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Curcumin: Isolation and health benefits on human health

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Abstract
Curcuma longa (Turmeric) is a rhizomatous medicinal plant from the Zingiberaceae family that is widely utilised in India. Curcuminoids are a group of turmeric components that include curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5- dione), also known as Diferuloylmethane, is well-known for its anti-inflammatory and anti-oxidant properties. Various clinical trials and their findings on these activities have been addressed in this article. Curcumin is a tautomer molecule that exists in both enolic and keto forms in organic solvents and water. This review article outlines Curcumin's different roles activities in humans and there side effect.

Keywords: *Curcuma longa*, curcuminoid, anti- inflammatory, anti- oxidant

1. Introduction
Turmeric is an Indian rhizomatous natural plant (*Curcuma longa*) of the ginger family (Zingiberaceae) of notable health advantages. (Panpatil *et al*., 2013) [21]. the therapeutic advantages of turmeric could be described to the presence of dynamic standards called curcuminoids. Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are all in all known as curcuminoids. These yellow hued curcuminoids are isolated from *Curcuma longa* L. (turmeric) rhizomes. (Majeed *et al*., 1999) [18]
Perhaps the most fascinating segments of curcuminoid is curcumin, which is a little atomic weight polyphenolic compound and liophillic in nature, subsequently insoluble in water and furthermore in ether however dissolvable in ethanol, dimethylsulphoxide, and other natural solvents. Curcumin is steady at the acidic pH of the stomach. Unpredictable oils such as Turmerone, allantoin, and Zingiberene, as well as sugars, proteins, and tars, are present. The dynamic constituent of turmeric-curcumin is secluded from *Curcuma longa* and it gives tone to turmeric. Such bioactive segment has been completely examined Curcumin (1, 7-bis (4-hydroxy-3methoxyphenyl) - 1, 6-heptadiene-3, 5-Dione) is additionally called diferuloylmethane.
Turmeric compound existing in enalia structure in natural solvents and as a keto structure in water. Turmeric is a plant known by its restorative use, tracing all the way back to 4000 years prior in the Vedic culture in India, where it was utilized as a culinary zest and had some strict importance. Turmeric is the bubbled, dried, and cleaned and sparkle rhizomes of *Curcuma longa*. Subsequent to gathering the entire rhizomes are gathered. They are generally similar to fingers 2 to 8 cm long and 1 to 2 cm wide having bulbs and parts. The dried rhizomes are additionally handled and reprocessed to acquire the turmeric powder. It has various names in various societies and nations. In Sanskrit, turmeric has in any event 53 distinct names. (Surbhi. *et al*., 2021)
It purpose of this review to provide a brief overview of the plethora of research regarding to optimize suitable method for curcumin isolation and potential health benefits of curcumin. I.e Anti-inflammatory activity Antioxident activity. Due to the extent of the review, we have chosen to focus on the benefits associated with some common health conditions and on benefits in healthy people.

2. Curcumin
Curcumin has been utilized in custom as a clinical spice because of its different benefits, for example, cell reinforcement, mitigating, antimutagenic, and antimicrobial and a few remedial properties Curcumin shows helpless assimilation, fast digestion, and quick disposal. A few

Specialists have been acquainted with improve the bioavailability of curcumin. Most intriguing one is piperine; it upgrades curcumin bioavailability by blockage of the metabolic pathway of curcumin. Piperine brings about an increment of 2000% in the bioavailability of Curcumin is a fundamental fixing in the root concentrate of *Curcuma longa*. The foundation of this plant, which is yellow because of the presence of curcumin, has been utilized as a seasoning and shading specialist for food and medication in Asian nations. Curcumin is accessible in a few structures including cases, tablets and treatments. Curcuminoids have been affirmed by the US Food and Drug Administration (FDA) as "By and large Recognized as Safe" (GRAS). It is the reason for this audit to give a short outline of the potential medical advantages of curcumin. In natural and customary medication, turmeric is utilized for rheumatoid joint inflammation, ongoing foremost uveitis, conjunctivitis, skin malignant growth, little pox, chicken pox, wound recuperating, urinary plot contaminations, and liver illnesses, reinforcing the general energy of the body, scattering worms, managing period, dissolving gallstones, purifying injuries, and in any event, for different stomach related problems, among different conditions. C. longa has on its synthetic creation over 3% curcumin, 1.4% DMC and 1.2% BDMC. Moreover, curcumin likewise showed a noticeable defensive impact on bone thickness problems, for example, osteopenia osteoarthritis while assisting with calming torment and expanding in mouth, gum disease and Periodontitis. (Surbhi. *et al*., 2021)

3. Chemistry of Curcumin

Curcumin, also known as diferuloylmethane, is a symmetric molecule. This compound's IUPAC name is (1E-6E) 6-heptadiene-3, 5-dione-1, 7-bis (4-hydroxy-3-methoxy phenyl)-1, 7-bis (4-hydroxy-3-methoxy phenyl)-1, 7-bis (4-hydroxy-3-methoxy phenyl)-1, 7-bis (4-hydroxy-3 Curcumin has the chemical formula C21H20O6 and a molecular mass of 368.385g/mole.

(Sunghwan Kim. *et al*., 2016) 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, 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%) in which the methoxy group is absent from both the aryl rings, **(**Fanti *et al*., 1999) 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. 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. (Kumar *et al*., 2016) [17]. Curcumin is soluble in polar solvents like DMSO, methanol, acetone and ethanol. **(**Goel *et al*., 2008) [14]

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. The regeneration reaction of phenoxy 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. It has been demonstrated that solvolysis is a minor pathway, and the primary pathway is autoxidation. (Shishodia *et al*., 2005) Pharmacokinetic studies showed that after oral consumption, curcumin is metabolized to give sulfate and glucuronidase 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) and derivatization of the β-diketone to decrease the activity of the enolate Michael acceptor. **(**Griesser *et al*., 2011) [13]**.** 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.

4. Historical Perspective

The Curcuma genus has a long history in Far Eastern medicine, dating back 5,000 (Ayurved.a) and 2,000 (Atharveda) years, respectively. C. longa contains a variety of curcuminoids, with curcumin being the most active, having been isolated in 1815 and distilled into a crystalline compound in 1870. Polish scientists suggested the curcumin structure for the first time in 1910. Although 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione is the most common name for the compound, it is also known as "curcumin I." Curcumin is a diferuloylmethane with the chemical formula C21H20O6 and a crystalline yellow-orange colour. It has a molecular weight of 368.39 g/mol, a melting temperature of 183 °C, and a molecular weight of 368.39 g/mol. It has keto-enol tautomerism chemically, which means it has a predominant keto form in neutral and acidic solutions, but its more stable enol form dominates in the solid state and in an alkaline solution. There are two additional compounds known as curcumin, which are curcumin II [demethoxycurcumin, 1-(4-hydroxy-3-methoxyphenyl)- 7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione] and curcumin III [bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene- 3,5-dione]. (Sharifi-rad *et al*., 2020) [25]

Surprisingly, this natural polyphenol is commonly referred to as the "wonder drug of life" (Gera *et al*., 2017) [12]. Turmeric was used to treat inflammatory diseases in different organs, liver and digestive tract disorders, and wound healing in ancient times in the Far East. The first studies on cur cumin's health benefits were conducted in the 1970s. Curcumin has been shown to have several therapeutic potentialities in these and subsequent research. Despite this, turmeric is still not considered a beneficial agent in the pharmaceutical industry

(Gera *et al*., 2017) [12], and its use in medical clinics is uncommon due to its poor bioavailability. Curcumin's hydrophobic nature causes slow absorption by the gastrointestinal (GI) tract after oral administration. Curcumin, on the other hand, appears to have a promising therapeutic potential from turmeric, as it is classified as a Generally Recognized As Safe (GRAS) substance with a stable metabolism and low toxicity (Nelson *et al*., 2017) [20]. Cur cumin's coloring properties for industrial applications are also worth noting (Joshi *et al*., 2009; Buckingham, 2018) [15, 6].

5. Isolation of Curcumin

Since curcumin is water insoluble, it was isolated using an organic solvent. CUR was isolated from turmeric powder using a process invented by the researchers. After magnetically stirring the ground turmeric, they heated it in dichloromethane at reflux for 1 hour. After being suction-filtered, the filtrate was concentrated in a hot-water bath held at 50 ^{0}C. After being triturated with hexane, the reddish-yellow oil residue was collected using suction filtration. TLC analysis verified the presence of all three components (3 percent methanol and 97 percent dichloromethane). (A.M. Anderson *et al*., 2000). CUR was extracted from turmeric powder using a solvent that was a combination of ethanol and acetone. Turmeric contains carbohydrates (69.4 percent), moisture (13.1 percent), protein (6.3 percent), fat (5.1 percent), and minerals, according to chemical analysis (3.5 percent). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%); curcumin (3-6%) is responsible for the yellow colour. (Bagchi *et al*., 2012) [2].

6. Mechanism of action in human

The majority of curcumin trials in humans have been conducted in people who already have health conditions. Perhaps this is due to the fact that research on healthy individuals may be difficult since the benefits might not be as obvious and observable if biomarkers are usual at the start. As a result, studies that track subjects over time can provide the best insight into any possible health benefits in healthy people, but these studies may be time-consuming and expensive. Since studies have used different doses, sometimes as high as 1 g, cross-comparisons between the few studies that have been performed can be difficult. It's worth noting that this is only called a high dose because it's more than most people will get from eating the spice alone. An 80 mg/day dose of a lapidated form of curcumin was used in one study on healthy adults aged 40–60 years. For four weeks, subjects were given either curcumin (N = 19) or a placebo (N = 19). The medication consisted of 400 mg of powder a day containing 80 mg of curcumin. Before and after the four weeks, blood and saliva samples were taken. Triglyceride levels were greatly reduced by curcumin, but not total cholesterol, LDL, or HDL levels. The levels of nitrous oxide (NO) and soluble intercellular adhesion molecule 1 (sICAM), a molecule linked to atherosclerosis, both increased significantly. Myeloperoxidase concentration increased in inflammation-related neutrophil activity, but C - reactive protein and ceruloplasmin did not. There was a decrease in salivary amylase activity, which can be a stress marker, as well as an increase in salivary radical scavenging capacities and plasma antioxidant enzyme catalase, but no change in superoxide dismutase or glutathione peroxidase. Furthermore, beta amyloid plaque, a marker of brain ageing, and plasma alanine amino transferase activities, a marker of liver damage, both decreased. This suggests that a low dose of curcumin may have health benefits in people who don't have any diagnosed health problems (DiSilvestro, *et al*., 2012) [8]

The acute (1 and 3 hours after a single dose), chronic (four weeks), and acute-on-chronic (1 and 3 hours after single dose following chronic treatment) effects of solid lipid curcumin formulation on cognitive function, mood, and blood biomarkers in 60 healthy adults aged 60–85 years were investigated in a randomised double-blind placebo-controlled study. The curcumin formulation included 400 mg of curcumin in a strong lipid formulation, with the remaining weight made up of typical pharmaceutical excipients and trace amounts of other curcuminoids found in turmeric extract. Curcumin significantly enhanced results on sustained concentration and working memory tasks one hour after administration as compared to the placebo. Following chronic therapy, working memory and mood (general exhaustion and changes in state calmness, contentedness, and fatigue caused by psychological stress) were dramatically improved. There was also a major acute-on-chronic care impact on alertness and contentment. Curcumin has been linked to lower total and LDL cholesterol levels (Cox K.H. *et al*., 2014)

Another study looked at how three months of curcumin and Boswellia serrata (BSE) gum resin supplementation affected plasma levels of oxidative stress, inflammation, and Gly cation markers in 47 male master cyclists. All of the participants were told to eat a Mediterranean diet, with 22 getting a placebo and 25 getting 50 mg of turmeric. For 12 weeks, I took 10 mg of curcumin and 140 mg of Boswellia extract (equivalent to 105 mg of Boswellia acid). In healthy male master athletes, there was a positive impact on glycoxidation and lipid peroxidation. This study suggests that combining curcumin with other agents may provide health benefits. (McFarlin *et al*., 2016) [19]

Defining the concept of safe is perhaps another difficulty in interpreting research on healthy people, particularly when considering that people who do not have an official diagnosis may still engage in behaviours or encounter conditions that challenge their everyday physiological homeostasis. An unfamiliar exercise routine, for example, can cause inflammation and oxidative stress. In a recent study, 28 healthy people who didn't do any resistance training were randomly assigned to receive either curcumin (400 mg/day) or placebo for two days before and four days after performing an eccentric exercise intended to cause muscle soreness. When compared to the placebo, curcumin supplementation resulted in slightly lower increases in creatine kinase (CK) (48%) TNF- (25%) and IL-8 (21%) following exercise. There were no major variations between the conditions in terms of IL-6, IL-10, or quadriceps muscle soreness. Curcumin intake decreased biological inflammation, according to the results. However, subjective quadriceps muscle soreness during workout rehabilitation is not one of them. This can aid in reducing recovery time and thereby improving performance in subsequent workouts

Twenty fit, moderately active male participants were randomised to receive either 1 g curcumin twice daily (200 mg curcumin twice daily) or a placebo 48 hours before and 24 hours after a downhill running test in a similar randomised placebo-controlled single-blind pilot study. Curcumin-treated participants showed substantially less pain in the right and left anterior thighs. The curcumin community had significantly

fewer participants with MRI proof of muscle damage in the posterior or medial compartments of both thighs. Increases in markers of muscle damage and inflammation were lower in the curcumin community, but only interleukin-8 showed a substantial difference at 2 hours after exercise. There were no variations in oxidative stress markers or muscle histology. These findings add to the evidence that curcumin can help to reduce exercise-induced muscle soreness (DOMS). (Drobnic, *et al*., 2014)

A research by Delecroix *et al*. adds to the proof. They found that supplementing professional rugby players with 2 g of curcumin and 20 g of piperine can help offset some of the physiological signs of muscle soreness after an intense workout.

In addition to acute physical pressures, humans may experience subclinical anxiety or depression, but they may also benefit from medications to alleviate the symptoms. In a randomised double-blind cross-over study, 30 obese adults were given curcuminoids (1 g/day) or a placebo for 30 days, then switched to the other protocol after a two-week washout duration. The curcumin was a 500-mg C3 Complex (standardised powder extract obtained from Aleppo finger turmeric containing at least 95 percent concentration of three curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin) plus 5 mg bioperine per serving to aid absorption. Each participant completed the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scales at baseline, four, six, and ten weeks after supplementation. Curcumin therapy resulted in a substantial reduction in mean BAI score ($p = 0.03$). Curcumin supplementation, on the other hand, had no effect on BDI ratings. Curcumin can have an anti-anxiety impact in otherwise healthy obese people, according to this study. (Esmaily, *et al*., 2015) [10]

7. Anti-Oxidant Activity

The majority of curcumin's effects on the different conditions described in this analysis are explained by its antioxidant and anti-inflammatory properties. Curcumin has been shown to enhance oxidative stress markers in the body. It has been shown to increase the serum activity of antioxidants including superoxide dismutase (SOD) (Banach, *et al*., 2014) [3]. A recent systematic review and meta-analysis of randomised control evidence on the effectiveness of distilled curcuminoids supplementation on oxidative stress parameters found that curcuminoids supplementation had a major impact on all examined oxidative stress parameters, including plasma SOD and catalase activities, as well as serum glutathione peroxidase concentrations. It's worth noting that all of the studies included in the meta-analysis used some kind of formulation to address bioavailability issues, with piperine being used in four of the six. Cur cumin's effect on free radicals is mediated by a variety of mechanisms. It has the ability to scavenge a variety of free radicals, including reactive oxygen and nitrogen species (ROS and RNS, respectively). It can control the activity of free radical-neutralizing enzymes like GSH, catalase, and SOD, as well as inhibit ROS-producing enzymes. Lipoxygenase/cyclooxygenase and xanthine hydrogens/oxidase are two examples. Curcumin is also a lipophilic compound, making it an effective scavenger of peroxyl radicals. As a result, like vitamin E, curcumin is classified as a chain-braking antioxidant. (Priyadarsini *et al*., 2003)

8. Anti-Inflammatory Activity

Many chronic diseases have been linked to oxidative stress, and its pathological mechanisms are closely linked to those of inflammation, in that one can easily be caused by the other. Inflammatory cells are known to release a number of reactive species at the site of inflammation, resulting in oxidative stress, demonstrating the connection between oxidative stress and inflammation. (Biswas, 2016) [5] A variety of reactive oxygen/nitrogen species may also cause an intracellular signalling cascade that boosts pro-inflammatory gene expression. Inflammation has been linked to the onset of a variety of chronic illnesses and disorders (Panahi, *et al*, 2016) [22] , Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, dementia, cerebral injury, cardiovascular disease, metabolic syndrome, cancer, allergy, asthma, bronchitis, colitis, arthritis, renal ischemia, psoriasis, diabetes, obesity, depression, and fatigue are just some of the conditions that people suffer from. And acquired immune deficiency syndrome are just a few of the diseases listed. AIDS. Tumor necrosis factor (TNF-) is a major mediator of inflammation in most diseases, and its effect is regulated by nuclear factor (NF)- B activation. Despite the fact that TNF-_ is the most potent NF- B activator, TNF-_ expression is also controlled by NF- B. Most inflammatory cytokines, in addition to TNF-_, cause NF- B. gram-negative bacteria, viruses, environmental toxins, biological, physical, mechanical, and psychological stress, high glucose, fatty acids, ultraviolet radiation, cigarette smoke, and other disease-causing factors As a result, agents that inhibit NF- B and NF- B–regulated gene products could be effective against a variety of diseases. Curcumin has been shown to inhibit NF- B activation, which is induced by a variety of inflammatory stimuli (Panahi, et.al, 2016) [22]. Curcumin has also been shown to suppress inflammation through a variety of mechanisms that are outside the reach of this study, indicating that it may be used as an anti-inflammatory agent (Panahi *et al*, 2016) [22].

9. Models associated with Anti-inflametry property of curcumin

According to the (Wal Saraswat, *et al.*, 2019) Edema and Inflammation: By inducing carrageen in mice, Srimal *et al*. were able to induce edema and inflammation. He discovered g4 that curcumin has an anti-inflammatory effect by reducing edema at doses of 50-200 mg/kg. A 50 percent anti-inflammatory effect was observed with a dosage of 48 mg/kg, which is approximately equal to the effect of phenylbutazone and cortisone at the same dose.

9.1 Ulcerative Colitis

Curcumin suppresses mucosal damage in mice with colitis, according to studies. Curcumin at a dose of 50 mg/kg before 10 days of 1, 4, 6-trinitrobenzene sulphenic acid induction improved colonic structure and reduced neutrophil infiltration, as well as inhibiting tissue peroxidation and suppressing inflammation.

9.2 Rheumatoid Arthritis

Before inducing arthritis in a Wistar female rat, a dose of 4 mg/kg per day for four days was administered, which blocked joint inflammation in the acute phase by up to 75% and in the chronic phase by up to 68 percent.

9.3 Pancreatitis

Curcumin has been shown to minimise NF-B stimulation and

block induction of TNF-, interleukin-6, and iNOS mRNA in pancreatic cells, all of which occur in the pancreatic cell. Curcumin blocked inflammatory mediators in the first case where pancreatitis was induced by cerulean, and in the second case where pancreatitis was induced by ethanol, reducing the severity of the disease.

10. Side effect of curcumin

Curcumin has a long history of being healthy. Curcumin's Allowable Daily Intake (ADI) value is 0–3 mg/kg body weight, according to JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) reports *(Kocaadam et.al,2017)* [16] Curcumin's protection and effectiveness have been shown in a number of studies on healthy people. Despite the fact that the drug's safety has been identified, some negative side effects have been documented. In a dose response sample, seven subjects who received 500–12,000 mg and were followed for 72 hours experienced diarrhoea, headache, rash, and yellow stool. Some people who took 0.45 to 3.6 g of curcumin a day for one to four months reported nausea and diarrhoea, as well as a rise in serum alkaline phosphatase and lactate dehydrogenase levels (Sharma et.al, 2004) [26]

11. Conclusion

Globally, curcumin is recognised because of its antioxidant, anti-inflammatory characteristics and other potential benefits which are helpful for public health. It improves bioavailability in conjunction with curcumin and piperin. Curcumin also might deal with oxidative, inflammatory, metabolic, arthritis, anxiousness and Hyperlipidemic diseases. Exercise-induced inflammation and sore muscles are monitored as well as enhanced by inactive individuals throughout rehabilitation and performance level. In addition, for people who have not yet been successfully treated with any disease, it's indeed beneficial.

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