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Health Benefits of Curcumin in the Prevention and Treatment of Diseases

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ABSTRACT

Medicines obtained from plants have portrayed the crucial involvement in both cultures' health, ancient and modern times because of their inexpensive properties and belief of the people that natural products have less or no side effects. Curcuma longa (turmeric), a perennial shrub integrated from the family Zingiberaceae, was used fora long as a spice to alleviate inflammation, discomfort, healing of wounds, and digestive ailments in Asian food. In various forms, curcumin is recognized and utilized globally for many health advantages, mainly due to its antioxidant and anti-inflammatory actions. The therapeutic effectiveness of curcumin against many illnesses, including arthritis, cardiovascular, diabetes, neurological, Crohn's disease, and tumor have already been recorded. The therapy of curcumin has been validated in a variety of respiratory diseases, such as asthma, bronchial hyperactivity, and allergy, as well as for liver, anorexia, rheumatism, and diabetic wounds according to Ayurvedic medicine. It is used to treat abdominal pain-related disorders as in traditional Chinese Medicine. It was utilized as a treatment for sprains and swelling in ancient Hindu medicine. This review paper outlines many health advantages and activities of Curcumin.

KEY WORDS: Antioxidant, Anti-inflammatory, Respiratory, Ayurvedic, Chinese medicine.

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INTRODUCTION

Natural products are the source of various active pharmaceuticals ingredients. From early times, natural products containing certain active chemical constituents are used as medicine to treat numerous diseases (1, 2). Approximately ten thousand of them are isolated from higher plants, produced as secondary metabolites which provide shielding from infection and illness (3). In comparison to standard combinational chemistry, natural products are prolonged to provide solitary structural diversity. This provides various opportunities for the introduction of many novel compounds. For many years, plants have been well recorded for their medicinal purposes in the form of oil, traditional medicines, and lotions with many of these bioactive natural products still being unknown (4). Natural products playa vital role in drug discovery and development (5, 6). The pharmaceutical properties of plants are extensively documented in the traditional medicines of many other cultures (7).

Concerning both ancient and modern times, plants derived medicines have a vital role in the welfare and health care of many cultures. No wonder in comparison to many exotic synthetic drugs, plant-based drugs is considered to be more suitable for medicinal human use. On average, natural products are more readily absorbed than synthetic drugs (3, 1). In recent times, approximately more than half of the clinically used pharmaceutical compounds are obtained from natural products. Plant-derived drugs are used to treat and control diseases and this has contributed to the discovery of the masses of modern pharmaceutical agents (8).

CURCUMIN

Curcumin, which is an active ingredient of turmeric is extracted from the roots of Curcuma longa. It is also known as diferuloylmethane and is a hydrophobic polyphenol. It is the yellow-pigmented fraction derived from turmeric. Chemically, these are desmethoxycurcumin (curcumin II)

and bisdemethoxycurcumin (curcumin III) and recently detected cyclocurcumin. Its melting point is 183.8-degree C andits molecular formula is C12H20O6 which makes its molecular weight 368.37 g/mol (9, 10, 11). Organic chemistry says that it is a bis-α, β-unsaturated β-diketone which is a keto-enol tautomeric compound with a predominant keto-form in acid or neutral solutions and its enol-form is predominant in alkalis solutions. This makes it suitable to act as a chelator of metal ions. It however is unstable at the basic pH, hence makes it unsuitable to store under alkaline conditions (12, 10, 13). Structurally, it is a crystalline compound having an orange-yellowish shade suitable either in alkali or in intensely acidic solvents (13).

For hundreds of years, turmeric and natural curcuminoids have been used as therapeutic preparations concerning traditional medicine. In Ayurvedic medicine, curcumin is well known for the treatment of many respiratory diseases such as bronchial hyperactivity, asthma, and allergy. Curcumin is also known for the treatment of rheumatoid arthritis, anorexia, diabetic wounds, liver disorders, rhinorrhea, cough, and sinus infection. In Indian and Chinese medicines, turmeric (containing curcumin as phytoconstituent) was considered to be a good anti-inflammatory agent used to treat flatulence, pectoralgia, odontalgia, colic, and menstrual disorders. It was also employed to treat liver and stomach problems, lightening scars and healing wounds, and as a cosmetic for skincare (14, 15).(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione is the IUPAC name of curcumin, shown in figure 1 (16).

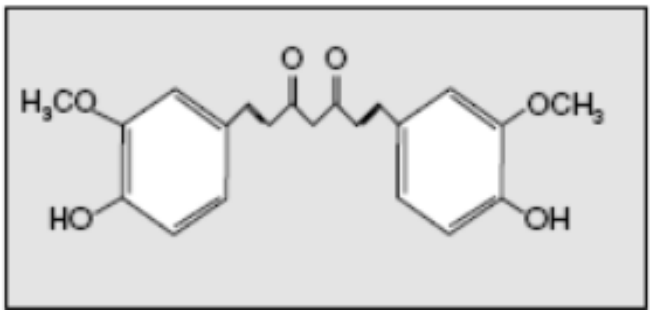


Figure 1. Structure of Curcumin.

Curcuma longa (known as Haldi in Hindi) is an Indian spice belonging to the family of ginger. Apart from being used as a spice, it is also used as a food coloring agent, flavoring agent, and food preservative (9, 14).Turmerone, atlantones, and zingiberene are among the curcuminoids found in them. It also includes water-soluble peptides and essential oils (10). Curcumin I (77%), curcumin II (17%) and curcumin III (3%) are commercially the most important components of curcumin (3).

DISEASE TARGETS OF CURCUMIN

The health-promoting effects of it cannot be denied, even though they are well-acknowledged and substantial (14).

Anti-inflammatory

Curcumin turned out to be effective in both acute as well as in chronic models of inflammation as production of Reactive Oxygen Species (ROS) moderates the manifestation of the nuclear factor-kβ (NF-kβ) and tumor necrosis factor-alpha (TNF-α) pathways which appear to have a dominant character in the inflammation response (17-18). It could impair regulated oxidative stress and the following inflammation via the Nrf2 pathway (19). Figure 2 represents the mechanism of action of curcumin as an anti-inflammatory effect.

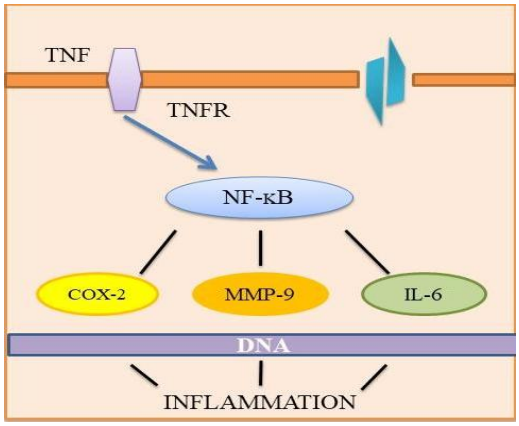


Figure 2. Mechanism of action of anti-inflammatory activity of Curcumin.

Anti-microbial

The mechanism for the antimicrobial activity of curcumin is not completely understood. However, the existence of methoxyl and hydroxyl groups is believed to be responsible for antimicrobial activity (20). Curcuma longa rhizome has been traditionally used as an antimicrobial agent as well as an insect repellant. Several studies have reported the broad-spectrum antimicrobial activity for curcumin including antibacterial, antiviral, antifungal, and antimalarial activities. The mixture of curcumin with other antimicrobial agents is used for the development of antimicrobial skin gels and emulsions with improved skin protection and wound dressing properties (21,22).

Antibacterial activity

Curcumin inhibits the FtsZ polymerization thereby suppresses the FtsZ assembly possibly leading to disruption of E. coli and B. subtilis proliferation (23). Curcumin also showed significant therapeutic potential against Helicobacter pylori (24).

Antifungal activity

The potential mechanism of antifungal activity of curcumin is due to the breach in the integrity of the plasma membrane which caused leakage of potassium ions from the cytosol and transmutes in membrane potential leading to cell death. The study also suggested that downregulation of desaturase (such as ERG3) leading to a significant reduction in

ergosterol of fungal cellsled to cell death via generation of ROS (25).

Anti-viral activity

The antiviral activity of curcumin (Figure 3) has been reported against numerous viruses, including influenza virus infection (IAV), human papillomavirus (HPV), coxsackievirus, Hepatitis C virus (HCV), adenovirus, and Herpes simplex 1 (HSV-1) (26). The coalescence of curcumin and IFNα inhibited the HCV viral replication through the Akt-SREBP-1 activation thereby inhibiting HCV gene expression (27).

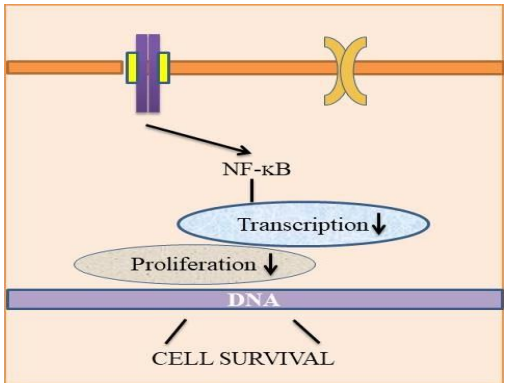


Figure 3. Mechanism of action of antiviral activity of Curcumin.

Anti-tumor

Curcumin represents a promising candidate as an effective anticancer drug to be used alone or in combination with other drugs. It affects different signaling pathways and molecular targets involved in the development of several cancers. It is known for its results in several target areas including transcription factors, growth regulators, adherence molecules, apoptotic genes, angiogenesis regulators, and cellular signaling molecules as a molecular basis for anti-carcinogenic and chemical preventative actions. Nuclear factor αB is a pro-inflammatory transcription factor that modulates the expression of different proteins—such as cytokines interleukin (IL)-1, IL-2, and interferon- (IFN)—involved in multiple cell signaling pathways associated with cancer progression and inflammation (28,29).The blocking of transformation, initiation, promotion, invasion of the tumor, inhibits the proliferation of an extension diversity of tumor cells (including B-cell and T-cell leukemia, colon carcinoma, epidermoid carcinoma, breast carcinoma cells), angiogenesis, and metastasis has been proclaiming by curcumin (17,30).

Anti-oxidant

Oxidative stress has a significant role in the pathogenesis of various diseases such as myocardial ischemia, cerebral ischemia (like reperfusion injury, hemorrhage, shock, neural cell injury, etc.). With inhibition of lipid degradation, lipid peroxidation, and cytolysis secures oxidative cell injury of nephrons (LLC-PK1) along with that it also reduced ischemia-induced biochemical changes in the heart in a feline mode (31).

There are seemed to be various factors of curcumin to be a potent antioxidant, either it may be due to the presence of a β-diketone groupin its structure or by the presence in its molecular structure of the chain break or H donating phenolic groups.Its mainstream activities are, inhibits the superoxide radicals, hydrogen peroxide, and nitric oxide radical, whilst it also enhances functions of many other antioxidant enzymes like catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), and heme oxygenase-1 (OH-1). These activities lead to a reduction of lipid peroxidation further decreasing hepatic damage (32,33).Figure 4 shows the anti-oxidant activity of Curcumin.Curcumin is at least ten times more active as an antioxidant than even vitamin E (34).

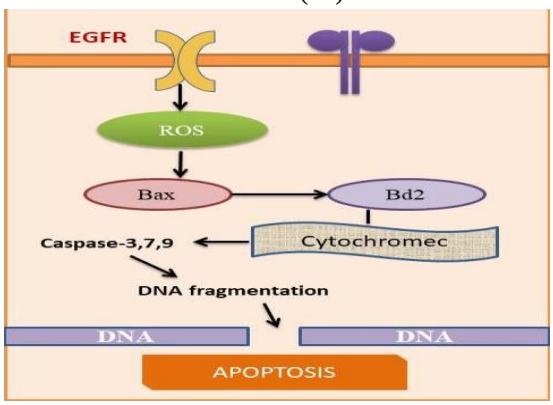


Figure 4. Mechanism of action of anti-oxidant activity of Curcumin.

Cardio protective Effects

Curcumin inhibits the proliferation of hallmarks of atherosclerosis which are peripheral blood mononuclear cells (PBMCs) and vascular smooth muscle cells (VSMCs), along with that it also inhibits platelet aggregation, prevents the oxidation of low-density lipoproteins (LDLs), and also reduces the chances of myocardial infarction (35). Curcumin reduces the degree of inflammation molecules such as TNF-α, p38 MAPK (Mitogen-activated protein kinase), JAK2/STATS3 as it advances cardiovascular risk inflammation-associated (36).

Skin Diseases

In addition to psoriasis, scleroderma, and dermatitis curcumin also shows its effect in other different skin diseases. Records indicate that it accelerates wound healing, likewise, it also prevents the development of scars and is involved in muscle regeneration following trauma. Curcumin appears to protect skin by quenching free radicals and reducing inflammation, and the primary target of curcumin is found to be NF-B inhibition (37).

Anti-Diabetes

Diabetes mellitus is a type of health condition which has a great influence on the liver, heart, brain, and kidney. In a

model of STZ-induced pancreatic damage, it is been observed that curcumin has an antihyperglycemic and hypocholesterolemic role in type 2 diabetes as it also shows protective effect against pancreatic injury (mostly on β cells which secrete insulin) through its anti-inflammatory and anti-oxidant impact and that inflammation is the major cause of Type 2 diabetes expansion and numerous inflammatory cytokines, enzymes, and transcription factors play a crucial part in the onset and development (38,39). Inhibition of hepatic glucose production, repression of inflammatory response arising from high blood sugar, increase in glucose transporter type 2, 3, 4 (GLUT2, GLUT3, GLUT4) gene expression, activation of 5'adenosine monophosphate-activated protein kinase (AMPK), an increase in glucose intake of cells are functions possessed by curcumin which may lead to decrease in blood sugar level decreasing insulin resistance. Thus, curcumin hasa cumulative impact on antihyperglycemic and insulin sensitivity (39).

Gastro-protective effect

Suppression of STAT3 pathways by curcumin further decreases the manifestation of TNFα, and IL-1β. In addition, it can also improve dextran sulfate sodium (DSS)-induced colitis due to reduction of myeloperoxidase activity, colon injury, oxidative stress, inflammatory reaction, and apoptotic cell death with blocking the c-Jun N-terminal protein kinase (JNK), p38MAPK pathways (13).

Neuroprotective effect

Curcumin effectively blocks the formation of tumor cells alongside also eliminates the brain tumor cells. It can interrelate and regulate various molecular targets for instance transcription factors, inflammatory cytokines, kinases, growth factors, and antioxidant systems and all these functions will be responsible in part for its neuroprotective activity. By reducing the expression of IL(interleukins)-1α, IL-6, and TNF-α in LPS stimulated BV2 microglia in a dose-dependent manner the potential of curcumin to reduce neuro-inflammation which generally takes place in the development of neurodegenerative diseases has been documented (38,13).

Anti-obesity effect

Curcumin was shown to be depressed mitogen-activated protein kinase (MAPK, ERK, JNK, and p38) which is connected with differentiation of 3T3-L1cells into adipocytes and activates Wnt/β-catenin signaling in different adipocytes which are almost related to obesity. It's been recorded that it reduces the macrophage infiltration, leptin, leptin receptor level (Ob-R) in white adipose tissue; which enhances the adiponectin level in inflammation-related obesity. It's been noted that adiponectin production, which increases due to the result of curcumin, may lead to an optimistic effect against obesity by decreasing NF-kBactivity (39). There are many other benefits of curcumin are also known which are not listed in this paper but we tried to show it in the form of Figure 5.

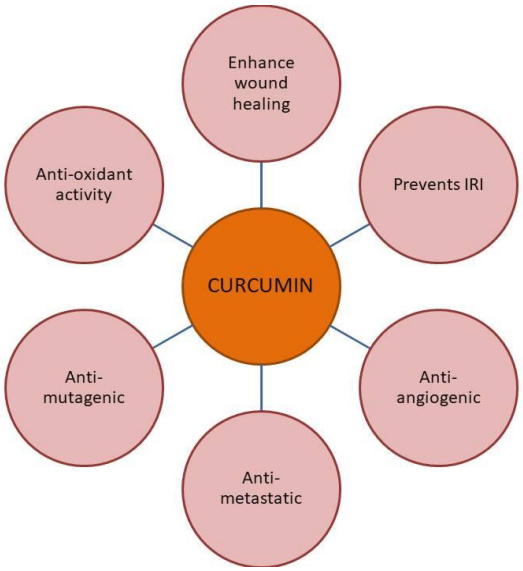


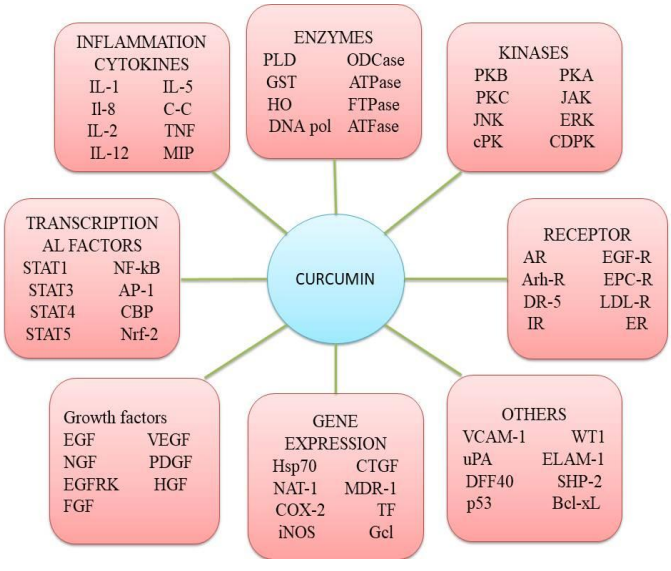
Figure 5. Represents the many other benefits of Curcumin.

COVID-19

Critical COVID-19 suffering individuals may experience pneumonia which in turn leads to low levels of oxygen in the blood. Curcumin isan effective antioxidant agent, in various studies. It accurately cleans out the reactive oxygen species being a potent antioxidant agent. Itexhibited to act against the possible actions of reactive oxygen species, on expressing inflammation cytokines, by decreasing the TIP (thioredoxin interacting protein).It may have the potential to block this disease, because it has findings in its favor explaining its anti-viral activities such as restriction of replication as well as restriction of adhesion of viruses to host cell, against CoV (40,41).

MOLECULAR TARGETS OF CURCUMIN

The pleiotropic effects of curcumin are dependent on its capacity of interacting and regulation multiple molecular targets (Figure 6).



Cytokines and Growth Factors

In the growth and promotion of tumors, a lot of factors have been associated. Several cytokines including TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2 have been exposed to down-regulate the expression(42).

Receptors

EGFR(epithelial growth factor receptor) and HER2 (Human Epidermal Growth Factor Receptor 2)/neu receptors have been shown to down-regulate by curcumin, Also, modulation of androgen receptors is seen(43).

Transcription Factors

Several transcription factors containing NF-kβ, STAT3, Egr-1 (Early Growth Response protein-1), AP-1 (Activator Protein-1), PPAR-γ (Peroxisome Proliferator-Activated Receptor), and β catenin activation is functioned by curcumin. In a wide range of cancers, the constitutively active form of NF-k β has been reported (44).

Pro-inflammatory Enzyme

The expression of COX(Cyclooxygenase 2), 5-LOX (5-Lipooxygenase), and iNos (Inducible Nitric Oxide Synthase) have been known to be suppressed by curcumin(45).

Protein Kinases

Protein kinases countingnitrogen-activated protein kinases, JNK, PKA (Protein kinase A), PKC (Protein kinase C), tyrosine kinase, phosphorylase kinase, IkBα kinase, JAK kinase, and the growth factor receptor protein tyrosine kinases are suppressed by curcumin (46).

METABOLISM

Curcumin is converted into curcumin glucuronide and curcumin sulfonate in the digestive system when ingested orally. However, it is converted into tetrahydrocurcumin, hexhyrdrocurcumin, and hexhydrocurcuminol, if given systemically or intraperitoneally.Curcumin glucuronide was identified in intestinal and hepatic microsomes, and curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin were found as curcumin metabolites in intestinal and hepatic cytosol (47).

PROMISES

The major reasons for the poor bioavailability of this interesting polyphenolic compound include absorption, biodistribution, metabolism. Adjuvants and nanoparticles are possible ways to overcome these problems(48).

Piperine has been the most studied adjuvant. Piperine is a bioactive alkaloid that inhibits hepatic and intestinal glucuronidation. In animal models, piperine enhances curcumin's bioavailability by 154% relative to curcumin without piperine. In human volunteers, the increase in the bioavailability was approximately 2000% when compared to curcumin without piperine. Importantly, this increase in the bioavailability of curcumin when administered with piperine was not associated with adverse effects in the human volunteers (49).

Another method that has been studied to increase curcumin's bioavailability includes curcumin nanoparticles, liposomes, micelles, phospholipid complexes, and structural analogs. All of these approaches are directed at achieving a longer half-life, increased concentrations in tissues, and resistance to metabolic processes (50).

Oral administration of curcumin formulated with phosphatidylcholine, compared with unformulated curcumin, resulted in higher plasma and liver concentrations in rats (51).

In studies, the author has used a mouse model of asthma and demonstrated the greatest enhancement in curcumin plasma and tissue concentrations by utilizing curcumin-solid lipid nanoparticles that were administered by intraperitoneal injection (52).

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