

Curcumin: A Review for Health Benefits

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ABSTRACT

Curcuma longa (Turmeric) is a popular and widely used Indian rhizomatous medicinal plant from the family Zingiberaceae. Curcumin, Demethoxycurcumin (DMC), and Bisdemethoxycurcumin (BDMC) are the constituents of the turmeric and are collectively known as curcuminoids. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) or Diferuloylmethane is well-known for its different biological activities such as Anti-inflammatory, Anti-viral, Anti-oxidant, Anti-cancer, Anti-bacterial, Anti-asthmatic, Anti-arthritis, Anti-diabetic, Anti-venom, Anti-obesity, Wound-healing, in depression and anxiety and other activities. Various clinical trials and their observations regarding these activities have been discussed here. Curcumin is a tautomeric compound existing in enolic form in organic solvents and as a keto form in water. This review article summarizes a various role and activity of Curcumin.

Keywords: *Curcuma longa*, Curcuminoids, Curcumin, Anti-cancer, Anti-asthmatic.

INTRODUCTION

Turmeric is an Indian rhizomatous herbal plant (*Curcuma longa*) of the ginger family (Zingiberaceae) of well-known medical benefits. [1, 2] The medicinal benefits of turmeric could be attributed to the presence of active principles called curcuminoids. [3] Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are collectively known as curcuminoids. [4] These yellow colored curcuminoids are

isolated from *Curcuma longa* L. (turmeric) rhizomes. [5, 6]

One of the most interesting components of curcuminoid is curcumin, which is a small molecular weight polyphenolic compound and lipophilic in nature, hence insoluble in water and also in ether but soluble in ethanol, dimethylsulfoxide, and other organic solvents. Curcumin is stable at the acidic pH of the stomach. The other constituents present are volatile oils including tumerone, atlantone and zingiberone and sugars, proteins and resins. [7] The active constituent of turmeric- curcumin is isolated from *curcuma longa* and it provides colour to turmeric. Such bioactive component has been thoroughly investigated [8] Curcumin (1, 7-bis (4-hydroxy-3methoxyphenyl)-1, 6-heptadiene-3, 5- dione) is also called diferuloylmethane. [9] It is a tautomeric compound existing in enolic form in organic solvents and as a keto form in water. Turmeric is a plant known by its medicinal use, dating back to 4000 years ago in the Vedic culture in India, where it was used as a culinary spice and had some religious significance. [10]

Turmeric is the boiled, dried, cleaned and shine rhizomes of *curcuma longa*. After harvesting the whole rhizomes are collected. They are usually like fingers 2 to 8 cm long and 1 to 2 cm wide having bulbs and splits. The dried rhizomes are further processed and reprocessed to obtain the turmeric powder. It has different names in different cultures and countries. In

Sanskrit, turmeric has at least 53 different names.^[11]

Curcumin has been used in tradition as a medical herb due to its various advantages such as: antioxidant,^[12] anti-inflammatory,^[13] antimutagenic,^[14] antimicrobial^[15] and several therapeutic properties^[16] Curcumin shows poor absorption, rapid metabolism, and rapid elimination. Several agents have been introduced to improve the bioavailability of curcumin. Most interesting one is piperine; it enhances curcumin bioavailability by blockage of the metabolic pathway of curcumin.^[17] Piperine results in an increase of 2000% in the bioavailability of curcumin^[18] Curcumin is an essential ingredient in the root extract of *Curcuma Longa*. The root of this plant, which is yellow due to the presence of curcumin, has been used as a flavoring and coloring agent for food and medicine in Asian countries.^[19]

Curcumin is available in several forms including capsules, tablets and ointments.^[20] Curcuminoids have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS).^[21] It is the purpose of this review to provide a brief overview of the potential health benefits of curcumin.

In herbal and traditional medicine, turmeric is used for rheumatoid arthritis, chronic anterior uveitis, conjunctivitis, skin cancer, small pox, chicken pox, wound healing, urinary tract infections, and liver ailments, strengthening the overall energy of the body, dispelling worms, regulating menstruation, dissolving gallstones, cleansing wounds, and even for various digestive disorders, among other conditions.^[10] *C. longa* has on its chemical composition more than 3% curcumin, 1.4% DMC and 1.2% BDMC.^[22]

Furthermore, curcumin also showed a prominent protective effect on bone density disorders, such as osteopenia^[23] osteoarthritis^[24] while helping to relieve pain and swelling in mouth, gingivitis and Periodontitis.^[25]

ISOLATION OF CURCUMIN

Curcumin is insoluble in water; an organic solvent has been used for its isolation.^[26] developed a technique for isolating CUR from ground turmeric. They magnetically stirred the ground turmeric in dichloromethane and heated at reflux for 1 h. The mixture was suction-filtered, and the filtrate was concentrated in a hot-water bath maintaining at 50° C. The reddish-yellow oil residue was triturated with hexane and the resulting solid was collected by suction filtration. Further TLC analysis (3% methanol and 97% dichloromethane) showed the presence of all three components.^[26] Extraction of CUR from turmeric powder with the use of a solvent consisting of a mixture of ethanol and acetone. Chemical analyses have shown that turmeric contains carbohydrates (69.4%), moisture (13.1%), protein (6.3%), fat (5.1%) and minerals (3.5%). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains α -phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpenes (53%), curcumin (3-6%) is responsible for the yellow color.^[27]

CHEMISTRY

Curcumin is a symmetric molecule, also known as diferuloylmethane. IUPAC name of this compound is (1E-6E)-1, 7-bis (4-hydroxy-3-methoxy phenyl)-1, 6-heptadiene-3, 5-dione. The chemical formula of curcumin is C₂₁H₂₀O₆ and the molecular mass is 368.385g/mole.^[28] The structure of curcumin contains three chemical entities: two oxy-substituted aryl moieties containing ortho-methoxy phenolic OH- groups, connected through a seven carbon chain consisting of a α , β -unsaturated β -diketone moiety. Curcumin is the most abundantly occurring natural analogue of a crude extract at 60%-70%, followed by demethoxycurcumin(DMC; 20%-30%) in which one methoxy group is absent, then bisdemethoxycurcumin(BDMC; 10%-15%)^[29] in which the methoxy group is absent

from both the aryl rings, ^[30] along with numerous and less abundant secondary metabolites. Important chemical reactions associated with the biological activity of curcumin are the hydrogen-atom donation reactions leading to oxidation of curcumin, reversible and irreversible nucleophilic addition reactions, hydrolysis, degradation and enzymatic reactions. ^[31] All these play important role in different biological activities of curcumin. Curcumin is a hydrophobic molecule with a calculated log P value is 3.43; however it is insoluble in aqueous physiologic media, which displays poor distribution and bioavailability. ^[32, 33] Curcumin is soluble in polar solvents like DMSO, methanol, acetone and ethanol. ^[34, 35]

Thus, it tends to accumulate in hydrophobic regions, for example, the membrane of cells. Taken together, curcumin can perform as a hydrophobic reducing (antioxidant) agent and thereby scavenge various reactive oxygen species (ROS). It has also been demonstrated that curcumin was better than vitamin E in suppressing oxidative stress. ^[36] The regeneration reaction of phenoxyl radicals by water-soluble antioxidants like Vitamin C restores curcumin for consecutive ROS elimination reactions. Curcumin is as efficient as intrinsic and lipid soluble antioxidants in the removal of superoxide radicals and stimulates the function of superoxide dismutase. The hydrogen donor site, α , β -unsaturated β -diketone moiety, is also considered the breakdown point in the curcumin structure, resulting in curcumin hydrolysis and degradation in water at room temperature and neutral pH. It has been reported that 90% of curcumin degrades within 30min in aqueous alkaline buffer, Being lipophilic in nature, the water solubility of curcumin could be enhanced when the diketo reaction site is binding in polymers, cyclodextrins, lipids, proteins and other macromolecular structures as the reaction site becomes protected from hydrolysis. ^[37] It has been demonstrated that solvolysis is a minor pathway, and the

primary pathway is autoxidation. ^[38] Pharmacokinetic studies showed that after oral consumption, curcumin is metabolized to give sulfate and glucuronide derivatives. The chemical stability of curcumin can be enhanced by encapsulation with lipids or nanoparticles. Other methods to enhancing stability have included synthetic manipulations to eliminate or protect the oxidation sites (phenolic-OH and enolic-OH) ^[39] and derivatization of the β -diketone to decrease the activity of the enolate Michael acceptor. ^[40] Besides, analogues of curcumin could be a more feasible way to for clinical application, further clinical studies are needed to evaluate and potentially confirm the beneficial effects of them.

PHARMACOKINETICS AND PHARMACODYNAMICS

Prior studies have discussed the difficulty in achieving optimum therapeutic concentrations of the molecule due to low solubility and poor bioavailability of curcumin. Studies suggest that curcumin is first biotransformed to dihydrocurcumin and tetrahydrocurcumin, and subsequently converted to monoglucuronide conjugates. ^[41] Preliminarily animal studies demonstrate that curcumin is rapidly metabolized and conjugated in the liver, and then excreted in feces with limited systemic bioavailability. A 40 mg/kg intravenous dose of curcumin given to rats resulted in complete plasma clearance at one hour post-dose. An oral dose of 500 mg/kg given to rats resulted in a peak plasma concentration of only 1.8 ng/ml. ^[42] A common method that has been employed to increase the bioavailability of curcumin is to use agents that block the metabolic pathway of curcumin. One study exploring methods to increase the bioavailability of curcumin found that co-administration of oral curcumin with piperine, an alkaloid found in black pepper (*Piper nigrum*) and long pepper (*Piper longa*), increased serum concentrations of curcumin in rodents, as piperine is a known inhibitor of hepatic and intestinal

glucoronidation. With high doses of oral curcumin (2000 mg/kg) and co-administration of piperine, systemic bioavailability was increased by as much as 154%.^[43]

Several phase I clinical trials report data on the pharmacokinetics, metabolites, and systemic bioavailability of curcumin in humans, mainly conducted on cancer patients. A trial conducted of 25 patients with various pre-cancerous lesions administered oral doses of 4, 6, and 8 g curcumin daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11 , 0.63 ± 0.06 , and 1.77 ± 1.87 mM, respectively. However safety and patient tolerance was appreciated even at 8 g of curcumin. Serum levels peaked between one and two hours post-dose and declined rapidly; urinary excretion of curcumin was undetectable.^[44] Another study of 15 patients with advanced colorectal cancer reported even lower serum curcumin concentrations. In this study curcumin doses between 0.45 and 3.6 g were given daily for four months. In three of six patients given the 3.6 g dose, mean plasma curcumin measured at all points during the first month of curcumin therapy was consistently 11.1 ± 0.6 nmol/L. Curcumin was not detected in the plasma of patients taking lower doses.^[45] Due to the low bioavailability of curcumin, Theracurmin, a synthetically derived nano-particle form of curcumin was developed that has a higher bioavailability. Previous studies exploring the pharmacokinetics of Theracurmin in healthy patients achieved satisfactory plasma concentrations after one dose. Other studies to evaluate the safety of curcumin in cancer patients have yielded similar findings. In one study, Theracurmin was orally administered every day with standard gemcitabine-based chemotherapy. Peak plasma curcumin levels (median) after 200 mg of Theracurmin administration were 324ng/mL and at 400 mg of Theracurmin peak plasma level was 440 ng/ml with no unexpected adverse events during the 9 months of drug administration.^[46] Another

study of 24 patients aimed to quantify levels of curcumin and its metabolites in colorectal mucosa of patients rather than measuring serum concentration. Curcumin C3-complex (2.35 g) was administered daily for 14 days prior to endoscopic biopsy or colonic resection. Curcumin and its metabolites were detectable in 9/24 plasma samples, 24/24 urine samples and in the colonic mucosa of all 23 biopsied participants with mean tissue levels at 48.4 mg/g. The only adverse event reported was mild abdominal discomfort in six patients, and 67% expressed acceptability of the therapy long-term should it be of proven benefit.^[47]

PHARMACOLOGICAL ACTIVITY WITH MODE OF ACTION OR BIOLOGICAL ACTIVITIES

1. ANTI-VIRAL ACTIVITY

It has been demonstrated that curcumin as a plant derivative has a wide range of antiviral activity against different viruses: papillomavirus virus (HPV), influenza virus, Hepatitis B virus (HBV), Hepatitis C virus (HCV), adenovirus, coxsackie virus, Human norovirus (HuNoV), Respiratory syncytial virus (RSV) and Herpes simplex 1 (HSV-1).^[48,49,50,51,52] Curcumin functionalized graphene oxide shown synergistic antiviral effect against respiratory syncytial virus infection. Respiratory syncytial virus (RSV), which is considered as the major viral pathogen of the lower respiratory tract of infants, has been implicated in severe lung disease.

Developing a β -cyclodextrin (CD) functionalized graphene oxide (GO) composite, which displayed excellent antiviral activity and curcumin loading efficiently, showed that the composite could prevent RSV from infecting the host cells by directly inactivating virus and inhibiting the viral attachment, which possessed the prophylactic and therapeutic effects towards virus. The antiviral effect of curcumin was a dose-dependent manner.^[53] Curcumin inhibit activity of inosine-mono phosphate

dehydrogenase (IMPDH) enzyme in either noncompetitive or competitive manner. By inhibition of IMPDH this led to reduce the level of intracellular guanine nucleotides which required for adequate RNA and DNA synthesis. Curcumin mechanism involve in viral entry or other life cycle stages rather than the replication of viral RNA. Therefore, by inhibition of IMPDH Curcumin have potential anti-proliferative, antiviral and antiparasitic effects. ^[54]

2. ANTI-INFLAMMATORY ACTIVITY (Here NF- κ B = nuclear factor kappa-light-chain-enhancer of activated B cells)

Curcumin possesses significant anti-inflammatory activity in acute as well as in chronic models of inflammation. It is as potent as phenylbutazone in the carrageenan oedema test but only half as potent in chronic tests. Curcumin has been demonstrated to be safe in six human trials and has demonstrated antiinflammatory activity. It may exert its antiinflammatory activity by inhibition of a number of different molecules that play a role in inflammation. ^[55,56] Curcumin has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation. ^[57] 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 to TNF- α , NF- κ B is also activated by most inflammatory cytokines; gram-negative 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 downregulate 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 stimuli. Curcumin has also been shown to suppress inflammation through many different mechanisms beyond the scope of this review, thereby supporting its mechanism of action as a potential anti-inflammatory agent. ^[58]

3. ANTI-OXIDANT

Curcumin has been shown to improve systemic markers of oxidative stress it can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of freeradicals. ^[59, 60 61] There is evidence that it can increase serum activities of antioxidants such as superoxide dismutase (SOD) A recent systematic review and meta-analysis of randomized control data related to the efficacy of supplementation with purified curcuminoids on oxidative stress parameters—indicated a significant effect of curcuminoids supplementation on all investigated parameters of oxidative stress including plasma activities of SOD and catalase, as well as serum concentrations of glutathione peroxidase (GSH) and lipid peroxides. ^[62] It is noteworthy to point out that all of the studies included in the meta-analysis utilized some sort of formulation to overcome bioavailability challenges, and four out of the six used piperine. Curcumin's effect on free radicals is carried out by several different mechanisms. It can scavenge different forms of free radicals, such as reactive oxygen and nitrogen species (ROS and RNS, respectively) also, it can inhibit ROS-generating enzymes such as lipoxxygenase/cyclooxygenase and xanthine hydrogenase/oxidase. ^[63, 64] In addition, curcumin is a lipophilic compound, which makes it an efficient scavenger of peroxy radicals, therefore, like vitamin E, curcumin is also considered as a chain-breaking antioxidant. ^[65]

4. ANTI-CANCER

One-fifth of the deaths worldwide annually are caused by various types of cancers ^[66] Cancer is a Result of successive

genetic and epigenetic alterations resulting in apoptosis, uncontrolled cell Proliferation, metastasis, and angiogenesis. [67, 68] Anti-cancer activity of curcumin has been extensively investigated recently, and significant improvements in gastrointestinal, melanoma, genito-urinary, [69,70] breast, and lung cancers have been seen [71,72] Many studies pointed out anticancer activities of curcumin alone or in combination with conventional chemotherapy drugs in treatment of cancer and its cancer-related complications. [73,74,75,76]

In-vitro and in-vivo studies have indicated that curcumin prevents carcinogenesis by affecting two primary processes: Angiogenesis and tumor growth [77] Curcumin analogs S1- S3 containing sulfone strongly inhibited the growth of human prostate, colon, lung and pancreatic cancer cells. [78,79] Scientific studies of plants used in various types of ethnic medicine have led to the discovery of many valuable drugs, including taxol, camptothecin, vincristine and Vinblastine. [80]

CURCUMIN AND ANTI-CANCER DRUGS COMBINATION (NANOMEDICINE)

Almost half a century ago, nanomedicine emerged as a specific niche for drug delivery, within the multidisciplinary field of nanotechnology. A principal focus for the last 20 years has been on the development of nano-formulation driven drug delivery of nanocarriers. Various nanocarriers that have been investigated for drug delivery include polymeric micelles, liposomes, magnetic nanoparticles, conjugates, and peptide carriers. [81,82] Integration of Nanotechnology within cancer research has proved to be advantageous in several ways, including (a) cancer treatment and detection (diagnostics and imaging agents); [83] (b) biomarker identification for disease prediction [84] and (c) mechanism of cancer progression. [85] A narrow therapeutic window of drugs however is one of the

major challenges with anticancer drugs and is the reason for serious side effects due to non-specific drug uptake by healthy cells. The efficacy of cancer drugs is also restrained due to multidrug resistance (MDR), often associated with chemotherapy. To overcome these issues the primary strategy of combination chemotherapy along with drug delivery systems using nanoparticles (NPs) is being actively explored. [86] Curcumin could be a potential elementary candidate to be used for combination chemotherapy as it could overcome the issues associated with anti-cancer therapeutics.

1) Type of Nanoparticles in Cancer therapy

There are two categories of therapeutic and diagnostic nanoparticles: (a) organic (e.g., polymeric, liposomes, micelles, etc.) (b) inorganic (e.g., gold, silica, iron oxide, etc.). Natural or synthetic organic molecules are the template for the formation of organic NPs. Organic and inorganic NPs differ in their technique of fabrication. For organic NPs, the encapsulation techniques of biodegradable materials used are relatively simple and require several self-organizing or chemical binding organic molecules. Whereas, inorganic NPs involve precipitation of inorganic salts in which atoms are often linked by covalent/metallic/magnetic bonding leading to formation of a three-dimensional array. [87, 88, 89]

2) Combination chemotherapy in cancer

The interconnected pathways in cancer physiology reduce effectivity of monotherapy strategy. Drug resistance and chances of tumor recurrence due to pathway overlapping [90] cross-talk [91] and neutralizing response, [92] could be various complications hindering full potential of independent drugs. The easiest approach to overcome this issue could involve utilization of combination chemotherapy strategy, which has shown to be successful in preliminary clinical trials. [93] Combination chemotherapy design involves an understanding of several principles like

non-overlapping toxicity, non-cross resistance, and enhanced tumor cell killing efficacy. [94] Nanocarriers like liposomes and polymeric micelles could further help to overcome mono-therapeutic complications. A previous generation of cancer combination chemotherapy comprised of traditional drug combinations including anthracycline, methotrexate, and paclitaxel (PTX)-based combinations. [95] A study on one such combination displayed an effective reversal of chemotherapeutic drug resistance with Dox and rapamycin codelivery. This combination leads to complete tumor remission, as compared to dox and rapamycin alone. [96] In another such study, in vivo effects of curcumin combination with antitumor drug was studied and displayed effectively. Docetaxel (DTX) and Curcumin (CUR) co-encapsulated lipid nanoparticles (LPN's) were evaluated on PC3 tumor xenografts in mice (human prostate cancer-bearing Balb/c nude mice model). These potent nanoparticles inhibited tumor volume growth significantly, when compared to other groups, with no visible side effects.

It was concluded that this combination could prove to be an effective prostate cancer treatment. [97] Curcumin has shown to be successful in several types of cancer lines, mainly because of its

Ubiquitous action on different modulator of anti-cancer effects. Curcumin inhibits tumor growth by arresting cell cycle progression, inducing apoptosis, inhibiting the expression of antiapoptotic proteins, inhibiting multiple cell survival signaling pathways and their cross-communication, and modulating immune responses. [98, 99, 100]

5. ANTI-BACTERIAL

The antibacterial study of curcumin shows the ability to inhibit growth of a variety of periodontopathic bacteria and *Porphyromonas gingivitis* Arg- and Lys-specific proteinase (RGP and KGP, respectively) activities. In addition, curcumin suppressed *P. gingivitis* homotypic and *Streptococcus gordonii*

biofilm formations in a dose-dependent manner. Bacterial growth was suppressed almost completely at very low concentrations of curcumin. A concentration of 20 µg/mL of curcumin inhibited these *P. gingivitis* biofilm formations by more than 80%. On the other hand, 100 µg/mL of curcumin did not suppress the growth of *Aggregatibacter actinomycetemcomitans*. Furthermore, at relatively high concentrations, curcumin targets bacterial membranes (*Escherichia coli*). [101, 102]

On another hands, Curcumin - Polymyxin B used clinically for topical therapy to treat or prevent traumatic wound infections of the skin. It would not only increase the spectrum of activity to include Gram-positive bacteria but also combat those isolated resistant. The use of the combination may also reduce the emergence of resistant isolates during treatments, due to the multiple antimicrobial targets of dual drug therapy and ease the selective pressure produced by broad-spectrum antibiotics. [103]

Additionally, curcumin loaded in zein (zein-CUR) fibers showed good antibacterial activity towards *S.aureus* and *E. coli* and the inhibition efficiency increased with the increase of curcumin contents. Due to the different cell membrane constituent and structure, the antibacterial activity towards *S.aureus* was better than that towards *E. coli*. The study displayed that the zein-CUR fibers might have potential as a promising material for antimicrobial applications to inhibit bacterial growth and propagation in food packaging. [104] Also, antibacterial activity of curcumin-chitosan film against *Staphylococcus aureus* and *Rhizoctonia solani* was studied by the zone inhibition method. [105] The natural blend films of curcumin and chitosan could be as a promising antimicrobial packaging for food and agriculture products. [106]

In addition, Surface charge as well as the small size of curcumin nanoparticles plays a key role in enhancing cell-antimicrobial interaction and antimicrobial efficacy. The fabricated curcumin nano-

particles showed the best antimicrobial activity against *Listeria monocytogenes*. A size reduction to nano-scale is a recently developed strategy used to improve drug/food delivery and matching the public demand for effective and safe antimicrobial formulations for control of food borne pathogen. [107]

6. ANTI-ALLERGY / ANTI-ASTHMA

Curcumin decreased the nasal airflow resistance by alleviating sneezing, rhinorrhea and nasal congestion. It also suppresses the IL-4, IL-8, and tumor necrosis factor α as well as also enhanced the levels of IL-10 and soluble intercellular adhesion molecule. Curcumin administered through nasal route inhibited allergic airway inflammations and maintaining structural integrity in allergic asthma mice model. The different treatments of curcumin (2.5 and 5.0mg/kg) in ovalbumin (OVA) of Balb/c mice markedly regulates airway inflammation and airway obstruction mainly by modulating cytokine levels (IFN- γ , IL-4, 5, and TNF- α) and sPLA2 activity thereby inhibiting PGD2 release and COX-2 expression. Furthermore, curcumin suppressed the ERK 42/44, p38 MAPK (mitogen-activated protein kinase) and JNK54/56 activation in asthma progression rats. [108]

7. ANTI-FUNGAL

Due to extensive traditional use of curcumin in food products, various researches have been done in order to study curcumin with the aspect of controlling fungal related spoilage and fungal pathogens. [109] The study of addition the curcumin powder in plant tissue culture showed that curcumin at the 0.8 and 1.0 g/L had appreciable inhibitory activity against fungal contaminations. [110] Reduction in proteinase secretion and alteration of membrane-associated properties of ATPase activity are other possible critical factors for antifungal activity of curcumin. [111] Finding new anti-candida substances seems to be crucial due to development of resistant strain against existing antifungal drug. [112]

The investigation of curcumin mediation for photo- dynamic therapy can reduce the biofilm biomass of *C. albicans*, *C. glabrata* and *C. tropicalis*. The results demonstrated that association of four LED influences for light excitation with 40 μ M concentration of curcumin at 18 J/cm² inhibited up to 85% metabolic activity of the tested *Candida* species. The use of curcumin with light proved to be an effective method for noteworthy improvement in the antifungal activity against planktonic form of the yeasts. [113] Photodynamic effect considerably decreased *C. albicans* viability in either planktonic or biofilm cultures probably through increasing the uptake of curcumin by cells. However, to a lesser extent, photodynamic therapy was found to be phototoxic to the macrophages. [114]

8. ANTI-ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by hyperplasia of the synovial fibroblasts. Curcumin is known to possess potent anti-inflammatory and anti-arthritis properties. [115] Curcumin treatment was carried out on patients with active rheumatoid arthritis and compared with diclofenac sodium reference group. Interestingly, the curcumin group showed the highest percentage of improvement in overall rheumatoid arthritis scores and these scores were significantly better than the patients in the diclofenac sodium group. More importantly, curcumin group was found to be safe and did not relate with any adverse events compared to diclofenac sodium group. [116] It is believed that curcumin antioxidant, antiproliferative, anti-inflammatory and immunosuppressive activities shared in the improvement of symptoms to patients suffering from rheumatoid arthritis. [117]

9. ANTI-VENOM

Curcumin was listed as a herbal plant metabolite that can effective against Snake Venom PLA2. [118] Researchers studied the structural relationship between

medicinally important herbal compounds such as acalyphin, chlorogenic acid, stigmasterol, curcumin and tectoridin and PLA2 from Russell's viper. The molecular modeling studies revealed favorable interactions with the amino acid residues at the active site of venom PLA2 that could result in the inhibition. ^[119]

10. ANTI-DIABETIC

Curcumin was reported to possess anti-diabetic activity. The effect of antidiabetic activity could be attributed to the antioxidant property of curcumin. ^[120] In their study, researchers demonstrated curcumin positive effect through the improvement of diabetes-induced endothelial dysfunction by decreasing superoxide production and vascular protein kinase C inhibition. Interestingly, recent studies demonstrated the ability of curcumin to have the capacity to directly quench reactive oxygen species (ROS) that can contribute to oxidative damage. ^[121]

This property is known to contribute to the overall protective effects of curcumin. Curcumin can attenuate cell death caused by oxidative stress, indirectly through induction and/or activation of antioxidant/cytoprotective enzymes, such as heme oxygenase-1 (HO^{-1}). The protective mechanisms of HO^{-1} in diabetes could present some emerging therapeutic options for HO^{-1} expression in treating diabetic diseases. ^[121]

Curcumin was evaluated for the prevention of type 2 diabetes in pre-diabetic human population. ^[122] The subjects received curcumin capsules for 9 month period versus placebo capsule group. The curcumin-treated group showed a better overall function of β -cells, with higher HOMA- β and lower C-peptide. The curcumin treated group showed a lower level of HOMA-IR (insulin resistance index) and higher adiponectin, when compared with the placebo group. The results indicated that curcumin intervention may have positive effect to a prediabetic population. ^[122]

11. ANTI-OBESITY

Promising results where curcumin improved lipid status as also fat content on treated individuals set the base for studies on obese patients. Only several clinical trials reported results on curcumin obesity effects. The first one investigated the effect of curcumin oral supplementation on lipid profile parameters, BMI and glucose levels in obese individuals. The results demonstrated significant changes only in TG levels, while other parameters remained unchanged after 30 days-curcumin administration. ^[123] BMI and body weight reduction were also recorded in the study who investigated these parameters in NAFLD patients. ^[124] The results obtained demonstrated that 4-week supplementation with turmeric in Dose of 2.8 g/day does not alter oxidative stress or inflammatory parameters in systemic inflammation overweight/obese females, nor cause a significant shift in global metabolic profile. ^[125] Although the mentioned studies showed no encouraging results, recent findings showed positive effects of curcumin on body weight and BMI. After one month of 1.6 g/day. Curcumin oral administration (in the form of phytosome in combination with 8 mg piperine), significant improvements in BMI, body fat and body measures were reported BMI and body weight reduction were also recorded in the study of who investigated these parameters in NAFLD patients. ^[126, 124]

12. CARDIO AND LIVER TOXICITY PROTECTION ACTIVITY

Researchers investigate the protective effects of curcumin on experimentally induced hepatotoxicity, and cardio toxicity using various animal models with biochemical parameters like serum marker enzymes and antioxidants in target tissues. The increased relative weight of liver and heart in CCl_4 induced liver injury and isoproterenol induced cardiac necrosis were also reduced by Curcumin treatment. Elevated serum marker enzymes, aspartate

aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) increased lipid peroxidation, decreased glutathione (GSH), glutathione peroxidase (GPx) and superoxide dismutase (SOD) in edematous, granulomatous, liver and heart tissues during liver injury and cardiac necrosis, respectively. The study demonstrated the in-vitro and in-vivo protective effect of curcumin on experimentally induced hepatotoxicity and cardio-toxicity in rats. [127]

13. WOUND- HEALING ACTIVITY

The ethosomal curcumin significantly recovered main aspects of wound repair including re-epithelization, neovascularization, collagen synthesis, granulation tissue formation. It also potentially inhibited growth of the burn bacterial flora including *Pseudomonas aeruginosa* as predominant bacteria among experimental isolations during 14 days treatment. It efficiently fights against wound infection and promotes wound repair in burn injuries in rats. [128] The growth factors are participated in wound healing process which stimulated by curcumin. [129]

The mechanisms of action of wound healing effect of curcumin include: immunohistochemical localization of transforming growth factor- β 1 showed an increase in curcumin-treated wounds as compared with untreated wounds [130] and modulating collagen and decreasing reactive oxygen species. [131]

14. ANTI-ALZHEIMER ACTIVITY

The first clinical trials investigating the effect of curcumin on Alzheimer's disease patients showed no such promising results, where no significant difference was observed between the curcumin and placebo group after 6 and 12 months of oral administration. [132] a marked increase in plasma vitamin E and of serum A β 40 levels were found in treated patients. Indeed, increased A β 40 levels in serum implied that curcumin can disaggregate A β -deposits in

the brain, leading to their consequent release into circulation. [133] In addition, the low curcumin efficacy towards dementia symptoms, [134] where an oral intake of 1500 mg/day for 12 months could not affect clinical measures nor cognitive measures of treated individuals. On the other hand [135] done on very modest number of AD subjects (3 patients), stated significant improvements in Neuropsychiatric Inventory (NPI) scores after 12 weeks with 100 mg/day curcumin treatment. Recent findings, where novel curcumin formulations (Longvida® and Theracurmin) were optimized to ensure a higher bioavailability, even given in much lower doses (80-180 mg/day), demonstrated both good acute and chronic activities improved sustained attention and working memory tasks immediately after a single dose, while after 4-week administration enhanced memory, mood, alertness and contentedness. [136,137]

15. DEPRESSION AND ANXIETY

The impact of curcumin oral administration on depression has been evaluated through several clinical trials In these studies, curcumin was given orally at doses ranging from 500-1000 mg daily, alone [138, 139, 140] with bioperine [141] or in combination with standard anti-depressive agents escitalopram, venlafaxine or fluoxetine. [142,143] In all trials, the studied individuals evidenced a marked improvement in depression-related symptoms, assessed through using relevant scales. Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Hamilton Depression Rating scale (HAM-D17), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory II (BDI-II) scores, IDS-SR30 total score and IDS-SR30 score were the most commonly applied. The only exception was the trial carried out, where curcumin administration reduced anxiety, but not depression, which might be a consequence of the shortest administration time (30 days vs. 5-8 weeks in other studies). In two additional trials,

together with symptoms scales, blood stress parameters and other clinical biomarkers were measured. It was found that curcumin decreased IL-1 β and TNF α levels, increased plasma BDNF and decreased salivary cortisol levels in curcumin-treated group, stated a significant increase in urinary thromboxane B₂, substance P, baseline plasma endothelin-1 and leptin, considered crucial molecular markers that can be related to the antidepressant mechanism of action of curcumin. [144]

16. CURCUMIN USED IN EYE DISEASE

Clinical trials on the subject of curcumin effect to various ophthalmological disorders demonstrated high efficacy of this compound, when either locally or systemically applied, by oral intake. It has been reported that 15-day eye drops application containing turmeric can improve symptoms of conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula) and of postoperative cataract patients. [145] Studies on patients with uveitis demonstrated a marked symptoms improvement in all treated patients [146] and reduced eye discomfort and number of relapses [147] after oral curcumin intake for 12 weeks and 18 months, respectively. Also, a significant improvement was observed in patients with central serous chorioretinopathy after oral curcumin administration. [148]

CONCLUSION

Curcumin has show worldwide used for its complete benefits for health, which appear to act primarily through its anti-oxidant and anti-inflammatory mechanisms. These benefits are best achieved when curcumin is combined with agents such as, carbohydrates, piperine, which increases its bioavailability significantly. Research suggests that curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, anti-inflammatory, anxiety, and anti diabetic,

hyperlipidemia. It may also help in the management of multifactorial used of Pharmacological activity in health and also improve the health for body benefits for human health, thus enhancing recovery and subsequent performance in active people. In addition, a relatively sufficient dose can provide health benefits for people that do not have diagnosed health conditions.

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