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CURCUMIN: A PLEIOTROPIC DRUG

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ABSTRACT

Curcumin in the form of Turmeric powder along with hot milk is widely consumed in India for its anti-inflammatory effects. Curcumin is widely used in traditional Indian ayurvedic medicine to treat hepatic disorders, anorexia, cough, diabetic wounds, rheumatoid arthritis, and sinusitis. Turmeric paste in slaked lime is a popular home remedy for the treatment of inflammation and wounds. Ancient texts of Indian medicine describe the use of curcumin in inflammatory diseases, wound healing, and abdominal problems. Curcumin, exhibits pleiotropic effects such as anti-inflammatory, antioxidant, anticancer, antiviral and neurotropic activity and therefore holds a promise as a therapeutic agent to prevent and treat several diseases. The purpose of this review is to provide a brief overview of the plethora of research regarding the five major pleiotropic effects of curcumin.

KEYWORDS

Curcumin; Turmeric; Antioxidant; Anti-inflammatory; Anticancer; Antiviral; Neurotropic.

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INTRODUCTION

Curcumin, a constituent from the rhizome of the herb *Curcuma Longa (turmeric)*, has received widespread attention over the past few decades¹. Excitement originated after encouraging *in-vitro* discoveries showed its influence on many biological mechanisms associated with several diseases. In particular, *in vitro* and animal models confirmed that curcumin has Pleiotropic effects (shown in Figure No.1) anti-inflammatory, antioxidant, anticancer, antiviral and neurotropic effects just to name a few¹. Curcumin was first extracted from turmeric in 1815 by Vogel and Pelletier. The two German scientists Milobedzka and Lampe determined its chemical structure in 1910². Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-

1, 6-heptadiene-3, 5-dione) is also known as diferuloylmethane³. It has been shown to benefit inflammatory conditions⁴, metabolic syndrome⁵, pain⁶, and to help in the management of inflammatory and degenerative eye conditions^{7,8}. *Curcuma longa* has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory properties⁹. Curcumin, a polyphenol, has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, and thus support its multiple health benefits⁹. The yellow color of turmeric is mainly due to the presence of polyphenolic curcuminoids, constitute approximately 3% to 5% of most turmeric preparations. The alcoholic extract of turmeric mainly contains three curcuminoids, namely curcumin (also referred as curcumin I or diferuloylmethane), desmethoxycurcumin (curcumin II), and bisdesmethoxy curcumin (curcumin III)^{10,11}.

In a study from India, daily administration of 1,200 - 2,100 mg of oral curcumin to patients with rheumatoid arthritis for 2–6 weeks did not cause any toxicity¹². In another study of high-dose oral curcumin (500, 1,000, 2,000, 4,000, and 8,000 mg) daily for three months to patients with pre-invasive malignant or high risk premalignant conditions, no noticeable adverse effects were detected¹³.

The clinical trials conducted so far have indicated the therapeutic potential of curcumin against a wide range of human diseases. It has also shown protection against hepatic conditions, chronic arsenic exposure and alcohol intoxication. It is marketed in several forms including capsule, tablets ointment, energy drinks soaps and cosmetics^{14,15}.

2. Pleiotropic Effects

2.1. Anti-inflammatory

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 up regulation 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 chemo-preventive effects on carcinogenesis. Hence, the past few decades have witnessed intense research devoted to the antioxidant and anti-inflammatory properties of curcumin¹⁶.

Tumor necrosis factor α (TNF- α) is a major mediator of inflammation in most diseases, and this effect is regulated by the activation of a transcription factor, nuclear factor (NF)- κ B. Whereas, TNF- α is said to be the most potent NF- κ B activator, the expression of TNF- α is also regulated by NF- κ B. In addition, TNF- α , NF- κ B is also activated by most inflammatory cytokines; gram (-ve) bacteria; various disease-causing viruses; environmental pollutants; chemical, physical, mechanical, and psychological stress; high glucose; fatty acids; ultraviolet radiation; cigarette smoke; and other disease-causing factors. Therefore, agents that down regulate NF- κ B and NF- κ B-regulated gene products have potential efficacy against several of these diseases. Curcumin has been shown to block NF- κ B activation increased by several different inflammatory stimuli¹⁷. This study demonstrated that curcumin had anti-inflammatory activity in LTA-stimulated microglial cells may through inhibiting NF- κ B and p38 MAPK activation, and may induce the expression of Nrf2 and HO-1. Furthermore, curcumin does not have cytotoxic effects in BV-2 microglial cells at its anti-inflammatory dose. Curcumin may have therapeutic potential for some neuro inflammation-associated disorders caused by Gram-positive bacteria¹⁸.

2.2. Antioxidant

Oxidative damage is believed to be one of the mechanisms behind aging and many diseases. It involves free radicals, highly reactive molecules with unpaired electrons¹⁹. Many people consume antioxidants as a defense against oxidative stress. Antioxidants in the form of commercial food additives have been manufactured synthetically and may contain high amounts of preservatives²⁰.

Identifying potential natural antioxidant sources can be a useful alternative to ensure sound health²¹. Anti-oxidant constituents in plant material have piqued the interest of scientists, food manufacturers, cultivators, and consumers for their roles in the maintenance of human health²⁰. Curcumin is a lipophilic compound, making it an efficient scavenger of peroxy radicals; However, the actual reaction site and the mechanism of free radical scavenging have not been clarified yet²². It is generally assumed that the phenolic moieties are responsible for radical scavenging properties of the pertinent antioxidant reactants. The clinical use of curcumin is limited because of its low bioavailability, due to the hydrophobic nature of the molecule²³.

2.3. Anticancer

Over half of the publications were published since 2014, which mainly focused on the effects of curcumin against cancer, inflammation, and oxidative stress. Frequently investigated cancer types were breast, colon, colorectal, pancreatic, and prostate cancer²⁴. Curcumin has shown considerable anticancer effects against several different types of cancer, including prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, and head and neck cancer both *in vitro* and *in vivo*²⁵. Cancer is the second most life-threatening disease and one of the main public health problems worldwide. In 2018, there were around 1.73 million new cases of cancer and more than 609,000 deaths in the United States alone²⁵. Curcumin and its derivatives have received immense attention in the past two decades due to their bio functional properties such as anti-tumor, antioxidant, and anti-inflammatory activities²⁶.

A recent report suggests that curcumin inserts deep into the cellular membrane in a trans bilayer orientation, anchored by hydrogen bonding to the phosphate group of lipids, thus inducing negative curvature in the bilayer²⁷. The promotion of negative curvature by curcumin may have a direct effect on apoptosis by increasing the permeabilizing activity of the apoptotic protein Bid²⁸. Curcumin has been shown to suppress multiple signaling pathways and inhibit cell proliferation, invasion, metastasis, and angiogenesis. The chemo preventive

action of curcumin might be due to its ability to induce apoptosis by several pathways. Curcumin directly or indirectly controls different gene or gene products involved in cell death pathways.

Curcumin inhibits the STAT3 (Signal transducer and activator of transcription 3) and NF- κ B signaling pathways, which play key-roles in cancer development and progression. Constitutive activation of the STAT3 and NF- κ B signaling pathways has been demonstrated in prostate cancer cell lines and clinical samples of prostate cancer²⁹⁻³². The nuclear factor (NF)- κ B, is a ubiquitous transcription factor that regulates many genes implicated in growth regulation, inflammation, carcinogenesis, and apoptosis. *In vitro* and *in vivo* studies have documented that constitutive activation of NF- κ B results in inhibition of chemotherapy-induced apoptosis in a number of cancer cells. Signal transducer and activator of transcription 3 (STAT3) is a ubiquitously expressed member of the STAT family of transcription factors that is activated by tyrosine phosphorylation *via* upstream receptors, such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and cytokines, such as interleukin-6 (IL-6). Recent studies have demonstrated that STAT3 may confer cancer resistance to chemotherapeutic agents³³.

2.4. Antiviral

Curcumin has been studied as an antiviral agent against numerous viruses like Herpes simplex virus (HSV), dengue virus (DENV), Human Immunodeficiency Virus (HIV), Hepatitis viruses, influenza type A virus, and Ebola virus³⁴. Dengue is the most common infective disease caused by dengue virus (DENV). Until now, there is no specific antiviral drug for dengue infection. Curcumin as major active compound has been identified for its antiviral effect³⁵. A number of research studies and scientific evidence suggest that turmeric has a potent antiviral activity³⁶ Curcumin, a relatively non-toxic natural product isolated from *Curcuma longa*, is a modest inhibitor of the HIV-1 and HIV-2 proteases. Boron complexes of curcumin cause time-dependent inactivation of the HIV-1 and HIV-2 proteases³⁷. Oncogenesis by

human T-cell leukemia virus type-1 as an etiology factor of adult t-cell leukemia (ATL) is critically dependent of the activator protein-1 (AP-1)⁴⁰. DNA Binding and transcriptional effect of AP-1 HTLV-1-Infected T-Cell lines were suppressed by curcumin treatment curcumin also inhibited the expression of JunD protein as an important factor in AP-1-DNA complex in HTLV-1 infected T-cells as well as HTLV-1(Human T-Cell Leukemia Virus Type 1) Tax-induced AP-1 transcriptional effect. Cell cycle arrest and including of apoptosis were found to be possible mechanism against HTLV-1 application in infected T cell line by curcumin. Suppression of AP-1 activity possibly through decreasing the expression of Jun D protein is introduced as possible pathway of anti-ATL activity of curcumin³⁸.

2.5. Neurotropic Effect

Diets rich in curcumin have been reported to be associated with a lower risk of Alzheimer's disease (AD) or cognitive impairment in epidemiological studies. *In vitro* and *in vivo* experimental studies with AD models have indicated that curcumin has anti-amyloidogenic effects in addition to their antioxidant and anti-inflammatory effects. In addition, it has been reported that curcumin has neuroprotective and anti-inflammatory effects in *In-vitro* and *In vivo* experimental studies on Parkinson's disease³⁹.

Findings indicate that curcumin can enhance postsynaptic electrical reactivity and cell viability in intact neural circuits with antidepressant-like effects, possibly through the up regulation of BDNF (Brain-derived neurotrophic factor) and reduction of inflammatory factors in the brain⁴⁰. In Alzheimer's disease (AD), a peptide called β -amyloid ($A\beta$ peptide) aggregates into oligomers and fibrils and forms deposits known as amyloid (or senile) plaques outside neurons in the hippocampus and cerebral cortex of patients. Another feature of AD is the accumulation of intracellular

neurofibrillary tangles formed by phosphorylated Tau protein⁴¹. Abnormal microglial activation, oxidative stress, and neuronal death are also associated with the progression of the disease. Curcumin has been found to inhibit $A\beta$ fibril formation and extension and to destabilize preformed fibrils *in vitro*⁴²⁻⁴⁴. Metal chelation by curcumin might interfere with metal ion (Cu^{2+}/Zn^{2+})-induced $A\beta$ aggregation. Curcumin might also affect the trafficking of $A\beta$ peptide precursor (APP) and the generation of $A\beta$ peptides from APP⁴⁵⁻⁴⁶. Abnormally activated microglia and hypertrophic astrocytes around amyloid plaques in AD brains release cytotoxic molecules, such as pro-inflammatory cytokines and ROS (reactive oxygen species), which enhance $A\beta$ formation and deposition and further damage neurons. Curcumin was found to reduce the inflammatory response triggered by $A\beta$ peptide-induced microglial activation and increase neuronal cell survival⁴⁷. When injected into the carotid artery of a transgenic mouse model of AD, curcumin was found to cross the blood-brain barrier, bind to amyloid plaques, and block the formation of $A\beta$ oligomers and fibrils⁴⁵. In other animal models of AD, dietary curcumin decreased biomarkers of inflammation and oxidative damage, increased $A\beta$ peptide clearance by macrophages, dismantled amyloid plaques in the brain, stimulated neuronal cell growth in the hippocampus, and improved $A\beta$ -induced memory deficits⁴⁸.

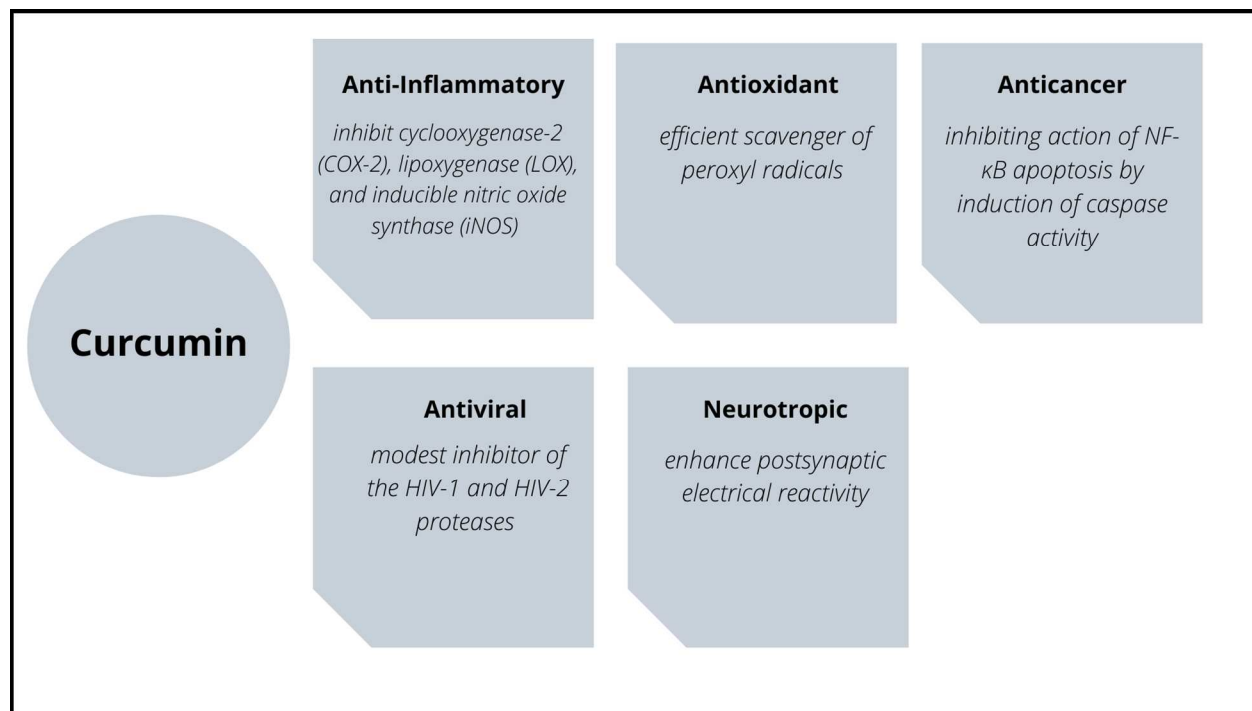


Figure No.1: Mechanism of action of curcumin in various conditions

CONCLUSION

Recently, many natural substances have been increasingly found to have significant biological properties which make them useful in the treatment of various diseases. Nature has plenty of substances having healing properties making them invaluable for its role towards promotion of a healthy world. Curcumin has received worldwide attention for its multiple health benefits, reported to act primarily through its pleiotropic effect. From preclinical studies to clinical trials, tremendous progress has been made with respect to this compound in the medical field. Research suggests that curcumin could help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery and subsequent performance in active people. Thus, we can conclude that a relatively low dose of curcumin or in the form of turmeric powder could provide health benefits for people that do not have diagnosed health conditions.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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