Curcumin: A multifaceted herbal medicine

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Abstract
Curcumin, a phenolic compounds isolated from the roots of Curcuma longa (Zingiberaceae), exhibit a variety of beneficial effects on health and on events that help in preventing certain diseases. These plant-derived chemicals have generated considerable interest recently for their potential to show great variety of pharmacological activities such as anti-inflammatory, antioxidant, neuro protection, anti-cancer etc by modulation of several important molecular targets including transcription factors, cytokines, cell cycle proteins etc. As a result of extensive epidemiological, clinical, and animal studies, several molecular mechanisms are developed that elucidate multiple biological effects of curcumin. The purpose of this review is to provide a brief summary for research awareness of the effects of curcumin on the subject of potential health benefits.

Keywords: Curcuma longa L., antioxidant, cytokines, anti-inflammatory, neuro protective, anti-cancer

1. Introduction
The use of medicinal plants for the treatment of many diseases is associated to folk medicine from different parts of the world. Natural products from some plants are continued to be used in pharmaceutical preparations either as pure compound or as extract. There are variety of compounds that can be extracted and characterized from plants, one good example is curcumin. Curcumin is a chemical of the polyphenol family derived from the rhizome Curcuma longa L. The dried, ground product of this root is the common spice known as turmeric. Referred to as “Haldi” in Hindi [1], this spice has been used as an aromatic and coloring in food [2], as well as having a significant role in both Asian medicine and ancient Hindu scripture. Most commercial turmeric preparations consist of ~2-8% active curcumin. Over the last few years, a number of studies have provided evidence of important pharmacological properties of curcumin including antioxidant, anti-carcinogenic, anti-infectious, wound healing, immunomodulatory, and anti-inflammatory activities [3-6]. Curcumin is a potential natural plant antioxidant and has been found to have beneficial effects on endogenous cellular antioxidants without any side effects [7]. Curcumin has been shown to be effective in acute as well as chronic models. Curcumin (di-feruloylmethane) is in the most important fraction of C. longa L. and its chemical structure, was determined by roughly and Whiting [8]. The other two curcuminoinds are demethoxycurcumin and bis-demethoxycurcumin. The curcuminoids are polyphenols and are responsible for the yellow color of turmeric [9].
2. Therapeutic Implications of Curcumin
Curcumin, has been shown to target multiple signaling molecules while also signifying activity at the cellular level, which has aided to support its multiple health benefits.

2.1 Anti-inflammatory and Antioxidant Properties
Unnikrishnan and Rao [11] studied the antioxidant properties of curcumin and its derivatives. The discovery of the antioxidant properties of curcumin explains many of its wide ranging pharmacological activities. Curcumin is an effective antioxidant and scavenges superoxide radicals, hydrogen peroxide, and nitric oxide from activated macrophages [12]. In fact, curcumin has been found to be at least 10 times more active as an antioxidant than even vitamin E [13]. The phenolic and the methoxy groups on the benzene rings and the 1,3-diketone system are the two important structural features that contribute to its antioxidant properties [14-18]. The highest antioxidant activity was obtained when the phenolic group was sterically hindered by the introduction of two methyl groups at the ortho position. The H-donating phenolic group is essential for free radical scavenging activity [19] and the presence of the methoxy group further increases the activity. Curcumin shows both antioxidant and pro-oxidant effects [20]. Ahsan et al [21] have shown that both of these effects are determined by the same structural moieties of the curcuminoids.

The anti-oxidation process is thought to be divided into two stages as shown in following schemes:

(1) Radical trapping stage

\[ \text{S-OOe- (or Se-) + AH} \rightarrow \text{S-OOH (or SH)} + \text{A} \]

(2) Radical termination stage

\[ \text{Ae} \rightarrow \text{non-radical materials} \]

S is the substance for oxidation, AH is the antioxidant, and A → is the antioxidant radical. Recent mechanistic studies of a plant phenolic antioxidant have been focused on the trapping stage using a kinetic approach or a structure-activity relationship approach [22, 23]. Vajragupta et al., [24] have evaluated the free radical-scavenging and neuroprotective potential of the manganese complexes of curcumin.

The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Curcumin has been shown to serve as a Michael acceptor reacting with glutathione and thioredoxin 1 [25]. Reaction of curcumin with these agents reduces intracellular GSH in the cells. Curcumin can lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase at higher levels. These enzymes play an important role in the regulation of lipid peroxidation [26]. Pulla Reddy and Lokesh [27] observed that curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are important to the initiation of lipid peroxidation. The suppression of lipid peroxidation by curcumin could lead to suppression of inflammation. Another article about curcuminoids as potent inhibitors of lipid peroxidation was described by Sreejayan Rao [28], in which the authors showed that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver microsomes. Elizabeth [27, 28], also reported a better correlation between anti-inflammatory activity and superoxide scavenging property. In the literature Arora et al., [29] investigated the anti-inflammatory activity in different fractions of the petroleum ether extract of the rhizomes of turmeric (two constituents) in animals. They found that the extracts reduced the granuloma growth and no toxic effects were observed. Chandra and Gupta [30] demonstrated the anti-inflammatory and anti-arthritis actions of volatile oil of C. longa L. Non-steroidal anti-inflammatory agents may act via single or combination of any of the mechanism involving inhibition of arachidonic acid metabolism, inhibition of cyclooxygenase(COX)/inhibition of PG synthesis, inhibition of lipo-oxgenase (LOX), inhibition of cytokines(IL, TNF, etc) release of steroid hormone from adrenals, stabilization of lysosomal membrane and uncoupling of oxidative phosphorylation, etc. Kiuchi et al., [31, 32] and Iwakami et al., [33] associate the anti-inflammatory activity of curcumin and its derivatives to the presence of hydroxyl and phenol groups in the molecule, being essential for the inhibition of prostaglandins (PG synthetase) and leukotrienes (LT). On the other hand, some authors suggested that the anti-inflammatory action is associated to the existence of the β-dicarboxylic system, which has the conjugated double bonds (dienes), being responsible for this activity [34, 35]. This system seems to be responsible not only for anti-inflammatory power, but also to antiparasitic activity [36]. The presence of diene ketone system provides a lipophlicity to the compounds, and thus probably better skin penetration.
2.2 Neuroprotective effect of Curcumin

Neurodegenerative diseases, ischemia, and trauma are among the major causes of morbidity and death, yet there are no reliable methods of preventing nerve cell loss in these conditions. Although there are innumerable insults that lead to nerve cell death, ranging from aberrant protein aggregation in the amyloid diseases [37] to the loss of neurotrophic support [38], it is very likely that there is a much smaller subset of mechanisms responsible for the ultimate demise of the cell. If this assumption is valid, then it should be possible to identify drugs that block the common pathways leading to nerve cell death. A good starting point for the identification of such lead compounds is the enormous family of natural products which form the basic scaffolds for the majority of our most widely used drugs [39-41].

Curcumin’s neuro protective role has recently been demonstrated in a fluoride exposed neuronal developmental [42] and adult hippocampal neurogenesis, and a biological activity that may enhance neuronal plasticity and repair [43-45]. The structure of curcumin, which has two methoxyphenol groups separated by a β-diketone bridge, allows it to chelate iron, and free iron has been implicated in a variety of neurodegenerative diseases [46]. Tripathy and Sharma et al., [47] demonstrate the anti-oxidative, anti-lipofuscinogenic and anti-ageing effects of curcumin in the brain. It also improves learning and memory deficits by protecting the nervous system against oxidative stress [48]. Thiyagarajan and Sharma [49] have demonstrated the neuro protective effects of curcumin against the effects of middle cerebral artery occlusion.
2.3 Multiple Sclerosis
Multiple sclerosis is characterized by the destruction of oligodendrocytes and myelin sheath in the CNS. Curcumin inhibits experimental allergic encephalomyelitis by blocking interleukin (IL)-12 signaling in T cells, suggesting it would be effective in the treatment of multiple sclerosis [51].

2.4 Alzheimer’s disease
Curcumin can suppress oxidative damage, inflammation, cognitive deficits, and amyloid accumulation in Alzheimer’s disease [51]. 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 [52-53].

2.5 Head Trauma
Head trauma is a severe test of neuro protective activity and a validated environmental risk factor for AD. Cummings [54] repeated head trauma is also the cause of boxer’s dementia (dementia pugilistica), which involves both tangles.

2.6 Anticancer Properties
Aggarwal, [25] reviewed the anticancer potential of curcumin in number of systems. Curcumin has been shown to block transformation, tumor initiation, tumor promotion, invasion, angiogenesis, and metastasis. Curcumin in In vivo conditions suppresses carcinogenesis of the skin, fore-stomach, colon, and liver in mice. Mammary carcinogenesis is also suppressed by Curcumin. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia, colon carcinoma, epidermis carcinoma, and various breast carcinoma cells.

2.7 Cardioprotective Effect
The study of Aggarwal, [50] clearly demonstrated the effectiveness of curcumin against atherosclerosis and myocardial infarction. The proliferation of peripheral blood mononuclear cells (PBMCs) and vascular smooth muscle cells (VSMCs), which are hallmarks of atherosclerosis, is inhibited by curcumin. Curcumin prevents the oxidation of low density lipoproteins (LDLs), inhibits platelet aggregation, and reduces the incidence of myocardial infarction.

2.8 Skin Diseases
Curcumin has emerged as effective protectant against different skin diseases including skin carcinogenesis, psoriasis [55], scleroderma [56] and dermatitis. Numerous studies advocate that curcumin accelerates wound healing. In addition, curcumin also prevents the formation of scars and plays a role in muscle regeneration following trauma [50].

2.9 Diabetes
In type II diabetes, administration of curcumin reduced the blood sugar, hemoglobin, and glycosylated hemoglobin levels significantly in an alloxan-induced diabetic rat model. Diabetic rats when given curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creative, and inorganic phosphorus in diabetic animals [50]. Diabetic rats fed a curcumin diet had a lower relative liver weight at the end of the study, compared to other diabetic groups. The mechanism by which curcumin improves this situation is probably by virtue of its hypcholesterolemic influence [57], antioxidant nature, and free radical scavenging property [58].

2.10 Cystic Fibrosis
Cystic fibrosis, the most common lethal hereditary disease in the white population, is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. In a recent report, Egan et al., [59] demonstrated that curcumin corrected the cystic fibrosis defects in Delta F508 CF mice.

3. Multiple Molecular Targets of Curcumin
Through various studies it has been concluded that curcumin modulates numerous molecular targets, it directly bind and modulate the activity, or indirectly regulate their functions including: regulating several cytokines and fibrolast growth factor-2 (gene expression), growth-factor receptors including modulation of androgen receptors (protein kinases), transcription factors, neuro transmitters (Nitric oxide) pro-inflammatory enzymes (including suppression of COX-2, 5-LOX and iNOS and regulation of NF-κB), modulation of cell-cycle-related gene expression, blocking the adhesion molecules, downregulating anti-apotic proteins and inhibiting multi-drug resistance [44,45,60,61], thus providing a strong scientific basis for its effectiveness in number of diseases. Extensive research shows most diseases are caused

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<th>LIMITS</th>
<th>MECHANISM</th>
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<tr>
<td>Pro-inflammatory cytokine induction</td>
<td>Inhibition of AP-1, NF-κB, HAT, HDAC stimulation</td>
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<tr>
<td>Reactive oxygen species (ROS)</td>
<td>Scavenger, metal/Fe chelator, induces AO defense enzymes</td>
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<td>Aβ production</td>
<td>Suppresses cholesterol, BACE1 induction</td>
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<td>Particulate toxins</td>
<td>Increases phagocyte clearance</td>
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<td>Neuron loss</td>
<td>Stimulates neurogenesis</td>
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**Table 1:** Ten Neuroprotective effects of curcumin

by dysregulation of multiple signaling pathways—casting doubt on the effectiveness of monotherapy, which is limited to a single target [60,61].

3.1 Cytokines and Growth Factors
In the growth and promotion of various tumors number of growth factors is responsible. Curcumin has been shown to down regulate the expression of several cytokines including TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2. [70]

3.2 Receptors
Aggarwal, [50] showed down regulation of both the epithelial growth factor receptor: (EGFR) and HER2/neu receptors on Curcumin administration. It also modulates androgen receptors.

3.3 Protein Kinases
In the study by Aggarwal, [50] Curcumin suppressed a number of protein kinases including mitogen-activated protein kinases, JNK, PKA, PKC, src tyrosine kinase, phosphorylase kinase, IcBζ kinase, JAK kinase, and the growth factor receptor protein tyrosine kinases.

3.4 Cell Cycle and Anti-Apoptotic Proteins
Curcumin modulates cell-cycle related gene expression. Specifically, curcumin induces G0/G1 and/or G2/M phase cell cycle arrest, upregulates CDK1s, p21WAF1/CIP1, p27KIP1, and p53, and slightly down regulates cyclin B1 and cdc2. Down regulation of cyclin D1 at the transcriptional and post-transcriptional levels has been observed on curcumin administration, it also induces apoptosis by releasing cytochrome c [62-64], caspase 9 and 3 activation and by down regulation of the anti-apoptotic proteins Bcl-2 and BclXL has also been observed by Aggarwal [25] on curcumin administration.

4 References


