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An Overview of Curcumin's Health Benefits for Humans

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ABSTRACT
Turmeric, being the primary source of polyphenol curcumin, has piqued the interest of both the scientific and medical communities, as well as food enthusiasts. Turmeric has long been recognized for its medicinal properties. It is effective in the treatment of anxiety, arthritis, metabolic syndrome, oxidative and inflammatory diseases, and hyperlipidemia. It may also help manage inflammation and muscle soreness caused by exercise, increasing recovery and function in persons who lead active lifestyles. Furthermore, persons without a medical diagnosis may benefit from the complex at extremely low doses. The majority of these benefits are due to its anti-inflammatory and antioxidant characteristics. Consuming curcumin by itself does not produce related health advantages because of its limited bioavailability, which is primarily caused by poor absorption, high metabolism, and rapid elimination. Many ingredients can boost bioavailability; for instance, it has been demonstrated that combining curcumin with piperine, the primary active ingredient in black pepper, can increase bioavailability by 2000%. When taken with other boosting medications, curcumin offers a host of health advantages. This review aims to give a concise overview of the vast amount of research on curcumin's health advantages.

KEYWORDS
Human health, *Curcuma longa*, curcumin, antioxidant, anti-inflammatory

INTRODUCTION

Curcumin is a yellow pigment found primarily in various species of Curcuma, i.e., turmeric. It gives the widely utilized spice turmeric its characteristic yellow color and a number of its beneficial contributions to human health. Following the general perception that naturally occurring antioxidants are better than most synthetic antioxidants, plant materials have been widely used as natural organic compounds. Curcumin has turned out to be among the most promising due to its wide range of activities[1]. This spice is the usual source of curcumin, a powerful anti-inflammatory compound. Not only do the Indian people believe in the long-term medicinal power of curcumin, but it is also used as part of the wider alternative medicine practice. It has been identified as a traditional topical remedy for a variety of conditions and when used regularly, one can also learn about the long-term protective effect of turmeric in some forms of cancer[2]. Although daily use of the spice would have you believe in its therapeutic and antioxidant capacities, the absorption of low doses could not directly account for their therapeutic effects[3]. The research has identified that the bioavailability of curcumin is extremely poor because it cannot completely dissolve in water. Consequently, curcumin possesses potential low permeability through cell membranes, as it is recognized as a substrate for transporters that help remove toxins and waste products from cells[4,5].

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Definition and sources: Curcumin, a polyphenol of the *Curcuma longa* plant, is the main component, ranging from 2 to 7% of turmeric. The majority of curcumin's health benefits are related to its antioxidant and anti-inflammatory actions[6]. The various health benefits associated with curcumin are a result of its ability to modulate multiple signaling molecules, such as cytokines, growth factors, and transcription factors. Botanical sources provide a rich diversity of chemical structures. The phytonutrients include carotenoids, flavonoids and related phenolics, polyacetylenes, glucosinolates and isothiocyanates, phenols, and polyphenols, particularly flavonoids with dietary implications. Furthermore, botanicals are non-nutrient substances of plants that have been associated with decreased risk of chronic diseases[7,8].

Historical and cultural significance: In many cultures, turmeric has also had a special significance, not only as a condiment but also as a detergent and a component of religious ceremonies, apart from being used in the Ayurvedic tradition to treat many disorders. Advancements in cell culture technology have made the study of these properties in detail possible. Phytocompounds contained in turmeric, curcumin is the most active in terms of its most important properties, such as reducing the risk of different human cancers and slowing down the spread of malignant cells, protecting the liver and pancreas, ensuring cardiovascular system health, both at a preventive and a therapeutic level, optimizing digestive function, and, specifically, inhibiting various strains. More important than the protection it affords from various disorders is personalizing and prescribing curcumin to optimize its safety and support the biochemical response of the single patient[9,10].

Chemical composition and properties of curcumin: Curcumin, a yellow pigment present in turmeric, a commonly used spice in Indian cuisine, is known for its pharmacological properties. That is why it is used in Chinese and Ayurvedic medicine. The major curcuminoids present in turmeric include curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Different therapeutic antioxidants, anti-carcinogenic, anti-inflammatory, hepatoprotective, thrombosuppressive, neuroprotective, and cardioprotective effects of curcumin have been described. Recent studies suggest that it can be used as an anti-human immunodeficiency virus agent[11,12]. Curcumin is a linear diarylheptanoid, a type of phenolic compound, and is a primary coloring agent of turmeric. It is thought to exhibit many beneficial effects. However, because of its physiological instability, the application of curcumin is limited. Profiles of curcumin metabolites that appear in the blood have been clarified using different analytical methods to characterize the curcumin metabolites, but these occur at trace levels, and quantification and evaluated analyses of the pharmacokinetic patterns, with high sensitivity, are needed. Low solubility and poor bioavailability of curcumin limit its benefits and are critical issues that need to be solved[13].

Chemical structure: Chemically, curcumin is a phenolic compound formed by two aromatic rings connected by an unsaturated 7-diol chain. This chain is responsible for the molecule's planarity and structure, as it contains conjugated double bonds, forming a system of heptadien-4-one aliphatic rings. Like other so-called "solid statins", the skeleton is extended by the addition of a hydrogenated cyclohexanone ring to one side of the heptadien chain, which confers a conjugation structure similar to the one ketamine presents (Fig. 1). Curcumin has a keto group near the cyclohexanone ring, and this ketone is responsible for the acidity of the molecule, making it pH-dependent with visible absorption. The stability of the molecule is due to the hydrogen bonds formed in the solid state between the hydroxyl groups of the aliphatic chain and the hydrogen atoms of the two hydroxyl groups in the exterior aromatic rings. These compact molecules provide a yellow color to curcumin[14,15].

Bioavailability: Curcumin's bioavailability was originally called into question when pharmacokinetic studies revealed low systemic levels and tissue exposure. Curcumin is absorbed by the intestinal mucosa in rats and rapidly metabolized to curcumin-O-glucuronides and curcumin-O-sulfate. According to studies, free curcumin is scarcely detectable in plasma after rats are given 2 and 10 mg/kg dosages of curcumin. Curcumin plasma concentrations in humans were less than 0.08 or 0.05 μM for 4 g and 100 mg curcumin,

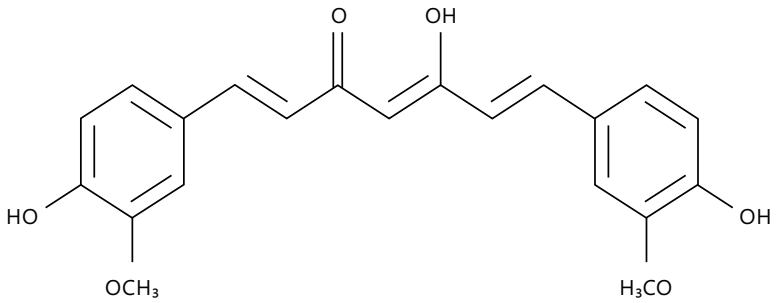

Fig. 1: Chemical structure of curcumin[14]

respectively, daily dosages, seven days after curcumin ingestion. However, refined nutrition profiling techniques on serum lipoproteins have indicated that enriched curcumin foods or curcumin supplements can deliver free curcumin to the liver and adipose tissues. In rodents, nC exhibited rapid and concentration-dependent uptake kinetics, and increases in the uptake of nC and other prominent active metabolites in rat primary hepatocytes occurred on an empty stomach or after N-acetylcysteine post-treatment. Additional optimization of drug delivery is currently being developed to improve the bioavailability and safety of curcumin for application in clinics[16-18].

Several approaches have been undertaken to overcome the limitations of the poor metabolic stability and bioavailability of curcumin for clinical uses. Dietary energy-assisted curcumin delivery formulations have been employed, showing that curcumin could be improved when used in preparation with lipids, emulsions, micelles, nanoparticles, and other analog compounds or when complexed with copolymers. For instance, curcumin treatment in the form of nanoparticles through integrin αvβ3 target delivery in prostate cancer xenografts resulted in more than a two-fold increase in plasma and tumor levels. These approaches significantly increased curcumin's tissue uptake and the upregulation of the CTs by integrin αvβ3 and other receptors, in comparison to treatments with free curcumin. It has been suggested that different dosages, time points, and modes of curcumin treatment and administration, combined with improved controlled drug delivery techniques, should be considered before the general application of curcumin diet supplementation, but curcumin formulated derivatives may serve as potential alternatives to cancer prevention and treatment[19,20].

Mechanisms of action: The pharmacological effects (anti-inflammatory, antioxidant, anticancer, and antidiabetic) of curcumin are attributed to the convergence of multiple signaling pathways at the cellular and molecular levels. Curcumin interacts directly with some different signaling compounds and modifies the activity of various genes or cellular structures, not only activating transcription factors but also inducing cell cycle arrest factors, DNMT1, SIRT1, and MTL, as well as activating BRCA1, which has a tumor suppression function. Other reports showed that curcumin can block the activation of certain osmoregulated genes. Over the past five years, the development and evolution of cancer cells have remained poorly explained. The mechanisms nature uses to perform multiple layers of regulation and the complexity of the interconnections are only now being discovered[21,22].

The JAK/STAT pathway is one such pathway that plays a critical role in the regulation and activation of gene expression related to immune response, apoptosis, cell cycle, and stem cell maintenance, and presents a major signaling function in immune cell communication and compass adjustment. Targeting STATs with curcumin provides a new strategy for anticancer drug development. It could also be useful to select appropriate JAK inhibitors for other diseases. Data showed that curcumin inhibited the phosphorylation of STAT1 and STAT3, possibly by acting through the suppression of the JAK/STAT pathway. Control experiments with a blocker showed that curcumin inhibited the expression of Hsp90 and

the phosphorylation of Akt. Moreover, a curcumin analog was found to effectively target STAT3, with effective antitumor activity in both *in vitro* and *in vivo* models. In addition, the Janus kinase (JAK) inhibitors block STAT3 activation and exhibit therapeutic antitumor effects, indicating that the inhibition of STAT3 signaling might be a promising therapeutic approach for treating aggressive neuroblastoma[23-25].

Anti-inflammatory effects: Substantial evidence has demonstrated that curcumin reduces acute and chronic inflammation by inhibiting the activation of cyclooxygenase-2, 5-lipoxygenase, and inducible nitric oxide synthase. Therefore, this compound has been investigated for the treatment of various inflammatory diseases, such as cardiovascular diseases, obesity, diabetes, arthritis, and renal diseases. The inflammation-reducing functions of curcumin are mediated by several mechanisms, including negatively regulating the signal transduction of NLRP3 inflammasomes, the production of cytokines and chemokines, the secretion of granules from mast cells, the infiltration and polarization of macrophages, and nitric oxide synthase, reactive oxygen species, and lipoxygenase, the expression of adhesion molecules, and apoptosis, among others. Recently, several studies developed curcumin preparations with modifications to promote the bioavailability of curcumin *in vivo* for anti-inflammatory or other health benefits[9]. Anti-inflammatory agents from natural products are usually safer and have fewer side effects than glucocorticoids. The spice turmeric, derived from the rhizomes of the plant *Curcuma longa*, has been widely used in food preparation and medicine for different kinds of diseases, especially as it shows an outstanding anti-inflammatory effect. The major chemical component in turmeric is curcumin, which accounts for 2-9% of most turmeric preparations. The therapeutic uses of curcumin are based on several beneficial properties, including antioxidant, anti-tumor, anti-inflammatory, anti-allergic, and other health benefits, which were obtained from numerous *in vitro*, *in vivo*, and randomized controlled trials. Particularly, curcumin was considered to be an NLRP3 inflammasome inhibitor for the essential pathological mechanism in most diseases. In addition, the unique bioactivities of curcumin were attributed to its low molecular weight and the potent hydrogen donors on the phenol groups within its chemical structure. The excellent anti-inflammatory effect of curcumin was reviewed[26-28].

Antioxidant properties: The antioxidant properties of curcumin have been investigated in many *in vitro* and *in vivo* studies, showing that it can attenuate oxidative damage and thereby protect different tissues and cell types from a wide range of harmful pathologies. Although curcumin is known for its complementary and distinct antioxidant properties, it is a pro-oxidant phenolic compound. Nonetheless, curcumin's pro-oxidant property is its greatest antioxidant property, since it can act on cis-diols and α,β-unsaturated carbonyl groups, and it can also generate reactive oxygen species. Despite this, curcumin can also generate reactive oxygen species originating from mitochondrial production in cells that are treated with high concentrations of curcumin. However, at low concentrations, it can increase the formation of endogenous cellular antioxidants, and it has been reported to improve hypoxia in pancreatic islets, reduce oxidative stress biomarkers in ischemic brains, and suppress adjuvant-induced arthritis in rats, while also taking the seedling quality loss in mung beans into account, as well as hepatic damage induced by the fungal toxin aflatoxin as a preventative and curative treatment[29,30].

It has been demonstrated that curcumin can suppress malondialdehyde and protein carbonyl levels, as well as inhibit increased levels of superoxide dismutase, glutathione, and catalase, suggesting that these compounds help to restore the pathology by modulating the endogenous antioxidant system. However, some studies demonstrate that curcumin acts as a pro-oxidant by generating singlet oxygen and reactive oxygen species concentrations. This property has shown that curcumin can activate the signaling function by targeting cysteine and essential metabonomics, which contain the nucleophilic sulfur center, inducing complete depletion. Due to these actions, curcumin can inhibit important major enzymes that react with cysteine-containing targets and succumb more rapidly to oxidative modifications. This is consistent with the findings that curcumin treatment decreased GSH levels in lipid-peroxidizing spermatozoa mitochondria[31,32].

Health benefits of curcumin: Curcumin is known for its potential health benefits, including anti-inflammatory and antioxidant activities. However, the reported bioavailability of curcumin is low. Human intervention studies have demonstrated health benefits with around 1.8 g/day of the efficacious dose of oral curcumin intake. These benefits include anti-inflammatory effects in different metabolic, inflammatory, and other associated diseases. The doses of curcumin used in these studies might exert protective effects through the anti-inflammatory, antioxidant, and antiangiogenic activities of curcumin, and the doses could be achievable through a reasonable diet or adjunctive dietary supplementation. The concentrations of curcumin could be achieved in target tissues following regular curcumin intake at around the efficacious intake dose of 1.8 g[33-35].

Curcumin has several functional properties, the compound can suppress inflammation and alleviate symptoms of osteoarthritis and rheumatoid arthritis. Curcumin inhibits the acute and chronic inflammatory responses through the inactivation of the nuclear factor-κB activation pathway. Clinical studies demonstrated that curcumin supplementation decreased systemic pro-inflammatory cytokines in patients with several chronic diseases, including metabolic syndrome, coronary artery disease, and rheumatoid arthritis. In addition to its anti-inflammatory activity, curcumin could alleviate allergic inflammation. The inhibition of IL-4, IL-5, and IL-13 supports that curcumin may alleviate the production of the regulatory T-cell phenotype[36].

Pain management and anti-inflammatory effects: The pain management and anti-inflammatory effects of curcumin. Pain is the most common reason people seek medical treatment, and pain relief has long been the most common use of medicinal medications. Pain and inflammation often coexist and are caused by various conditions and tissue types; diseases associated with pain and inflammation can range from headaches to those concluding with death[37]. Although acute pain is an important adaptive protective mechanism in response to injury, in many pathophysiological conditions, chronic and excessive inflammation and pain reduce the quality of life of individuals. The most common diseases associated with inflammation and pain, including diabetes, cardiovascular diseases, and cancer, are also the causes of the world's most common chronic diseases that have not been effectively controlled by available treatment methods and have a huge impact on the world economy. Epidemiological, clinical, and laboratory studies revealed that inflammation and pain have a close relationship and share common cell-signaling mediators[38].

Data from experimental studies have also demonstrated the effectiveness of anti-inflammatory agents in treating acute pain as well as in controlling acute and chronic inflammation. The use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) is commonly used for pain relief and inflammation in the clinic to control symptoms associated with inflammation and pain by blocking the activities of cyclooxygenase, an upstream enzyme in the arachidonic acid-catabolizing pathway. However, NSAIDs may harm the stomach lining and cause undesirable side effects. Therefore, it is important to develop new agents that are both effective and safe to control symptoms and treat the root causes of inflammation and pain. Data from *in vitro*, *in vivo*, and small clinical trials that were initially published by investigating the pharmacological effects and the mechanisms underlying curcumin's anti-inflammatory activities in inflammation-associated diseases suggest that curcumin has the potential to be a safe and effective alternative treatment to NSAIDs[39]. The fact that curcumin is a safe and effective therapeutic agent for a variety of diseases has sparked an interest in researching its mechanisms as well as its chemotherapeutic potential by researchers worldwide. More than 40% of clinical trials that focused on curcumin also investigated its anti-inflammatory activities and the associated molecular targets. These trials reveal curcumin's effects on inflammation in many human disorders, such as metabolic

syndrome, arthritis, neuropathic pain, cardiovascular diseases, and cancer[40]. However, the effectiveness of curcumin in treating a particular disease is still under debate, since ingesting curcumin provides a low concentration of the agent in the plasma and a very low bioavailability. To overcome these limitations, several new curcumin formulations, such as nanoparticles, liposomal encapsulated curcumin, complex curcumin, microemulsion-based curcumin, and curcumin phospholipid complexes, are being used in preclinical and clinical trials to enhance the bioavailability and plasma concentration of curcumin from oral administration. However, there is still no consensus on the development of a method that delivers highly bioavailable curcumin. In the present review, newly developed curcumin compounds will not be discussed. Instead, we will summarize and compare the results of the use of the free form of curcumin to enable the accurate demonstration of its therapeutic efficacy when it interacts with cell membranes[41,42].

Cardiovascular health: Curcumin has been shown to improve vascular function, reduce oxidative stress, decrease inflammation, and modulate plaque vulnerability, while potentially attenuating high blood pressure in the process. These effects are achieved through a medley of molecular actions in the body, including activation of AMP-activated protein kinase, suppression of angiotensin II, and inhibition of NF-κB. Arguably the most striking application of curcumin on cardiovascular health is its effect on the gut-heart axis, where curcumin has been demonstrated to reduce cholesterol gallstone formation, improve vascular function, and restore efferocytosis in heart failure patients with a history of cholecystectomy. These incredible vascular benefits have been further bolstered by the observation that curcumin can reduce neuritis resulting from chemotherapy[43,44].

Cardiovascular diseases represent the main cause of morbidity and mortality worldwide, causing approximately 17.7 million deaths in 2015. Epidemiological evidence has indicated a relatively low incidence of cardiovascular diseases in people from India, the Southern part of Asia, and Japan. The relative protection against cardiovascular diseases has been associated with the regular use of curcumin in the diet, being part of the curry spice that is normally ingested in these populations. Due to the synthetic biology of this molecule, curcumin has been demonstrated to possess effective pharmacological activity at low micromolar concentrations in almost all cell culture and animal studies. Since 95% of ingested curcumin stays in the gastrointestinal tract, a very low amount will reach the bloodstream, with plasma levels in the nanomolar range where only its biologically inactive reduction products are dominant[45].

Digestive health: The positive effects of curcumin on the digestive system have been documented very widely. Curcumin promotes better digestion by encouraging bile production in the liver and excretion from the gallbladder to protect the liver from toxins. It also acts as a soothing agent for gastrointestinal problems, reducing stress and ensuring that the digestive system runs smoothly. It can help to relieve symptoms of gas and bloating, promote regular bowel movements, and help to maintain healthy liver function. Due to its anti-inflammatory and antioxidant properties, curcumin can work wonders for our digestive systems. It can help treat conditions such as gastritis, peptic ulcers, and other digestive disorders. Curcumin promotes gut health by nourishing the eubiotic microflora while killing the dysbiotic flora, thereby supporting normal bowel function. Curcumin has also been highlighted for its potential in the treatment of patients with inflammatory bowel diseases, including Crohn's disease and ulcerative colitis. Scientists have looked at the ability of curcumin to block many different inflammatory chemicals, including prostaglandins, thromboxanes, leukotrienes, cytokines, and more. By blocking these chemicals, the body is unable to experience inflammation, in essence relieving the gastrointestinal tract of symptoms[46,47].

Brain health and cognitive function: Chronic prenatal treatment of curcumin can facilitate spatial learning and memory in offspring rats. Because of its bioavailability, ease of use, and safety, turmeric, and its active compound curcumin have the potential to not only prevent disease but also enhance the general health and functioning of the aging population. However, consumption of curcumin, in principle, represents an approach to work synergistically with physical activity and diet, which is of particular importance for population subgroups who are unable or unwilling to engage in regular physical activity and maintain a healthy diet. Since the adult hippocampus is capable of generating new neurons which are important for memory and learning pharmacological stimulation of hippocampal neuronal growth could be essential to combat cognitive decline in old age. Besides physical exercise, diet composition is another lifestyle factor known to modulate hippocampal plasticity through adult neurogenesis. Importantly, the capacity of the adult hippocampus to generate progenitors and new neurons can be modulated by the presence of bioactive food factors in the diet. The most striking example of a dietary factor positively regulating adult neurogenesis in rodents is curcumin, a polyphenol constituent of the plant turmeric. Dietary administration of curcumin not only affects the number of newborn neurons generated in the hippocampus but also results in decreased cognitive deficits in aged animals[48-50].

Clinical studies and evidence: It is well known that curcumin possesses anti-inflammatory, cell protective, and antioxidant activities at supraphysiological concentrations because these activities were discovered in cell culture at micromolar levels. In addition, it has not been fully demonstrated in humans that physiologic doses are being metabolized to the described metabolite. However, the phase I clinical trial evaluating the pharmacokinetics and tolerability of different oral doses of curcumin in humans reported that the turmeric constituent was well tolerated at all doses administered, and following dosing, free or conjugated curcumin was detected in the plasma of subjects. It was interesting that plasma concentrations of free or conjugated curcumin at a steady state were dose-proportionately reaching systemic levels compatible with the bioactive profile observed in preclinical models. How physiological plasma concentrations of curcumin were reaching effective antiproliferative cell and colon mucosal tissue concentrations in individuals who were taking 100 mg/day, which is 5 to 10 times lower than the doses commonly used in preclinical models for disease progression, remains unclear. It is also recognized that it may be difficult to translate preclinical findings on curcumin to the clinic because chemical and biological characteristics can affect the bioavailability of curcumin. Furthermore, curcumin metabolite plasmalogens could be an effective biomarker of increased exposure[51].

***In vitro* and *in vivo* studies:** In contrast to *in vitro* studies that use the direct application of curcumin to cells or tissues, *in vivo* studies can be more informative but are more difficult and expensive. Curcumin is poorly absorbed by the body. However, this is offset by its rapid metabolism. Curcumin metabolites have been found in the blood of healthy volunteers soon after they consumed curcumin, but these levels rapidly declined to one-tenth within just 1 hr after consumption[52,53]. Therefore, details of the *in vitro* studies on the potential benefits of curcumin and its metabolites are significant. The effects of curcumin in such studies include anti-inflammatory activity, antioxidant activity, antiviral activity, and anticancer activity. Activities are found that inhibit the production and synthesis of enzymes, proteins, lipids, and other additional substances that are essential for instances of chronic, allergic, urinary, skin, and bowel inflammation. Cells involved are neutrophils, eosinophils, monocytes, macrophages, mast cells, platelets, and dendritic and T lymphoid cells. Curcumin can also suppress the immune response to delay rejection of transplanted organ or tissue grafts, decrease neurodegeneration following exposure to methyl-4-phenyl-1,2,5,6-tetrahydropyridine or transgenic AβPPswe mice, and block or eliminate emissions from hypoxia-activated glioma cells[54-56]. Furthermore, when investigating the effect of aqueous and alcoholic extracts of turmeric rhizomes on various fungi isolated from stored wheat seeds, chemical detection revealed that the aqueous turmeric extract contains flavones, saponins, and terpenes. The alcoholic turmeric extract includes flavones, resins, saponins, and alkaloids, which are active compounds with antifungal properties[57]. According to a recent study, adding curcumin to cornstarch films enhances their mechanical and antibacterial qualities and releases curcumin into the films' aqueous solutions[58].

Human clinical trials: In addition to *in vitro* experiments, curcumin is shown to increase levels of decreased antioxidant enzymes, and it is also able to inhibit inflammatory pathways. From its anti-cancer ability to its protective ability against various non-communicable diseases or risk-related symptoms, curcumin is proven to have a wide range of health effects. These health benefits of curcumin make it widely studied in clinical trials to investigate its efficacy for human health conditions. Some of the evidence on the positive effects of curcumin on human health comes from clinical trials with promising results; others are underway. So far, there are unique clinical trials on curcumin, respectively. According to the results of the database search, by using the keyword curcumin, the highest percentage of human clinical trials are designed to be related to cancer prevention and treatment in different disciplines or organ sites. Following that, those clinical trials, are related to other diseases such as depression, traumatic brain injuries, diabetes, head and neck cancer, oral dysplasia, oral mucositis, colon cancer, and effects of indoor fungi on human health, through testing the toxicity of synthesized curcumin compounds in healthy volunteers has also started, this compound is published in very low doses and has no therapeutic effect[59,60].

Safety and side effects of curcumin: The curcumin, the active ingredient in the dietary spice turmeric, has often been considered responsible for turmeric's medicinal properties, which include anti-inflammatory, anti-cancer, antioxidant, anti-arthritic, anti-amyloid, anti-aging, and anti-neurodegenerative effects. However, curcumin is not a major component of turmeric: Curry powder contains 3% curcumin, and other turmeric powders contain 1% curcumin. Although some of curcumin's medicinal effects have been confirmed by experiments, others have not. Nowadays, more than 120 clinical trials are completed or are ongoing to examine the safety and efficacy of curcumin in various conditions, including the assessment of its preventive effects against the development of many chronic conditions[61-63]. Generally, curcumin is safe for most adults when used at low doses for up to 12 weeks. You must be cautious about using curcumin if you are pregnant, as it may stimulate your uterus or put your pregnancy at risk. Moreover, it has been noted that the consumption of excessive amounts of turmeric can lead to an upset stomach, nausea, vomiting, or diarrhea, and supplement side effects may include skin rashes and hives, along with other signs of allergic reactions. Consult your healthcare provider about possible interactions with drugs you're taking or problems of overdosing. Keep in mind that health considerations are primarily associated with curcumin supplement consumption, not with fortified beverages or food. Furthermore, the safety of curcumin with certain underlying health conditions has not been established. Remember that to avoid possible turmeric and curcumin disadvantages, you should always follow the given guidelines[64,65].

Dosage and toxicity: Unlike drugs, the deficiency of curcumin in the average diet suggests that we should aim to get the desired health benefits of this compound. For that, a specific scientific approach is required to define the corresponding dosage. For multiple health benefits in adults, a curcumin supplement should contain at least 25 mg of complexed botanical curcuminoids. For maximum antistress support, a 50 to 100 mg dosage of curcumin once to twice per day is probably optimal. Long-term experienced holistic physicians believe that doses of curcumin should be less than 25 mg a day. For children seven years old and older, the recommended dosage for a 95% botanical complex is 7-10 mg per day. While the acute clinical studies have not had any adverse effects on children, infants, and weaker patients, the risk and benefit assessments and the optimum doses for varying patient subgroups remain undetermined[42].

A refined curcumin complex was tested for acute, subacute, and single-administration toxicity in rats. The complex was nontoxic with significant anti-inflammatory activities at a nontoxic dose. Its high efficiency and safety suggest its use as a drug with anti-inflammatory action. Wild-type mice fed a diet containing 3% curcumin had a significantly lower volume of adipose tissue than the unsupplemented group,

indicating that curcumin possibly increased thermogenesis and altered the brain-adipose axis. Too many curcuminoids result in very limited bioavailability because of the very low absorption rate following oral administrations in humans. The degrading metabolic mechanisms are briefly described in the present overview. Because curcumin is also believed to act as an iron chelator and its antioxidant activities reach upper limits at higher concentrations, overdoses of pure curcumin can lead to a potentially fatal condition known as iron deficiency anemia accompanied by hemorrhagic symptoms. These nutritional concerns help explain why the anti-inflammatory and anticancerous effects for the average concentration at a cellular level could be produced with only a higher concentration of curcumin *in vitro*[53,66].

Interactions with medications: Numerous *in vitro* studies have indicated curcumin to have a strong inhibitory effect on drug-metabolizing enzymes that metabolize a wide range of medications, including nitrates, phenylbutazone, paracetamol, phenytoin, warfarin, and theophylline. Because of this, it is hypothesized that while taking curcumin, one might reduce the capacity of the liver to metabolize medications that are taken. A recently conducted double-blind randomized trial aimed at assessing the interactions between curcumin and paracetamol found no significant effect on the efficacy of paracetamol, though a steeper rise in plasma levels for both paracetamol and its metabolite was witnessed in the presence of lower curcumin concentration. Very recently, emerging phase I clinical trials have established doses of 8 g/day for three months to be associated with curcumin levels of 11,600 ng/mL in human plasma. Such high levels, which can potentially interact with drug-metabolizing enzymes, are not easily attainable after usual curcumin ingestion. More trials using both single and repeated doses need to be conducted on curcumin to elucidate its interaction pathways with some commonly prescribed drugs, such as those needed for controlling diabetes, cancer, and drugs used to treat cardiovascular-related issues[67,68].

Future research and potential applications: Curcumin, which is extracted from the rhizome of the plant *Curcuma longa* L., has received wide attention mainly due to its chemopreventive and chemotherapeutic potential, but also due to its increased consumption associated with beneficial health effects. The safety of curcumin following prolonged oral intake, the maximum tolerated dose after repeated oral administration, and evidence for specific therapeutic properties in humans with potential curcumin use have been reported. This narrative review presents experimental and clinical evidence that suggests that curcumin has a wide range of biological actions, which are not fully exploited, with a favorable safety and tolerability profile, making it an attractive compound for future clinical development, particularly for cancer chemoprevention, anti-inflammatory, and antiviral drug development. However, future experimental and extensive translational research, supported by an efficient, selective, and quantitative human pharmacokinetic assessment, is required[69,70]. The noticeable increase in the number of preclinical trials with curcumin over the last few years could perhaps lead to a robust amount of information essentially on its therapeutic efficacy. Nonetheless, major advances with curcumin have not been paralleled. Future experimental research should consider an idealized arduous development or preclinical investigation, carefully designed to identify not just tumor growth inhibition, but also the capability of treatments to increase survival, deter metastases, and lessen adverse events associated with infection and cancer in patients, which could be achieved by using translational sophisticated models. Such models have been demonstrated in other studies and will present critical platforms that will assist future evaluation of the overall potential of curcumin in fighting off complex diseases that rely on reducing excessive inflammation, such as infections and cancer. These models might even have the capability to predict the pharmacokinetics and pharmacodynamics of curcumin in cancer patients in a highly desired attempt to associate the preclinical and clinical outcomes. Hence, a coordinated effort among the preclinical researchers is essential to guarantee that preclinical explorations have this focus and to circumvent studies that are incapable of translating their findings and bringing the clinical impact to fruition in patients[71,72].

Emerging areas of study: A growing body of work seeks to elucidate curcumin's potential health benefits via mechanisms that are not yet well understood and draws upon techniques such as liposome systems to deliver curcumin effectively. In an investigation that builds off the observed anti-cancer properties of curcumin, researchers sought to determine the efficacy of curcumin (in a liposome system) to target the mitochondria, the structures of the cell that regulate the health and metabolic activity of the cell, to encourage selective apoptosis of lung cancer cells. In multi-drug-resistant Acute Myeloid Leukemia (AML) models, curcumin was found to sensitize cancer cells, therapeutically widening the number of treatment choices for a condition associated with a poor prognosis. Curcumin liposomes were also used as adjuvant therapy to protect against cognitive impairment after anesthesia exposure. The cognitive performance impairment of aged rats was ameliorated through this therapy, with a reduction in apoptosis, as curcumin reduced the harmful oxidative stress effects and activation of the PPARγ pathway in the hippocampal neurons[73,74].

The anti-cancer properties of curcumin have also been the subject of other investigations. Researchers used curcumin nanoparticles to target the microsomal prostaglandin synthetase 1 (mPGES1) found in cancer tumors; mPGES1 inhibitors offer the potential for more effective anti-cancer treatment, and hence this approach could lead to improved treatment of cancer. Similarly, repeated cycles of nanoparticle-mediated inhibition of gelatinase B/mMP-9 are thought to have potential clinical utility; as with many curcumin-based therapies, however, the research is still at the in vitro stage. Although the impact of curcumin on cancer cells has been the object of significant study, selected protection of non-tumorigenic cells from associated side effects has also been investigated through the use of cyclodextrin-based delivery methods to improve curcumin solubility. Such methods allow much more controlled and targeted delivery to the cancer cells, leading to fewer cytotoxic side effects in healthy cells[75,76].

Combination therapies: It has been widely recognized that combination therapy may improve the therapeutic effectiveness of natural products. In the course of phytochemical, pharmacological, and clinical research on curcumin's efficacy and its bioavailability constraints, curcumin has been discovered to exhibit a synergistic effect with several common anticancer and anti-inflammatory chemotherapeutic agents, such as camptothecin, 5-fluorouracil, doxorubicin, paclitaxel, and vinorelbine in the treatment of human cancers. Curcumin also enhances the sensitivities of various treatment-resistant cancer cells to common chemotherapy agents, such as cisplatin-resistant and anisomycin-resistant human ovarian cancer cells, tamoxifen-resistant human MCF-7 breast cancer, and adriamycin-resistant hepatocellular carcinoma. At the same time, curcumin also reduces the toxic side effects of a vast number of medicines, such as doxorubicin, fosters the expression of P-glycoprotein against apoptosis, and boosts tumor apoptosis. In the treatment of cardiovascular disorders, curcumin demonstrates an improvement in the cardioprotective effect of chemical drugs within combination therapy by disclosing a synergistic protective effect. When administered in a variety of human disease therapies, such as malignant tumors, neurodegenerative conditions, and cardiovascular diseases, a synergistic effect with curcumin and other compounds from natural products can also be observed. Familiar compounds from natural products with curcumin, such as epicatechin, resveratrol, and other flavonoids, with or without working in combination for the treatment of various diseases, exert a significantly improved therapeutic effect. Curcumin's combination with natural products such as epicatechin, silymarin, soybean, lycopene, and rosemary also presents good chemopreventive activities[77-79].

CONCLUSION

An impressive number of publications clearly show that curcumin offers health benefits to the human body and can be considered a supplement or in combination with other compounds to prevent, alleviate, and cure various diseases. However, like any other compound, the benefits and possible risks of curcumin need to be carefully considered for each person individually to evaluate the most appropriate treatment.

Lipid solubility and metabolism by enzymes are important for the bioavailability of curcumin. Therefore, more work is needed to increase the bioavailability of curcumin, which may improve its therapeutic effect. Lastly, despite the growing number of promising results, the true effectiveness and use of this compound remain a challenge, and as a field, we hope to accumulate more quantitative data to provide more solid information on this supplement.

SIGNIFICANCE STATEMENT

The botanical substance curcumin functioned historically both as a food seasoning and medical compound, which also served to color foods. People currently acknowledge the multiple health benefits of curcumin as scientific research about the substance has progressed. The traditional food application of "golden spice" continues, yet modern technological methods enable curcumin to generate different food-oriented applications and health products. The world has developed a broad interest in curcumin because of its various health benefits, which stem predominantly from its anti-oxidative and anti-inflammatory nature. When piperine or similar pharmaceuticals are mixed with curcumin their levels of absorption into the body increase. Modern research indicates curcumin assists human beings in managing both oxidative and inflammatory disease states and metabolic syndrome conditions alongside arthritis anxiety, and hyperlipidemia disorders. Active individuals benefit from curcumin supplements by enabling better pain management during recovery following exercise, which enhances both performance and the control of exercise-induced inflammation. The supplement delivers medical advantages to people without defined medical conditions when used in low doses.

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