases. Curcumin was found to have a spellbound effect in the suppression of TNF production.[51] The constitutive activation of NF-κB in mantle cell lymphoma (MCL) cells is due to autocrine expression of TNF. TNF mRNA is constitutively expressed in the MCL cell lines; curcumin inhibits the expression of both TNF mRNA and TNF protein in MCL cell lines.[51] Suppression of TNF by curcumin led to inhibition of NF-κB and cell proliferation, as was the case when TNF secretion was neutralized using anti-TNF antibody.[51]

Thus, curcumin exerts a protective role against inflammatory diseases through the suppression of COX, LOX, iNOS, NF-κB, TNF and some other inflammatory mediators.

6. THERAPEUTIC USE OF CURCUMIN

6.1. Cancer

Curcumin has proved its credentials as a wonderful chemopreventive agent against a variety of cancers. Oxidative stress induced by ROS has been linked to tumor promotion in mouse skin and other tissues.[52–54] Hydrogen peroxide promotes the transformation of chemically initiated mouse epidermal cells.[52] When different types of tumor promoter were applied topically to mouse skin, there

was a distinct increase in the production of hydrogen peroxide in the epidermis, which correlated with their promoting potential.[55] Superoxide anion radicals were also formed in keratinocytes stimulated with the tumor promoter such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA).[56] Further support for the association between pro-oxidant status and tumor promotion derives from the observation that many structurally unrelated antioxidants and radical scavengers exert antipromotional activity.[52,53] Exogenous superoxide dismutase (SOD) inhibited the promotion by TPA of JB6 mouse epidermal cell transformation, providing additional evidence for a critical role of ROS in tumor promotion.[57] Similarly, the lipophilic biomimetic SOD cupric 3,5-diidopropylsalicylic acid inhibited tumor promotion in mouse epidermis.[58] Ornithine decarboxylase (ODC), a rate-limiting enzyme in polyamine biosynthesis, has been utilized as a biochemical marker for tumor promotion. ODC induction was found to be suppressed by SOD and catalase in murine mammary tumor cells and by butylated hydroxytoluene in mouse epidermal cells, suggesting the intermediacy of Reactive oxygen intermediates (ROIs) in the tumor promotion.[52]

Persistent, local inflammation has been considered to contribute to multistage carcinogenesis. ROS produced during the inflammatory tissue damage can trigger a series of reactions responsible for malignant transformation, particularly in the stage of promotion.[52]. There is accumulating evidence that ROS influence the intracellular signaling cascades mediating cell proliferation. Activity or expression of several protein kinases have been shown to be regulated by the pro-oxidant state of cells. ROS are typical by-products of eicosanoid metabolism.[59] ROS are released from the cells of the inflammatory skin infiltrate. A correlation exists between the ability of a compound to induce PG release *in vitro* and its ability to promote papilloma formation in mouse skin *in vivo*. Verma et al.[60] suggests that PGs play a crucial role in the induction of ODC activity and mouse skin tumor promotion by TPA. Both ROI generation by inflammatory cells and skin tumor promotion are efficiently inhibited by protease inhibitors, indicating an interrelationship between the two processes.[54]

Chemopreventive properties of curcumin have been extensively investigated and well documented.[61,62] One of the most plausible mechanisms underlying the chemopreventive effects of curcumin involves suppression of tumor promotion. Thus, topical application of curcumin strongly inhibited TPA-induced inflammation, hyperplasia, proliferation, ODC activity, ODC mRNA expression, generation of ROIs, oxidized DNA base modification, and papilloma formation in mouse skin.[62–63] Curcumin inhibited COX-2 and LOX activities in TPA-treated mouse epidermis.[20] Treatment of several human gastrointestinal cell lines with curcumin suppressed expression of COX-2 protein and mRNA, PGE_2 production, and AP-1 DNA binding induced by TPA or chenodeoxycholate.[27] Suppression of TPA-induced activation of c-Jun/AP-1 in cultured NIH3T3 cells has been proposed to be responsible for the antitumor-promoting activity that curcumin retains.[64]

In conclusion, the anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, downregulate transcription factors NF-κB, AP-1, and Egr-1, downregulate the expression of COX-2, LOX,

iNOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules, and cyclin D1, downregulate growth factor receptors (such as EGFR and HER2), and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases, and protein serine/threonine kinases. It also influences the free-radical production during the activation of carcinogen and helps in detoxification of carcinogens.

6.2. Atherosclerosis

The most common form of heart disease is atherosclerosis. Atherosclerosis involves the deposition of fatty substances, cholesterol, complex carbohydrates and fibrin (a clotting material in the blood), and so forth in the inner lining of the major artery. The deposition that results (referred to as plaque) can partially or totally block the flow of blood through the artery. This can lead to the formation of a blood clot (thrombus) on the surface of the plaque. If either of these events occurs and blocks the coronary artery, a heart attack might result. Some controllable mechanisms that are involved in the development of atherosclerosis are oxidation of low-density lipoprotein-cholesterol (LDL-C), abnormal platelet aggregation, and inflammation.[65,66] Curcumin has gained importance because of its antioxidant and antiplatelet aggregating qualities. Curcumin's ability to control platelet aggregation appears directly to be related to thromboxane inhibition (a promoter of aggregation) and an increase in prostacyclin activity, an inhibitor of aggregation.[67,68] Curcumin, being a powerful antioxidant, quenches free radicals, thereby decreasing the cellular damage. It also helps in reducing blood lipid levels, particularly cholesterol. Rats fed 0.1% curcumin, along with a cholesterol diet, had about one-half of the blood cholesterol as rats fed equal amounts of cholesterol but without curcumin.[66]

Curcumin, with its potent anti-inflammatory activity, reduces the inflammation, promotes fibrinolysis, and inhibits the leukotriene formation,[69,70] which are important steps in the prevention of atherosclerosis.

6.3. Aging

A number of theories have been proposed to explain the nature of aging and one such is the free-radical theory.[71] According to the free-radical theory of aging, these very reactive species, produced continuously during normal metabolism, eventually accumulates, damaging DNA and other macromolecules. This is due to progressive defects in the defense systems against reactions that generate free radicals. The result is the appearance of degenerative lesions and cellular death. Then the organism ages and, finally dies. Different observations support the hypothesis of the major role of free radicals in aging. The potential life span of a species is determined genetically. However, it can be altered by environmental conditions such as diet. Harman[72,73] has demonstrated, for example, that life expectation of many species is increased by 20% by adding antioxidants to the diet. It has also been shown that animals, which live longer or with longer life spans, present higher SOD levels.[74] Curcumin might have been delaying the aging of human beings with

its effective antioxidant property, as it is known that billions of people consume curcumin daily in their diets.

6.4. Neurodegenerative disease

Oxidative stress has been implicated in mechanisms leading to neuronal cell injury in various pathological states of the brain. Alzheimer's disease (AD) is a progressive disorder with cognitive and memory decline, speech loss, personality changes, and synapse loss.[75] Many approaches have been undertaken to understand AD, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease. However, increasing evidence indicates that factors such as oxidative stress and disturbed protein metabolism and their interaction in a vicious cycle are central to AD pathogenesis.

Increasing interest has been focused on identifying dietary compounds that can inhibit, retard, or reverse the multistage pathophysiological events underlying AD pathology. AD, in fact, involves a chronic inflammatory response associated with both brain injury and β-amyloid associated pathology. All of the above evidence suggests that stimulation of various repair pathways by mild stress has significant effects on delaying the onset of various age-associated alterations in cells, tissues, and organisms.

Curcumin has emerged as a strong inducer of the heat shock response. In light of this finding, curcumin supplementation has recently been considered an alternative, nutritional approach to reduce oxidative damage and amyloid pathology associated with AD.

The potential neuroprotective action of curcumin was discovered during a screening of its potential to protect against the adverse effects from high doses of alcohol, which revealed positive results. Since then, studies have indicated potential benefits for AD and Parkinson's disease, based on laboratory animal models; clinical work is now beginning. In addition, studies in animal models of AD indicate a direct effect of curcumin in decreasing the amyloid pathology of AD. As the widespread use of curcumin as a food additive and relatively small short-term studies in humans suggest safety, curcumin is a promising agent in the treatment and/or prevention of AD. Just as in AD, inflammation and oxidative damage play a strong role in the neurodegenerative process of Hodgkin's disease (HD): Oxidative damage helps to degrade nerve cells in the basal ganglia and cerebral cortex and chronic inflammation in the brains of people with HD is believed to play a significant role in the progression of the disease. As shown previously, curcumin was able to reduce inflammation and oxidative damage in mouse models of AD.[76]

6.5. Liver Fibrosis

Liver fibrosis and cirrhosis result from the majority of chronic liver insults and represent a common and difficult clinical challenge of worldwide importance. At present, the only curative treatment for end-stage cirrhosis is transplantation.

Hence, there is a considerable imperative to develop antifibrotic strategies that are applicable to liver fibrosis. Development of liver fibrosis entails major alterations in both the quantity and quality of the extracellular matrix (ECM).[77,78] The remodeling of ECM both in normal and pathological conditions is controlled by a group of enzymes called matrix metalloproteinases (MMPs).[79]

Curcumin has been extensively investigated for its hepatoprotective potential. Normally, oxidative stress and inflammation play an important role in the development of alcohol and heated polyunsaturated fatty acids (PUFAs) and CCL_4-induced liver fibrosis.[80] Curcumin, due to its effective antioxidant and anti-inflammatory properties, inhibits liver fibrosis.[81] Curcumin is also reported to influence the hepatic expression patterns of MMPs.[82] Thus, curcumin emerged as an potent antifibrotic compound.

6.6. Diabetes

Environmental factors play an important role in the etiology and management of diabetes, and antioxidants in food and medicinal plants are potential modulators of diabetes onset, progression, and complications. Among the naturally occurring compounds, curcumin has received the most attention as an antidiabetic compound.

Oxidative stress as a consequence of hyperglycemia and changes in energy metabolism and inflammatory mediators play an important role in the pathophysiology of diabetes in association with depleted cellular antioxidant defense systems and enhanced production of ROS.[82] Oxidative stress associated with hyperglycemia impairs cellular function and alters vascular and neural function. High glucose concentrations promote free-radical production via the following three biochemical pathways: advanced glycation end products (AGEs),[83] protein kinase C activation,[84] and aldose reductase pathway.[85] Another important factor that increases ROS is TNF[86]; it forms a possible connection between obesity and diabetes[87] and has been linked to insulin resistance[88] and diabetic complications.

Curcumin generally improves oxidative status, protects and enhances endogenous defenses, and directly mediates various mechanics of pathology. Many studies have shown that curcumin prevents AGE-induced complications in rats.[89] Curcumin might act by sparing or enhancing the function of the endogenous antioxidants.[90] Antioxidant activities of curcumin might occur synergistically with glucose-lowering activity.[90] The antidiabetic action of curcumin seems to be mediated through (1) stimulation of the pancreas to produce and secrete insulin, (2) interference with dietary glucose absorption, (3) insulin-sparing action of the constituent bioactive compounds, and (4) antioxidant and anti-inflammataory properties of curcumin.

6.7. AIDS

More recently, curcumin has been shown to inhibit HIV replication,[91] and currently it is in clinical trials. Mazumder et al.[92] have shown that curcumin inhibits p24 antigen production and Tat-mediated transcription. They also shown that curcumin

inhibits purified HIV-l integrase, suggesting that the anti-HIV activity of curcumin could be due to several mechanisms. Energy minimization studies suggest that the anti-integrase activity of curcumin could be due to an intramolecular stacking of two phenyl rings that brings the hydroxyl groups into close proximity (antioxidant property). The present data suggest that HIV-l integrase inhibition might contribute to the antiviral activity of curcumin. These observations suggest new strategies for antiviral drug development that could be based on curcumin as a lead compound for the development of inhibitors of HIV-l integrase.[92]

6.8. Autoimmune Disease

The immune system has evolved to discriminate self from nonself antigens, thereby protecting the host from microbial pathogens and malignant tumors.[93] Nevertheless, a breakdown in this fundamental immunoregulatory process often results in the development of chronic infectious diseases, malignant tumors, and organ-specific autoimmune diseases. Recent studies have used nutraceuticals (human diets of plant origin, containing many hundreds of biologically active compounds called nutraceuticals) to successfully target organ-specific autoimmune diseases.[94] The pathogenesis of autoimmune diseases involves complex immune mechanisms in which the pro-inflammatory cytokines contribute to manifestation of the diseases.

The anti-inflammatory action of curcumin is associated with its ability to inhibit reactive-oxygen-generating enzymes such as COX, LOX, xanthine dehydrogenase, and iNOS.[95] The involvement of interleukin (IL)-12 in the pathogenesis of rheumatoid arthritis and myocarditis has been well established, and inhibition of IL-12 has decreased the clinical symptoms of these autoimmune diseases.[96] In view of the central role played by IL-12 in Th1 differentiation, the IL-12/Th1 axis has become a novel molecular target in the treatment of Th1 cell-mediated autoimmune diseases.

Many studies suggest that nutraceuticals ameliorate autoimmune diseases by blocking Th1 cell-mediated inflammation and/or by promoting the progenitor cell growth and differentiation in the repair process.

6.9. Psoriasis

Curcumin, by its immune-modulating, anti-inflammatory, and antioxidant properties, shows a favorable effect on a mouse model of psoriasis.[97] Heng et al.[98] showed that topical treatment with curcumin results in resolution of the psoriatic activity as assessed by clinical, histological, and immunological criteria in patients. According to them, this antipsoriatic effect is linked to a curcumin-caused modulation of phosphorylase-kinase (Phk) activity that integrates multiple calcium/calmodulin-dependent signaling pathways. These pathways are coupled to glycogenolysis and ATP-dependent phosphorylation, thus ensuring the required energy supply for cell proliferation and migration.

The effectiveness of curcumin is shown by the fact that the raised Phk activity found in untreated psoriasis, that was decreased by the vitamin D_3 analogue (and indirect inhibitor of Phk) calcipotriol, was even more decreased to near-normal values by the curcumin treatment.

Previous reports suggest additional mechanisms for the antipsoriatic effects of the antioxidants from *C. longa*.[99,100] Thus, *in vitro* exposure of human keratinocytes of the HaCaT line to a hydroalcoholic extract of the rhizome of this plant was as effective for inhibition of the ultraviolet-induced secretion of IL-6 and IL-8 as medium supplementation with betamethasone-17-valerate. This observed downregulation of pro-inflammatory cytokines supports the view that the curcumin might exert a favorable effect on psoriasis-linked inflammation.

Curcumin, by its effective antioxidant and anti-inflammatory properties, was evaluated as a remarkable antipsoriatic compound.

6.10. Drug/Environmental Carcinogen-Induced Toxicity

The two most commonly abused substances in the general population are alcohol and nicotine.

Alcohol is considered to be an important recreational beverage, which is nontoxic at lower concentrations, but it is toxic at higher concentrations. Alcohol-related problems are one of the world's major public health concerns. Alcoholism is seen in all races, ethnic groups, and socioeconomic strata. Oxidative stress plays an important role in the development of alcohol-induced tissue injury.[101] Antioxidant compounds are important in treating this condition. Curcumin received much attention as a hepatoprotective agent. It is well established that curcumin protects experimental rats from chronic alcohol toxicity by its effective antioxidant property.[102]

Nicotine, a major toxic component of cigarette smoke, plays an important role in the development of cardiovascular disease and lung cancer in smokers.[103] Nicotine damages the system through the production of free radicals and inflammatory mediators.[104] Curcumin was found to offer significant protection to the experimental rats from nicotine-induced toxicity.[105]

Benzo(*a*)pyrene [B(*a*)P] is a classical environmental carcinogen present in cigarette smoke and generally regarded to be involved in the development of lung cancer. Curcumin is reported to inhibit the B(*a*)P-induced DNA mutations and thus protects the host organism from the development of lung cancer.[106]

7. CONCLUSION

Curcumin, with its impressive antioxidant and anti-inflammatory properties, was found to be a genuine natural product in treating a wide array of diseases. Its antioxidant property is believed to be due to the presence of different functional groups, including methoxy, phenoxy, and carbon–carbon double bonds in its structure. Its remarkable anti-inflammatory property kept it in the limelight over the decades

in treating inflammatory-mediated diseases including cancer, atherosclerosis, diabetes, rheumatoid arthritis, and so forth. Its anti-inflammatory property appears to be mediated through the inhibition of induction of COX-2, LOX, and iNOS and the production of cytokines such as interferon-γ, tumor necrosis factor, and many other transcription factors such as NF-κB.

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