Review

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Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability

Mohamed E Abd El-Hack,[a] Mohamed T El-Saadony,[b] Ayman A Swelum,[c] Muhammad Arif,[d] Mahmoud M Abo Ghanima,[e] Mustafa Shukry,[f] Ahmed Noreldin,[g] Ayman E Taha[h] and Khaled A El-Tarabily[i,j*]

Abstract

Turmeric (*Curcuma longa* L.) is a spice utilized widely in India, China, and Southeast Asia as an aromatic stimulant, a food preservative, and coloring material. The commonly used names of turmeric are castor saffron, turmeric, and saffron root. Turmeric is a yellow–orange polyphenolic natural substance derived from *C. longa* rhizomes. It has been used to treat common inflammatory diseases, tumors, biliary diseases, anorexia, cough, topical wounds, diabetic injuries, liver disorders, rheumatism, and sinusitis. Extensive studies on the biological properties and pharmacological consequences of turmeric extracts have been conducted in recent years. Curcumin, the primary yellow biocomponent of turmeric, has anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antibacterial, antiprotozoal, antiviral, antifibrotic, immunomodulatory, and antifungal properties. Defense assessment tests showed that curcumin is tolerated well at high doses, without adverse effects. Thus, curcumin is a highly active biological material with the potential to treat different diseases in modern medicine. This review article focuses on curcumin's biological characteristics. The most popular methods for curcumin encapsulation are also discussed. Several effective techniques and approaches have been proposed for curcuminoid capsulation, including nanocomplexing, gelation, complex coacervation, electrospraying, and solvent-free pH-driven encapsulation. This review also highlights curcumin's chemical properties, allowing the readers to expand their perspectives on its use in the development of functional products with health-promoting properties.

Keywords: bioavailability; biological activity; curcumin; electrospraying; gelation; nanocomplexation

INTRODUCTION

With the advent of drug resistance and the adverse effects of chemosynthetic drugs, the interest in medicinal herbs and plant extracts/metabolites has increased, both among the general public and researchers worldwide.[1-3] Turmeric (*Curcuma longa* L.) is a perennial herbaceous herb with yellow flowers, belonging to the Zingiberaceae family (Fig. 1). It grows in the tropics and subtropics of Asia, especially in India, China, Indonesia, Jamaica, Peru, and Pakistan. The plant's primary roots under the earth are shaped like eggs and pears, and the lateral roots are shaped like tubers (rhizomes).[1]

The tubers are filled with yellow pigments, which originate from *C. longa* tubers.[4] The pigment curcumin (bis-α,β-unsaturated β-diketone) is the main derivative of turmeric and is a bioactive, hydrophobic, and polyphenolic compound, which has been used to treat various ailments.[5,6] Curcumin is also a natural antioxidant and is used as an aromatic (it has a hot and/or bitter taste) and natural coloring material in food products.[7,8] It is chemically a diarylheptanoid and comprises two aromatic rings with two hydroxyl and two methoxyl groups (Fig. 1). The aliphatic unsaturated carbon chain, with two carbonyl groups centered at C-3 and C-5, joins the phenolic ring.[8,9]

* *Correspondence to: KA El-Tarabily, Department of Biology, College of Science, United Arab Emirates University, 15551 Al-Ain, United Arab Emirates. E-mail: ktarabily@uaeu.ac.ae*

a *Department of Poultry, Faculty of Agriculture, Zagazig University, Zagazig 44511, Egypt*

b *Department of Agricultural Microbiology, Faculty of Agriculture, Zagazig University, Zagazig 44511, Egypt*

c *Department of Theriogenology, Faculty of Veterinary Medicine, Zagazig University, Zagazig 44511, Egypt*

d *Department of Animal Sciences, College of Agriculture, University of Sargodha, Sargodha, Pakistan*

e *Department of Animal Husbandry and Animal Wealth Development, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt*

f *Department of Physiology, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh 33516, Egypt*

g *Department of Histology and Cytology, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt*

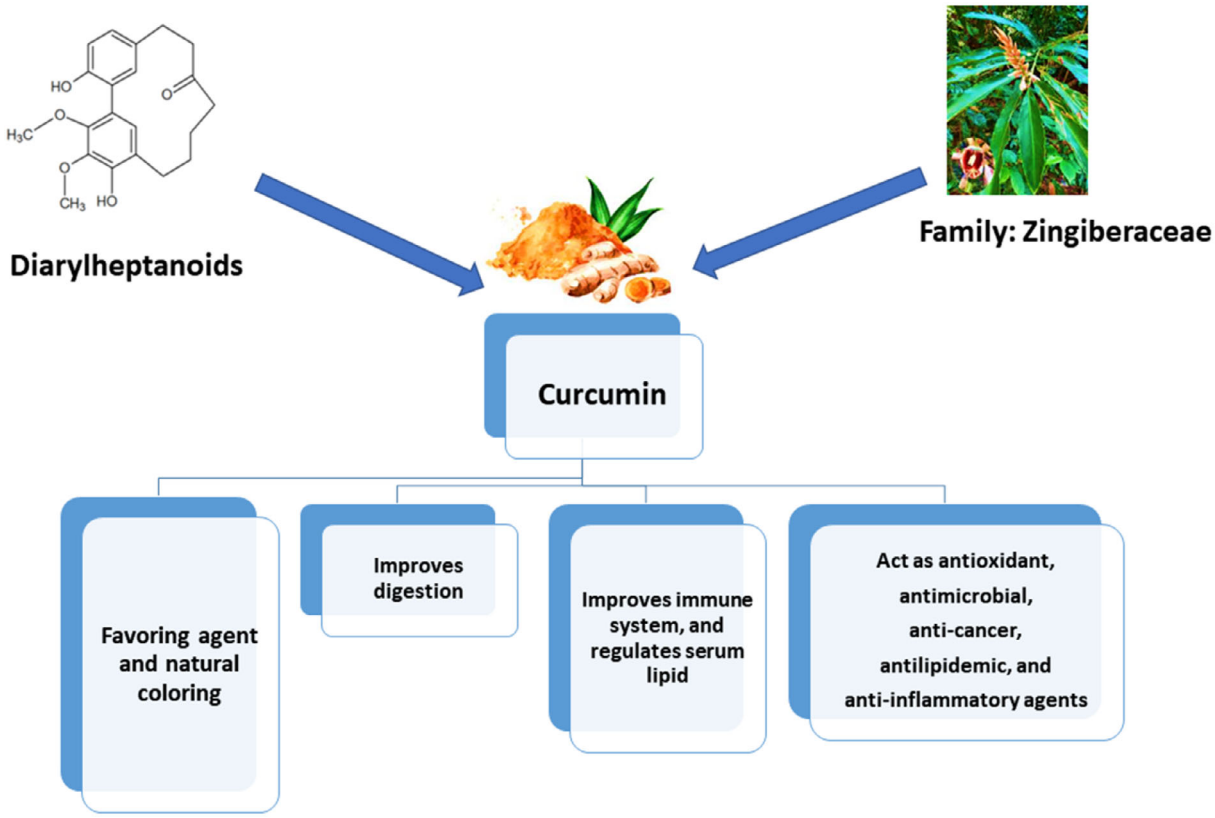

Figure 1. Origin and chemical composition of curcumin, and its important functions.

Various experiments have been performed to study curcumin's biofunctional properties (Fig. 1). These studies have documented several biological and pharmaceutical properties, including antioxidant, anticancer, antitumor, anti-inflammatory activity, and antiphlogistic and antilipidemic effects.[10-12]

Interestingly, curcumin was selected by the National Cancer Institute of America as the third generation of cancer chemoprevention agents, which widens its applications in various areas (e.g., food industry and medicine).[12] Moreover, curcumin has been found to block nuclear factor kappa B (NF-κB), which regulates inflammation, cell propagation, apoptosis, and cell resistance.[13,14] Despite many proven health benefits, the use of curcumin in food and medicines is still limited and faces many challenges. The low water solubility of 11 ng/mL of curcumin is the key factor restricting its use.[5] Curcumin also has a high rate of metabolism and low gastrointestinal absorption in the body.[15,16] It may be damaged during processing and under gastrointestinal conditions, thus reducing its bioavailability.[17] However, curcumin is stable in systems with low physiological pH and acidic conditions but breaks down quickly and has poor photostability under alkaline conditions.[8,17,18]

To enhance the curcumin solubility, durability, and bioavailability, different methods are used such as encapsulation in various carriers.[13,19] This encapsulation technique can be used to preserve and distribute curcumin.[13,19,20]

This review focuses on curcumin's chemical properties, and its antiviral, antibacterial, anti-inflammatory, and antioxidant activity. It will also address curcumin's neuroprotective, antidiabetic, and angiogenesis activity in humans and animals, and discuss different methods to improve curcumin bioavailability through nanocomplexation, gelation, complex coacervation, and electrospraying, which will allow researchers to expand their perspective on curcumin application in the development of functional health-promoting products.

HISTORY OF TURMERIC

Old scriptures described turmeric as an essential plant.[8,10] Turmeric is described as 'Indian saffron' and has been utilized for more than 4000 years. It is also prevalent in ancient Indian medicine, Ayurveda. Indeed, the use of turmeric as paint, a condiment, and medicine has spread to many countries. Turmeric is called *haridra* in Sanskrit and is used as a flavoring agent with digestive properties.[21]

Turmeric is highly regarded by the Hindus and, interestingly, is given in several temples as 'Prasad' (usually, a food offering made to God, which is later distributed to devotees). The great ancient Indian doctors have documented the various uses of turmeric.[21]

Dioscorides, a Roman Army Greek scientist, also spoke of turmeric. In the 14th century, Europeans discovering the Asian continent took turmeric to the West. For 4000 years, the crushed and

h *Department of Animal Husbandry and Animal Wealth Development, Faculty of Veterinary Medicine, Alexandria University, Edfina 22758, Egypt*

i *Department of Biology, College of Science, United Arab Emirates University, 15551, Al-Ain, United Arab Emirates*

j *Harry Butler Institute, Murdoch University, Murdoch, 6150, Western Australia, Australia*

powdered turmeric rhizome was commonly used in Asian cooking, medicine, cosmetics, and fabric dyeing. Around 40 *Curcuma* species are native to India, suggesting their Indian origin.[21] However, approximately 70–110 species have been recorded in tropical Asia, and the most diverse species are found in India, Myanmar, and Thailand. Certain species are distributed in China, Australia, and the South Pacific, and others are cultivated in all tropical regions.[21]

CURCUMIN

Curcumin was first isolated from turmeric in 1815 and was identified as diferuloylmethane (curcumin) in 1910.[22] The curcumin preparations currently available contain approximately 77% diferuloylmethane (curcumin); 18% of them contain demethoxycurcumin, and 5% of them contain bisdemethoxycurcumin. Turmeric is composed of '3–5%' curcuminoid. However, curcumin is responsible for the main biological activity of turmeric.[22]

Curcumin and two other related compounds, bisdemethoxycurcumin and dimethoxy curcumin, are present in the plant, at around 77%. These compounds are diarylheptanoid compounds.[23] Furthermore, these three compounds are curcuminoids.[23]

Curcumin is a yellow–orange crystalline compound used as a food additive and coloring. Although it is almost insoluble in acidic or neutral pH water, it is soluble even in strong acidic solvents (e.g., glacial acetic acid) and in polar or nonpolar organic solvents.[24] The melting point of curcumin is 183 °C; its molecular formula is $C_{21}H_{20}O_6$, and its molecular weight is 368.38 Da. Most studies on curcuminoid compounds have been conducted on animals (mice, rats, or dogs), and there are few publications on humans.[25]

Clinical studies have shown that curcumin is healthy for humans, even at large doses, but its medicinal application is extremely poor because of its limited bioavailability.[26] Consequently, preclinical trials have stated that curcumin concentrations in plasma and target tissues are low because of their high metabolism rates.[27] Furthermore, curcumin has been used as an anti-inflammatory agent in traditional Indian and Chinese medicines for centuries.[27]

Several studies in recent years have shown that curcumin has anticarcinogenic, antioxidant, immunomodulatory, and antiangiogenic effects.[28] However, many studies found that the potentially positive impacts of curcumin on the prevention and treatment of numerous illnesses are reduced because of its imbalance under physiological conditions that hinder its therapeutic benefits.[28] Its key structural problems include active methylene and *p*-diketone fragments, which contribute to curcumin's poor absorption and rapid metabolism.[28]

Curcumin also focuses on many signal molecules and functions at the cellular scale, promoting several health benefits in many research studies. Thus, curcumin supplements have various therapeutic benefits owing to their antioxidant and anti-inflammatory properties.[29] Its poor bioavailability is one of the greatest issues in curcumin ingestion, mainly because of poor absorption, fast metabolism, and rapid removal, even with the benefits provided by its anti-inflammatory and antioxidant mechanisms.[30]

Different compounds have been studied to boost curcumin bioavailability using different methods. Some methods were designed to inhibit the curcumin metabolism to make it more bioavailable. For instance, piperine, a known bioavailability enhancer, is the major effective component for black pepper and increases curcumin bioavailability by 2000%. The problem of low bioavailability therefore seems to be solved by incorporating agents such as piperine to improve bioavailability and build a curcumin complex.[30] The synthesis of synthetic analogs can be one of the methods to improve curcumin's biological activity. Other techniques considered to increase curcumin's natural action include the use of adjuvants, nanoparticles, liposomes, micelles, and phospholipid complexes.[30] Adjuvants were selected according to their ability to prevent the rapid metabolism of curcumin by interacting with enzymes that catalyze curcumin metabolism. All other formulations were referred to improve curcumin absorption in the tissues.[30]

Nanoparticles may provide greater penetration into the membrane barriers because of their small scale. In addition to their size, their ability to modify specific mechanisms makes them excellent drug carriers. Liposomes, micelles, and phospholipid complexes can minimize curcumin hydrophobicity and interact with membrane components to improve membrane barrier permeability. Moreover, curcumin's water solubility can be increased by 12 times with the use of heat.[31]

Curcumin is recognized and used for many possible health benefits worldwide. For example, turmeric, which contains curcumin, has been used in curries, served as tea in Japan, used in cosmetics in Thailand, used in China, served in drinks in Korea, used as an antiseptic in Malaysia, used as anti-inflammatory agent in India and Pakistan, and used in mustard sauces, cheese, butter, and chips in the USA.[30]

Curcumin capsules, tablets, ointments, power drinks, soaps, and cosmetics are some of the several types of products available. Curcuminoids are classified by the United States Food and Drug Administration as 'generally recognized as safe' products, and clinical trials have shown strong tolerability and safety profiles at doses ranging from 4000 to 8000 mg.[30] The major effects of curcumin are summarized in Table 1.

BIOLOGICAL PROPERTIES OF CURCUMIN

Curcumin has many health benefits, biological functions, and therapeutic, antioxidant and anticancer effects.[56] Its antioxidant activity is controlled by different enzymes, such as catalase, superoxide dismutase, and glutathione peroxide (Fig. 2). It exhibits ten times more antioxidant activity than vitamin E, which is a common antioxidant agent.[57] Its antioxidant property is attributed to the 1.3-diketone system and phenyl ring with a methoxyl group.

Curcumin can prevent diabetes, heavy metal absorption, and hypertension through its antioxidant, chelating, and inhibitory effects on hypertension.[6,57] Furthermore, curcumin and many of its complex forms triggers glutathione *S*-transferase and inhibits free radical generation, thereby acting as a free radical scavenger, including as a scavenger of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS), releasing antioxidants to prevent lipid peroxidation.[4]

The chemical composition of curcuminoids also accounts for their antioxidant function.[6] Several reports have shown that they have the highest ability in macrophage activation to clean superoxide radicals (hydrogen peroxide and nitric oxide), minimize iron complexity, and prevent lipid peroxidation (Fig. 2). These act as the key mechanisms of curcumin, used in pharmaceuticals and therapies.[56] According to this analysis, curcumin can be used a natural antioxidant in the pharmacological and food industries.

Curcumin is a favorable bioactive molecule among many natural anticancer agents. Studies have shown that curcumin

Table 1. Major effects of curcumin

Activity	References	Outcomes
Antioxidant activity of curcumin	The antioxidant activity of curcumin could be due to the 1.3-diketone system and phenyl ring with a methoxyl group.	32
	Hinders free radical generation.	
Anticancer activity	Curcumin efficiently induces apoptosis through several different molecular targets and inhibits metastasis, invasion, and angiogenesis.	27
	It was found that curcumin is an extremely pleiotropic molecule with multiple mechanisms to mediate chemotherapy and cancer chemo-preventive effects.	
Antibacterial effect	Plays an important role in eliminating pathogenic bacteria that cause great harm to humans and animals.	33
	Curcumin is 32-fold more potent than fluconazole in the inhibition of the growth of *Paracoccidioides brasiliensis*.	34
	Curcumin shows an inhibitory property against some foodborne pathogenic and spoilage bacteria such as *Escherichia coli*, *Yersinia enterocolitica*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus cereus*.	35
	Curcumin at the concentration of 75 μM in combination with a blue LED effectively inhibits the growth of *Staphylococcus aureus*, *Aeromonas hydrophila*, *Salmonella typhimurium*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus mutants*, *Lactobacillus acidophilus*, *Listeria monocytogenes*, and *Salmonella typhimurium*.	36
Antiviral activity	Curcumin (0.32 mg mL^{-1}) partially inhibits the activity of the human simplex virus-2.	37
	Inhibits type I human immunodeficiency virus (HIV) long terminal repeat, which directs gene expression and viral replication.	38,39
	Curcumin inhibits the production of p24 antigen in acute or chronically infected cells with HIV-1. However, curcumin was unable to inhibit HIV 1 proliferation in acute infected MT-4 cells.	39,40
Anti-inflammatory	Curcumin diminishes inducible nitric oxide synthase activity in rats.	41
	Curcumin supplementation reduces muscle damage caused by eccentric exercise in rats.	42
Wound healing	Wound contraction is faster in myofibroblasts treated with curcumin. As a result of curcumin treatment, fibronectin and collagen expression increases.	42
	Epithelial cell damage in the gastric lumen is reversible by providing re-epithelialization with curcumin.	43
Angiogenesis activity	Curcumin analogs reduces overexpression of genes associated with angiogenesis.	43,44
	Curcumin and its analogs inhibits metalloproteinases and reduce angiogenesis in tumor tissues.	
Neuroprotective activity	Curcumin significantly improves the memory ability of AD mice.	17
	Curcumin relieves neuropathological changes in the hippocampus and inhibits apoptosis with an increase in Bcl-2 level.	45
Antidepressant activity	Curcumin produces a marked increase in serotonin and noradrenaline levels at 10 mg kg^{-1} in both the frontal cortex and hippocampus.	46
	Dopamine levels also increased in the frontal cortex and striatum. Curcumin also inhibits monoaminoxidase activity in the mouse brain.	
Antiprotozoal activity	Curcumin inhibits thioredoxin reductase which reduces proliferation of protozoa.	47,48
Antidiabetic activity	Curcumin shows anti-inflammatory, antioxidant, hypoglycemic, and lipid-lowering effects.	49
Anticardiovascular activity	Lowers cholesterol and triglyceride levels, lowers the sensitivity of low-density lipoprotein (LDL) to lipid peroxidation, and inhibits platelet aggregation.	50
Anti-AIDS activity	Curcumin may have potential against AIDS. Curcumin inhibits human immunodeficiency virus (HIV) replication, inhibits long terminal repeat and HIV protease.	51
Antigastrointestinal and anti-immunomodulator	Sodium curcumin inhibits intestinal spasm and turmeric component *p*-tolmethylcarbinol, increases gastrin, secretin, bicarbonate, and pancreatic enzyme secretion.	52
	Turmeric inhibits the formation of stress, alcohol, indomethacin, and pyloric ligation, and significantly increases gastric wall mucus in rats exposed to gastrointestinal insults.	53
Immunostimulant	Curcumin inhibits autoimmune diseases by regulating inflammatory cytokines in immune cells such as IL-1β, IL-6, IL-12, TNF-a, and IFN-y and associated JAK–STAT, AP-1, and NF-kB signaling pathways.	54
Anti-ischemia	Application of curcumin to laboratory rodents prevents edema and maintains the integrity of the blood–brain barrier.	55
	Curcumin provides significant protection from the harmful effects of ischemia.	

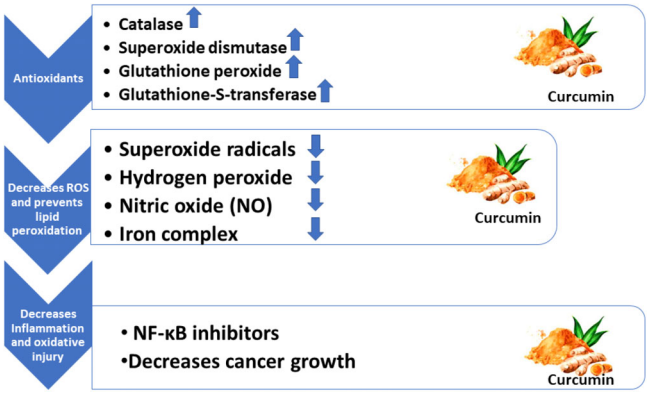

Figure 2. Intracellular antioxidant curcumin pathway.

effectively induces apoptosis and prevents metastasis, invasion, and angiogenesis.[58,59] It has also been detected as an extremely pleiotropic molecule with several pathways to mediate chemotherapy while being safe to consume, with small or no side effects.[60] For instance, Yallapu *et al.*[59] observed the effectiveness of curcumin-loaded poly[lactic-co-glycolic acid] in prostate cancer cells and that curcumin was distributed to the cytosolic partition of cells for successful therapeutic action. They reported that nanoparticles loaded with curcumin have been internalized successfully.[59] Furthermore, they investigated encapsulated curcumin and found that it inhibited the ability of prostate cancer cells to proliferate and colonize.[59]

In contrast, free curcumin did not hinder the proliferation and colony-forming ability of prostate cancer cells. Koohpar *et al.*[61] detected the anticancer effects of curcumin on human breast adenocarcinoma. Their findings showed that curcumin significantly inhibited the production of human MCF-7 breast cancer cells in a dose-dependent manner and by the timely induction of apoptosis, coupled with a decrease in MCF-7 cell viability.[61]

Curcumin also appears to have a high potential for use as a natural anticancer agent in the production of drug formulations or functional foods for patients with cancer.

Curcumin and antibacterial activity

Some natural compounds play an essential role in eliminating pathogenic bacteria in humans and animals.[62-64] Curcumin, a polyphenol that originates from *C. longa* rhizomes, has attracted research attention worldwide in recent years because of its numerous biological effects. It has historically been used in Asian countries for various purposes, including as a coloring agent, and in curries, tea, and cosmetics.[30] It is also used as a medication in some countries because of its antioxidant, anti-inflammatory,[65] antimicrobial,[66] and anticancer properties.[67]

Curcumin has a wide spectrum of activity against bacteria,[68] viruses,[69] and fungi.[70] It reduces the endodontic bacterial strains of *Streptococcus mutans*, *Actinomyces viscosus*, *Lactobacillus casei*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Enterococcus faecalis*, with minimum inhibitory concentration (MIC) values of 333.33, 167.67, 125, 125, and 208.33 mg L^{-1}, respectively.[71] Its application effectively inhibited the *S. mutans* biomass and its biofilm creation.[20] Parallel findings have also been noted on numerous periodontopathic bacteria, including *Fusobacterium nucleatum* and *Treponema denticola*, which were destroyed by curcumin in a dose-dependent manner.[72] Moreover, curcumin was 32-fold more powerful than fluconazole in the reticence of the growth of *Paracoccidioides brasiliensis*,[34] which is the pathogen that triggers one of the most prevalent systemic mycoses in Latin America – paracoccidioidomycosis.[73]

Curcumin has inhibitory effects on many pathogenic foodborne and spoilage bacteria (e.g., *Escherichia coli*, *Yersinia enterocolitica*, *Streptococcus aureus*, *Bacillus subtilis*, and *Bacillus cereus*).[35] The repressive impact is also seen on *Listeria monocytogenes* and *Salmonella typhimurium*.[74] Thus, researchers have been drawn to curcumin as a complementary complex in conjunction with other medicines to regulate bacterial growth. The use of a subtilosin and curcumin mixture on *Listeria monocytogenes* infection achieves a lower minimum effective dose than that with subtilosin application alone.[75]

The synergistic activity of oxacillin, ampicillin, ciprofloxacin, or norfloxacin used against methicillin-resistant *S. aureus* was supported by Mun *et al.*[76] Curcumin mixed with [–]-epigallocatechin gallate markedly lowers the biofilm development in wastewater bacteria.[77] However, activating photosensitive compounds with light in the presence of oxygen results in creating reactive radicals capable of causing cell death. Thus, the effect of curcumin-mediated photosensitization on bacterial inhibition was investigated. Curcumin at a 75 μM concentration, combined with a blue light-emitting diode, effectively inhibited the development of *Aeromonas hydrophila*, *S. typhimurium*, *E. coli*, *Pseudomonas aeruginosa*,[78] *S. mutans*, and *Lactobacillus acidophilus*. Moreover, curcumin is sensitive in the presence of blue light.[79]

However, the use of curcumin in the dark was not harmful to bacteria.[80] Studies showed that curcumin weakened the bacterial membrane to inhibit bacteria.[81] A membrane permeabilization assay showed that curcumin addition results in membrane leaks in both Gram negative and Gram positive bacteria, including *S. aureus*, *E. faecalis*, *E. coli*, and *P. aeruginosa*.[5] Nevertheless, according to Yun and Lee,[82] curcumin induced membrane damage at relatively high concentrations, as shown in Fig. 3, but no effect was observed at the MIC.[82]

Furthermore, curcumin inactivates *B. cereus* and *E. coli* by inducing the substantial production of reactive oxygen species (ROS), including single oxygen and hydroxyl radicals.[83] Curcumin-treated cells showed different apoptotic markers at the MIC (12 μg/mL), including ROS accumulation, membrane depolarization, and Ca^{2+} flux.[82] Curcumin has been shown to act as an efflux pump inhibitor in multidrug-resistant *P. aeruginosa*.[84] Joshi *et al.*[85] indicated that some bacterial efflux was inhibited by curcumin.[85] The proliferation of bacterial cells through disruption of the assembly and inhibition of bacterial cytokinesis was prevented by curcumin.[86] The study on *E. coli* and *B. subtilis* by Kaur *et al.*[87] also showed that curcumin triggered prokaryotic cell division disturbances.[87] Consequently, it decreases the short-term development of extracellular polysaccharides.[88] Gene expression associated with the extracellular metabolism of polysaccharides and carbohydrates, as well as adherence, decreased after curcumin treatment.[88] Thus, curcumin has been regarded as a promising antibacterial agent.[88]

Curcumin may theoretically be used for clinical care, but its poor bioavailability is a major problem, mainly because of its poor absorption, quick metabolism, and rapid removal.[26] However, questions about enhancing the bioavailability of curcumin have risen in recent years. Some agents have been tested to shape a curcumin complex to boost curcumin bioavailability. Piperine, for example, increases curcumin bioavailability by 20-fold.[89] Similarly, curcumin microemulsions made from foodstuff, such as

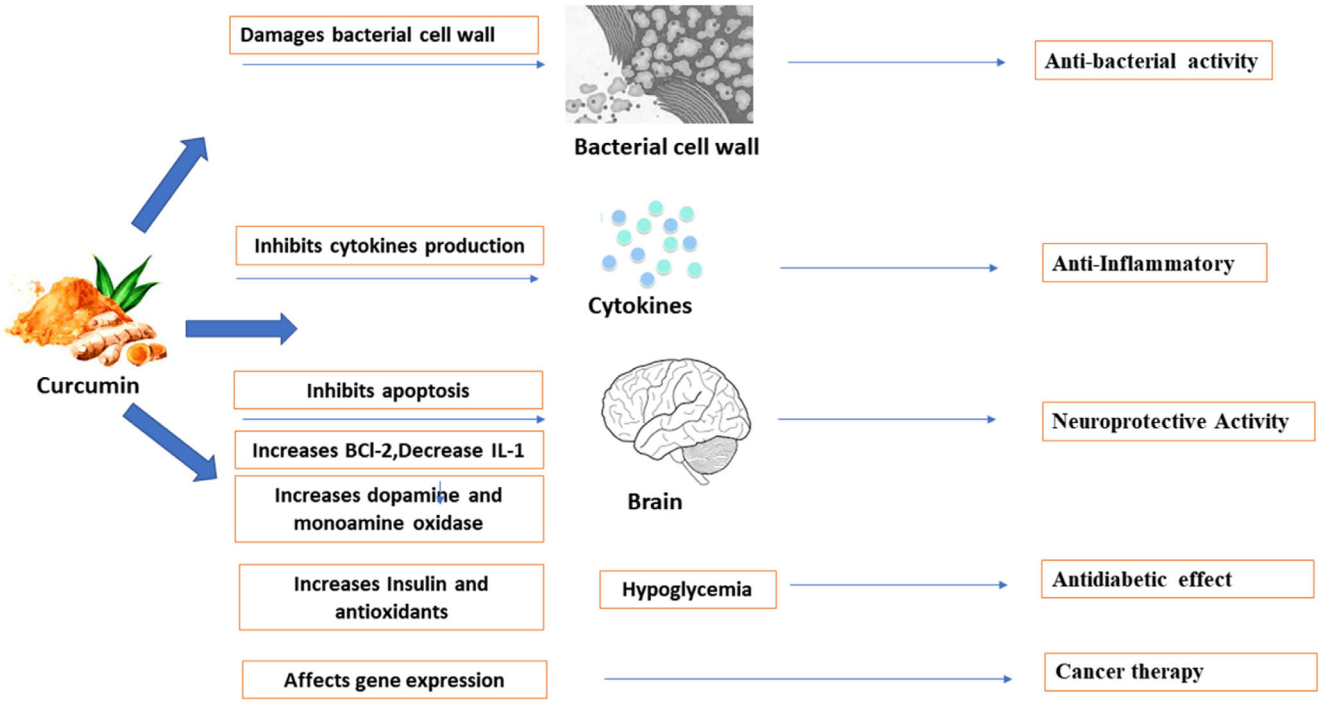

Figure 3. Biological properties of curcumin.

Tween 20, lecithins, vitamin E, and ethanol, increase curcumin's water dispersibility between 1000- and 10 000-fold.[90]

Nanocurcumin has also been deemed an alternative to enhance curcumin's bioavailability.[91] Curcumin nanoparticles (2–40 nm) exhibit substantial antimicrobial activity against *S. aureus*, *E. coli*, and *P. aeruginosa*.[92] The water distribution and chemical stability, water dispersibility, and antioxidant and anti-inflammatory properties of curcumin are improved by encapsulation in liposomes.[90]

Curcumin and antiviral activity

Curcumin has partly inhibited human simplex virus activity type 2.[37] Moreover, it provided important protection against the intravaginal human simplex virus 2 in the mouse model.[37] Moreover, curcumin was highly successful in inhibiting the long terminal repetitive gene expression of the human immunodeficiency virus (HIV) type I and its replication.[38] Curcumin inhibited the development of the p24 antigen in acute or chronically infected HIV-1 cells.[88] However, it could not inhibit the spread of HIV-1 in acutely infected MT-4 cells.[40] Mazumder *et al.*[93] synthesized and examined curcumin analogs to analyze this compound family's structure–activity relationship and its action in greater details.[93] The two curcumin analogs, dichopoylmethane and rosmarinic acid, impeded the IC_{50} integrase activity below 10 μM. Consequently, both curcumin analogs showed equivalent ability towards lysine (needed for viral DNA binding) and wild-type integrase. However, the binding site for curcumin and the substratum do not overlap.[93]

Combining a curcumin analog with the recently mentioned NSC 158393 integrase inhibitor, a consequence of the drug-binding sites that could not fit, showed synergistic or reflective integration inhibition. The enzyme could also prevent its binding to viral DNA, but this inhibition was independent of the divalent metal ion. Furthermore, these analogs' kinetic studies showed that they bind slowly to the enzyme.[93,94]

Curcumin and anti-inflammatory and antioxidant activity

The main field of application of natural products is in the prevention of oxidation of animal cells and their products.[95,96] Many studies on curcumin have been carried out, particularly in respiratory diseases. Curcumin is used in Eastern medicine to treat various chronic diseases and inflammatory disorders, including airborne diseases, and to minimize the synthase activity of inducible nitric oxide in rats.[41]

Curcumin's antioxidant property was noted because of its phenolic composition. It prevents apoptosis by restoring the growth of inhibited cells. Turmeric increases the safety time by preventing peroxide formation in food. Moreover, turmeric is more effective than vitamin E in preventing lipid oxidation. The components extracted from *C. longa* have significant antioxidant effects and are necessary for lipid oxidation.[57,97]

Curcumin also inhibited platelet production by removing mitogens that rapidly triggered the growth of mononuclear blood cells.[98] The protein kinase enzyme is also partly inhibited.[39] The pathogenesis of many diseases (e.g., myocardial ischemia, ischemia–reperfusion, bleeding, shock, nerve cell damage, and cancer) is well known to include oxidative stress. The anti-inflammatory and antioxidant properties of curcumin are proven because it eliminates various forms of ROS, including hydroxyl radicals[99] and nitrogen dioxide radicals.[100] Khanna *et al.*[101] stated that the antioxidant capacity of curcuminoids is equivalent to that of ascorbic acid.[101]

Curcumin is a powerful hydroxyl radical scavenger and also captures superoxide radicals. It protects DNA from oxidative injury owing to its capability to retain free radicals.[102] Consequently, it turns into tetrahydrocurcumin by hydrogenation in the intestines when taken orally. It is absorbed from the intestines, distributed into the blood and tissues, and is excreted in the bile.

Davis *et al.*[103] showed that curcumin supplementation reduced muscle damage caused by eccentric exercise in rats. For many years, the local, topical application of turmeric has been used for skin

diseases, insect bites, and chickenpox in India and as an alternative medical support for wound healing.[42] Wound contraction was quicker in myofibroblasts treated with curcumin. Thus, fibronectin and collagen expression increased as a result of curcumin treatment. Moreover, granulation tissue formation and neovascularization re-epithelialization increased in mouse-wound models formed with diabetes and hydrocortisone.[43] Curcumin reduced hydrogen peroxide-induced injuries in yellow keratinocytes and fibroblasts. Similarly, wound contraction and the average wound healing time were reduced markedly when curcumin was administered before treatment.[43] Consequently, collagen, hexosamine, DNA, nitrate, and nitrite synthesis increased before radiation, collagen accumulation, fibroblast, and vascular densities with curcumin treatment. Furthermore, the acute ulcer model created in mice also showed the antiulcer effect by decreasing lipid peroxidation and protein oxidation. Epithelial cell damage in the gastric lumen was reversible by providing re-epithelialization with curcumin.[43]

Thus, curcumin has strong modulative effects on wound healing. Research showed that curcumin does this by inflammatory, proliferative, and remodeling phases of wound healing, thereby decreasing the time needed to heal the wound. Unfortunately, the low bioavailability, rapid metabolism, inadequate solubility, and sensitivity of curcumin restricts its applications. New formulations, such as nanoparticles, should be studied to mitigate these effects and to use curcumin to its full potential.[104]

Curcumin and angiogenesis activity

Angiogenesis is a physiological procedure characterized by the creation of new vascular capillary canals.[105] These steps extend from embryonic development, production processes, wound treatment, to bone healing.[106] Many pathological conditions related to uncontrolled angiogenesis exist such as tumor growth, rheumatoid arthritis, diabetic retinopathy, and hemangiomas.[106]

Over the last 30 years, intensive studies have been conducted on the growth of the primary tumor and its role in angiogenesis in distant metastases.[107] Curcumin has been beneficial in many models as a regulator of uncontrolled angiogenesis. Angiogenic differentiation with curcumin in human umbilical vein endothelial cells, mouse oral mucosa cells, and chicken chorioallantoic membrane cells was inhibited under laboratory conditions.[25] In a different study, corneal neovascularization was suppressed in the mouse cornea with a basic fibroblast growth factor stimulus.[108] Curcumin analogs can therefore minimize the overexpression of genes associated with angiogenesis. Thus, curcumin and its analogs inhibits metalloproteinases and reduces tumor tissue angiogenesis.[32,43]

Curcumin and neuroprotective activity

Curcumin is applied in the treatment of inflammatory disorders, cancer, acquired immunodeficiency syndrome (AIDS), and other diseases. Engineering process intensification and catalysis (EPIC) chemical studies of turmeric revealed that the prevalence of Alzheimer's disease (AD) in people aged between 70 and 79 years is 4.4 times lower in India than in the USA.[45]

The researchers used a transgenic APPSw mouse model to investigate curcumin's therapeutic effects. The results showed that low-dose curcumin significantly suppressed inflammatory cytokine IL-1 and astrocytic marker glial fibrillary acidic protein and reduced oxidative damage.[45] The findings showed that low-dose curcumin substantially suppressed IL-1 and astrocytic markers (Fig. 3) and decreased insoluble amyloid quantity. Consequently, curcumin has fewer side effects than other antioxidant medications (e.g., nonsteroidal anti-inflammatory drugs or ibuprofen).[45] Evidence suggests that metals are concentrated in the AD brain and that curcumin can bind iron (rather than zinc) to beta-amyloids, which can theoretically help minimize amyloids.[45]

In vivo, curcumin can protect cells against a beta-amyloid attack and subsequently use the antioxidant pathway against oxidative stress. Moreover, curcumin considerably increased the memory capacity of AD mice in step testing by reducing the number of step-by-step errors and extending step-by-step latency.[45]

Similarly, it also alleviated neuropathological changes and prevented apoptosis at the Bcl-2 level, although the Bcl-2 associated X (BAX) function did not improve. Furthermore, curcumin enhanced cell viability in the presence of aluminum chloride. Conversely, the apoptosis rate decreased considerably in the curcumin-treated group when calculated by a flow cytometric study. However, curcumin conserved cells by increasing the Bcl-2 level without changing the BAX level. Furthermore, this study found that curcumin improved the memory power of AD mice.[17,45]

Curcumin and antidepressant activity

Many traditional Chinese herbal medicines, including Xiaoyao-san and Jieyu-wan, were recommended thousands of years ago by the renowned Chinese folk doctor, Zhong-jing Zhang;[109] they were used to treat mental stress, severe hypochondria, and hysteria, and in manicure.[109] In recent preclinical research, numerous results have supported the therapeutic benefits of herbal medicines in a clinical setting. Moreover, Xiaoyao-san has antidepressant effects using tail suspension and forced swim testing in animal laboratory tests.[110]

The effects of curcumin on depressive behavior in mice were analyzed using two models of animal depression.[111] The findings showed that 5 and 10 mg kg^{-1} (PO) curcumin therapy substantially decreased inactivity in forced swimming tests and tail suspension, respectively. However, the inactive response did not affect locomotive operation with these doses.[111] Furthermore, neurochemical analyses revealed that curcumin induced a substantial rise in both the frontal and hippocampus levels of serotonin and noradrenaline at 10 mg kg^{-1}.[109] Consequently, dopamine levels in the frontal cortex and striatum also increased. Curcumin was also found to hinder the activity of monoaminoxidase in the mouse brain.[112] These results indicated that central monoamine neurotransmitters may have antidepressant-like effects on curcumin. The study's findings suggested that curcumin has antidepressant features and affected monoaminergic structures in behavioral hopelessness studies.[113]

These studies may help to explain the antidepressant mechanisms of curcumin. Acute increases in monoamine levels in synapses can only be the first stage in a potentially complex series of incidents that eventually lead to the antidepressant activity theory of modified amine.[114] The long-term impacts of curcumin are often seen after chronic therapies, and more research should concentrate on receptors and signal transduction to understand the comprehensive processes of the antidepressant effects of curcumin.[46]

Curcumin and antiprotozoal activity

The antiprotozoal effects of curcumin have been studied extensively in the last decade. A concentration of 0.05% curcumin seems to be effective in minimizing infections of the upper and middle small bowel.[25] It is also helpful in *Eimeria tenella* infections. However, the *in vitro* incubation of *E. tenella* sporozoites with

curcumin has an important effect on the morphology and viability of sporozoites, resulting in decreased Madin-darby bovine kidney (MDBK) cell invasion.[115] An antiprotozoal effect of curcumin alcohol extract was also found against *Entamoeba histolytica*. Curcumin's antiprotozoal activity was also documented in *Plasmodium*, *Leishmania*, *Trypanosoma*, and *Giardia lamblia*, both *in vitro* and *in vivo*.[25]

Curcumin decreased parasitemia in mice infected with *Plasmodium berghei* by 80–90%. In another analysis, *Cryptosporidium parvum* was affected in cell culture and was more susceptible to curcumin than *Plasmodium*, *Giardia*, and *Leishmania*.[116] Synergistic antiprotozoal effects were seen when curcumin was mixed with other medications. For example, the combination of artemicin and curcumin showed additional activity in killing *Plasmodium falciparum* cultures and enabled the survival of *Plasmodium berghei*-infected mice.[25] Drug resistance is a significant obstacle in malaria control. In cultures and mice, chloroquine-resistant *P. falciparum* and artemisinin-resistant *Plasmodium chabaudi* were found to be susceptible to curcumin.[117] These encouraging data can open alternatives to malaria control, especially where drug resistance has become a relevant problem.

The antiparasitic effects of curcumin were obtained through gene transcription efforts. Recent studies indicated that histone acetylation plays a significant role in expressing eukaryotic genes and in antiparasitic therapy.[118] Histone acetyltransferase (HAT) and histone deacetylase equilibrium maintains the balance between acetylation and histone deacetylase. Curcumin also induces histone hypoacetylation primarily *in vivo* by the inhibition of HAT and has simultaneous effects on ROS development.[119] Curcumin inhibits intracellular adhesion molecules that lead to *Toxoplasma* sequestration and development and is correlated to the *P. falciparum* glutathione transferase (PfGST) chloroquine resistance.[120] Curcumin is therefore a powerful PfGST inhibitor that can open up alternative prospects for drug-resistance management in malaria. Thus, thioredoxin reductase inhibition by curcumin can reduce parasite proliferation, which is beneficial for control strategies.[47,48]

Curcumin and antidiabetic activity

Curcumin is used to treat diabetes (Fig. 3) in Ayurveda and traditional Chinese medicine. This treatment of diabetes and its complications is considered a reasonably safe and cost-efficient method that reduces glycemia and hyperlipidemia in diabetes models.[121] The effects of curcumin's antioxidant and anti-inflammatory properties on diabetic oxidative stress and inflammation in mice retina were investigated. One group of diabetic mice induced with streptozotocin was given a powder diet supplemented with 0.05 curcumin (w/w).[122] Conversely, a diet without curcumin was applied to the other group. The mice were sacrificed 6 weeks after the initiation of diabetes. The retina was utilized to identify oxidative stress and proinflammatory signs. The antioxidant capacity, intracellular antioxidants, and glutathione levels were decreased by about 30–35% at the end of the study.[122]

Moreover, curcumin application prevented the decrease in antioxidant capacity from diabetes. Curcumin effects were achieved without severe hyperglycemia corrections. In this case, curcumin has beneficial effects on metabolic abnormalities.[49] In a study on the anti-inflammatory, antioxidant, hypoglycemic, and lipid-lowering effects of turmeric extract, live subjects induced by a high-fat diet were divided into two groups with one group given determined doses of turmeric extract. In the extract group, turmeric showed a strong inhibitory impact against the oxidation of low-density lipoproteins (LDLs) and glycation caused by fructose because of the high radical-scavenging effect of the antioxidant activity. Thus, the risk of atherosclerosis (vascular stiffness) was reduced.[123]

Moreover, studies on the effect of curcumin extract on plasma glucose and insulin were conducted on 14 healthy volunteers (seven men and seven women). Consequently, 6 g of curcumin extract was given orally on certain days, and insulin levels were checked at certain time intervals. Satiety insulin levels increased in the groups of people given the curcumin extract. Thus, curcumin extract has positive effects on the insulin release in humans.[124]

Curcumin and anticardiovascular activity

Turmeric decreases cholesterol and triglyceride levels, reduces lipoprotein LDL susceptibility to lipid peroxidation and inhibits platelet aggregation. These effects are noted even with a low turmeric dose. The LDL susceptibility to lipid peroxidation in addition to low plasma cholesterol and triglyceride levels was demonstrated to decrease in a study of 18 atherosclerotic rabbits given low-dose turmeric extract (1.6–3.2 mg kg^{-1} body weight per day).[50,52]

The higher dose did not minimize LDL lipid peroxidation, but the amount of cholesterol and triglycerides decreased to a lesser degree than the low dose. The effect of turmeric extract on cholesterol levels can be attributed to decreased intestinal cholesterol intake and an increased cholesterol conversion to bile acids in the liver.[50,52]

Curcumin and anti-AIDS activity

Several studies have indicated that curcumin may be used against AIDS because it inhibits long-term HIV repetition, HIV protease, and HIV replication. Moreover, curcumin inhibits HIV-1, binds protein-specific acetyltransferase p300/CREB and histone/nonhistone protein-dependent chromatin, and inhibits HAT integration. Thus, it also has a decent potential in the treatment of AIDS.[51,93]

Curcumin and antigastrointestinal spasm and anti-autoimmunity activity

Curcuma longa has different protective effects on the gastrointestinal tract. Moreover, sodium curcumin has been shown to inhibit intestinal spasms, and *p*-tolmethylcarbinol increased gastrin, secretin, bicarbonate, and pancreatic enzyme secretion. Turmeric also inhibits stress formation, alcoholism, indomethacin, pyloric linkage, and ulcers, and significantly increases gastric mucus in rats exposed to these gastrointestinal conditions and injuries.[52,53]

The immune system is developed to protect the host from microbial invasion. However, an immune system deficiency also leads to infections, cancer, and autoimmune diseases.[54] Multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel diseases, myocarditis, thyroiditis, uveitis, systemic lupus erythematosus, and myasthenia are autoimmune diseases unique to the organ, affecting over 5% of the world's population. Although the etiology is not understood in patients with autoimmune diseases, herbal and dietary supplements are growing because they are predominantly effective, cheap, and relatively secure.[54]

The latest studies showed that curcumin prevents multiple sclerosis, arthritis rheumatoid, psoriasis, and inflammatory bowel disease in human or animal models. Moreover, it prevents these autoimmune disorders in immune cells (e.g., IL-1β, IL-6, IL-12,

tumor necrosis factor-a, and interferon-y, and related the JAK–STAT, AP-1, and NF-κB pathways) by regulating inflammatory cytokines (Fig. 3). While nutraceuticals historically had beneficial effects on low levels of dietary intake for a long time, treatment using distilled active compounds, such as curcumin, requires severe caution.[54,125]

Many studies showed that curcumin enhances immunity and can help the body combat cancer if those cells escape apoptosis. Researchers found that the number of $CD4^+$T helper cells and B-type immune cells were greater when the bowel lining was evaluated after curcumin intake.[126] Furthermore, curcumin enhances immunity in general, in addition to this localized immune stimulation. Researchers in India have reported increased antibodies and increased immune response in mice administered curcumin.[52,126]

Curcumin and anticarcinogenic activity

In recent years, curcumin's cancer-suppressant characteristic has attracted much attention in cancer research. Curcumin has been used to treat various inflammatory diseases for decades, and its uses in the treatment of leukemia and lymphoma, gastrointestinal, genitourinary, breast, ovarian, squamous (flat) carcinomas of the head and neck, lung cancer, melanoma, and neurological cancers have been documented.[26] Although traditional herbal medicines are considered healthy, their active principles and how they mediate cancer are unknown.[26]

Curcumin exhibits antioxidant and anticancer effects because of its free radical-scavenging properties. Curcumin's phenolic and enolic functional classes have great antioxidant activity as well.[41] Studies have reported that aromatic curcumin rings and their analogs exhibits cytostatic activity. Furthermore, curcumin has antineoplastic activity, low molecular weight, and no toxicity, making it the perfect precursor molecule for future chemotherapeutic drugs. Various analogs have been synthesized and their effects tested based on curcumin's chemical structure.[127,128]

Metabolic and circulatory function of curcumin

Neuronal energy metabolism relies on oxygen and glucose and cannot tolerate a hypoxic or hypoglycemic status.[129] A drop in brain oxygen or glucose levels eventually contributes to neuronal function loss. Consequently, ischemia is caused by a blood flow deficiency to the brain, as in stroke.[130] Furthermore, ischemia results in increased intracellular Ca^{2+} levels through excessive mitochondrial ROS development, astrocyte stimulation, and neuronal death. Animal models showed that curcumin can protect against ischemic damage.[130]

Aside from maintaining the brain's damaged region, curcumin can minimize oxidative damage and mitochondrial dysfunction and inhibit neuronal apoptosis and microglial activation.[131] Other inflammatory agents (e.g., leukotriene and cytokine) are developed during and after ischemia, promoting leukocyte infiltration. Proteolytic enzymes from recruited leukocytes disperse the blood–brain barrier, resulting in a weakened brain tissue edema.[132] Applying curcumin to laboratory rodents prevents edema and maintains blood–brain barrier integrity. Interestingly, curcumin may provide substantial protection from the adverse effects of ischemia, regardless of the administration route (intraperitoneal injection, gavage, or dietary supplement).[133]

Human studies are scarce, despite the wide evidence available regarding curcumin's anti-ischemic effects in animal models.[133] However, the proposed therapeutic use of curcumin in stroke and ischemia is controversial. Curcumin and its synthetic analogs are considered possible neuroprotectants based on epidemiological findings and preclinical evidence.[55] However, high curcumin concentrations are needed daily to achieve levels comparable to those used in animal models.[55,133]

WAYS TO IMPROVE CURCUMIN BIOAVAILABILITY

Despite various biological attributes and bioactivity, curcumin has limited applications in food products because of its extremely low bioavailability, caused by poor chemical stability, low water solubility, and rapid metabolism.[88,134]

Different strategies and techniques were used to address these obstacles. Encapsulation was suggested as a promising method to improve curcumin's aqueous solubility and stability.[134] The following sections address some of the most important and commonly used methods for curcumin encapsulation (Fig. 4).

Nanocomplexation

Transforming a substance from its standard form to a nanoscale is also useful in obtaining certain specific characteristics of the material.[33,62] Furthermore, curcumin's nanocomplexity with biopolymers (e.g., proteins) provides a way to encapsulate it. Nanocomplexation with food biopolymers was introduced to improve the solubility, stability, absorption, and bioavailability of hydrophobic bioactive compounds such as curcumin.[16] Curcumin can form complexes with carriers through hydrophobic interactions. Hydrogen bonds may also contribute to nanocomplex formation.[5] Producers are the most common carriers in preparing nanocomplexes with curcumin–hydrophobic interactions owing to their amphiphilic nature.[135] Nanocomplexation is a simple process of dissolving curcumin in a suitable solvent, such as ethanol, and then applying it to the protein solution. The resulting mixture is stirred to form the nanocomplexes. Consequently, the outcomes of nanocomplexes are centrifuged to extract free curcumin in certain instances. Curcumin–protein nanocomplexes may be used as dispersions or converted into powders by freezing for further use.[16]

In a study conducted by Tapal and Tiku,[5] who studied soy protein complexation effects on curcumin solubility, they reported that curcumin's aqueous solubility increased 812-fold through soy protein nanocomplexing. Moreover, the complexation improved the stability and antioxidant activity of curcumin. Li *et al.*[136] also reported that curcumin's antioxidant activity was significantly improved by binding to β-lactoglobulin. Chen *et al.*[44] also showed that curcumin nanocomplexing with soy protein nanoparticles increased its water solubility by 98 000-fold compared with free curcumin in water. They reported that nanocomplex formation greatly improved curcumin's storage stability. *In vitro*, simulated digestion experiments showed that soy protein-based particle nanocomplexing improved the bioaccessibility of curcumin.[44]

For soy proteins, structural modifications using glutaminase before complexation with curcumin have been reported to boost their ability to load curcumin.[18] Glycosylated α-lactalbumin-based nano complexes are applied as nanocarriers for curcumin.[137] The loading of curcumin into these nanostructures increased its antioxidant activity due to enhanced curcumin water solubility.[138] Curcumin also developed a new bioavailability enhancement strategy by self-assembly curcumin nano-complexing and bovine serum albumin.[138]

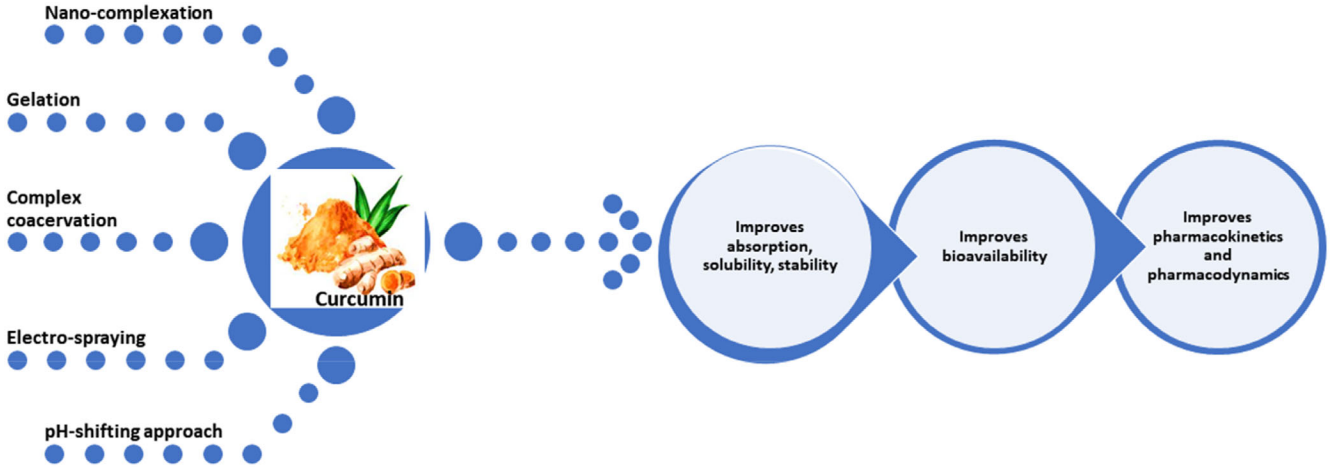

Figure 4. Common methods for curcumin encapsulation.

The resulting nano-complexes had sufficient solubility, stability, and bioactivity. Ovalbumin nanocomplexation also increased curcumin solubility 370 times compared with free curcumin.[20] Curcumin's photostability has also been greatly improved by ovalbumin nanocomplexing, suggesting that it is an effective way to increase curcumin's stability by contributing to its use in dietary supplements or functional foods.[20] Egg-white proteins could be used as efficient systems to increase curcumin's aqueous solubility and antioxidant activity, expanding its applications in various fields including food, cosmetics, and the pharmaceutical industry.[7]

Whey protein nanofibrils have been used as a carrier for curcumin by nano-complexing.[135] Mohammadian *et al.*[16] reported significantly increased curcumin aqueous solubility by binding to nanofibrils. These nanofibrils were prepared by heating the acidic whey protein solution. Nanofibrils' high ability to load curcumin was due to their high surface hydrophobicity.[16] The results of antioxidant capacity quantities (DPPH radical scavenging activity and lowering power) suggested that curcumin's antioxidant activity was improved through nanofibril complexation.[135]

Evaluating *in vitro* curcumin release from nano-complexes under simulated gastrointestinal conditions revealed that curcumin was slowly released from the nanocomplexes. This study proposed using whey protein nanofibril as a nanomaterial to improve curcumin food applications as a water-insoluble bioactive compound.[16]

Gelation

Gels are three-dimensional networks of polymer chains, cross-linked by either physical or chemical bonds and highly capable of retaining water or biological fluids. Different methods and gelling agents can generate gels. There are numerous gel-based delivery vehicles, including hydrogels, organogels, emulsion gels, emulsion-filled gels and aerogels.[139,140]

The gelation process for curcumin encapsulation first adds curcumin to a protein or protein/polysaccharide solution and then adds the gelling agent. Here the curcumin-loaded hydrogels are made. Curcumin may also be applied to an emulsion, and after adding the gelling agent, the curcumin-loaded emulsion gels are formed.[16,141]

Different studies have been conducted to produce curcumin-loaded hydrogels and emulsion gels. Brito-Oliveira *et al.*[142] studied the durability of curcumin embedded in strong lipid microparticles integrated into cold-set emulsion gels of soy protein and xanthan gum. They reported that curcumin stability was improved by loading into the gels, and for 15 days, curcumin showed high stability. These authors proposed that curcumin in solid lipid nanoparticles embedded in emulsion-filled gels may be used as a potential alternative to replace yellow artificial colors in gelled food items.

Geremias-Andrade *et al.*[143] also studied the rheological and mechanical properties of emulsion-filled curcumin gels produced with whey protein isolate and xanthan gum. This study showed that the curcumin-loaded mixed biopolymer gels could be considered as a promising alternative to safe food processing, decreasing total fat content, and preserving attractive texture properties.[143]

Mixed protein/polysaccharide hydrogels were manufactured using curcumin-loaded whey protein accumulates and κ-carrageenan, to study their gastrointestinal fate.[143] Alavi *et al.*[144] stated that the resulting gel samples not only have a high ability to load curcumin but could also prevent release and degradation of the loaded curcumin in the upper gastro intestinal tract; thus, these hydrogels are very appropriate for colon-specific delivery of hydrophobic bioactive compounds, particularly curcumin.[144]

More recently, in a report by Liu *et al.*,[20] cold-set hydrogels of whey protein chitosan were used to control curcumin release. The curcumin release test showed that the complex hydrogel had enormous advantages in continuously releasing curcumin, eventually hitting ~7% at 4 h and maintaining release. They therefore proposed that the whey protein-chitosan complex hydrogel could be considered as an efficient delivery mechanism for applying the controlled release of bioactive compounds in functional foods and pharmaceutical products.

Complex coacervation

Complex coacervation is a tool to encapsulate, preserve, and distribute bioactive molecules like curcumin.[145] This process is considered as the spontaneous liquid/liquid phase separation in colloidal systems resulting from the electrostatic interaction between two opposite charged colloids or biopolymers, especially proteins and polysaccharides, thus enabling trust and an efficient encapsulation strategy for bioactive compounds.[145]

The dynamic co-preservation mechanism creates coacervates the structures of which can be used to hold curcumin. Different

biopolymer pairs such as protein–protein pairs, protein-polysaccharides pairs, and polysaccharides pairs may be used to create coacervates.[146] Various pairs of biopolymers such as chitosan/gum Arabic,[147] albumin/gum Arabic,[146] whey protein nanofibrils/gum Arabic,[7] ovalbumin/κ-carrageenan,[148] and lysozyme/κ-carrageenan[149] have been used to fabricate curcumin-loaded coacervates.

Shahgholian and Rajabzadeh[146] used complex albumin and gum coacervates to load curcumin. They concluded that the optimum condition's encapsulation efficiency was 92%, indicating the complexes' high capacity to load curcumin as a bioactive hydrophobic molecule. In a study conducted by Tan *et al.*[147] chitosan and gum Arabic, curcumin encapsulation efficiency was also stated as 90%.[147] This study also showed that curcumin capsulation in complexes improved its stability and delayed curcumin release in a simulated gastrointestinal setting. The encapsulation also dramatically improved curcumin's antioxidant activity, as calculated by ferric reduction of antioxidant strength assay and radical DPPH scavenging test.[147]

Mohammadian *et al.*[16] encapsulated curcumin in complexes made of whey protein nanofibrils and arabic gum. The resulting complexes displayed a high loading potential for curcumin; the encapsulation efficiency was around 99%. Fluorescence spectroscopy showed that curcumin was loaded in the coacervates' hydrophobic cores. This study showed that curcumin's reduced power and photostability were significantly improved by complex coconservation in whey protein nanofibrils/gum Arabic. This study also indicated that electrostatic-driven complexes made of gum Arabic and whey protein nanofibrils could be used as promising carriers for curcumin safety and delivery.[16]

In another study conducted by Xie *et al.*,[148] complexes consisting of ovalbumin and κ-carrageenan were used to deliver curcumin. Curcumin encapsulation performance ranged from 91.2 to 84.5% for various initial curcumin concentrations. Curcumin encapsulation efficiency for lysozyme and κ-carrageenan complexes was also stated by 96.2%.[149] These results showed that complex coacervation could be considered an effective method with high loading efficiency for curcumin encapsulation and safety.

Electrospraying

Curcumin encapsulation can be achieved using the electrospray process, which generates monodisperse particles ranging from sub-micrometers to hundreds of micrometers by applying a high positive voltage between a needle and the field.[150] In this process, a liquid droplet at the tip of a capillary nozzle once exposed to a high electrical field undergoes a deformation due to internal electrostatic repulsions and external attractive coulombic forces from which a jet is expelled. This will subsequently breaks into fine droplets due to varicose instability.[151]

The electrospraying process is a cost-effective and scalable technology for the development of encapsulating structures, making it very important for scientists in food science and the delivery of drugs.[11] Furthermore, many other advantages of electrospraying encapsulation have been reported, such as improving the bioavailability and solubility of bioactive compounds, small particle size, having only one step, high loading efficiency, masking of undesirable substances, controlling the release profile, high particle deposition rate, narrow particle size distribution and protecting bioactive molecules.[152] This method was used to generate curcumin-loaded microcapsules. In work conducted by Yuan *et al.*[150] coaxial electrospray produced lactic-co-glycolic acid (PLGA) microparticles for sustained drug release. They demonstrated that the electrospray process yields profiles with improved drug release relative to conventional microencapsulation methods.[150]

Manufacturing curcumin-loaded microcapsules based on polylactic acid (PLA) demonstrated 95% trap efficiency for curcumin.[11] Curcumin-loaded microcapsules have demonstrated excellent antibacterial activity against *E. coli* and *S. aureus*. These microcapsules may also scavenge DPPH's free radicals, showing their high antioxidant activity. They also revealed strong biocompatibility and low cytotoxicity of PLA-based microcapsules.[11] They also concluded that the PLA-based electrospray strategy combined with spherical microcapsules could have a wide range of applications in different fields, especially in the drug supply and food industry.

The electrospray method was also used to render curcumin-loaded zein-chitosan particles.[153] The method showed high curcumin encapsulation efficiency, about 90%. The studies mentioned above generally showed that the electrospraying method can be considered an efficient and promising approach for the encapsulation of bioactive ingredients such as curcumin.

pH-shifting approach

One way to encapsulate curcumin is a pH-shifting approach. Typically, proteins are used as carriers for loading curcumin in a solvent-free phase.[154] This approach is based on curcumin's high solubility in unfolding protein structure under alkaline conditions. Using this form, a protein solution's pH will be adjusted to high pH values (more than 11.5).[154] Curcumin crystals will be added at this stage, to combine the resulting protein/curcumin mixture. The mixture will be returned to a neutral pH (pH 7.0). During this process, the unfolding and refolding of proteins will enable them to hold hydrophobic molecules like curcumin in their structure and carry them easily in an aqueous environment that will enhance their water dispersibility.[154]

Many advantages of pH-driven curcumin encapsulation in proteins were reported, such as inexpensiveness, high loading power, and encapsulation efficiency. Moreover, this method does not need toxic organic solvents like ethanol to solubilize curcumin.[155] Different proteins, for example, casein,[9] whey proteins,[155] porcine plasma protein,[156] zein,[157] and walnut proteins,[154] have been used for the pH-driven encapsulation of curcumin.[9]

Self-assembled casein nanoparticles for pH-driven curcumin encapsulation depends on the incubation period at alkaline conditions and the initial curcumin concentration.[155] This method recorded encapsulation efficiencies between 70% to 100%. Curcumin's encapsulation efficiency was reduced by raising the initial curcumin concentration in casein solution.[155] Kevij *et al.*[155] also stated that the solvent-free pH-shifting process significantly enhanced curcumin's antioxidant activity and aqueous solubility. They prepared curcumin-loaded whey protein with pH values of 3.0 and 7.0 using pH shifting. They reported significantly improved curcumin solubility by loading into whey proteins.[155] They also proposed that, due to their high water solubility, excellent antioxidant activity, and chemical stability, the curcumin-loaded whey proteins produced by the pH-shifting method could be used in the aqueous formulation of functional foods and beverages.[155]

Moghadam *et al.*[154] used the pH-shifting method to load curcumin in walnut proteins and they also compared it with the effectiveness of traditional encapsulation. They reported that the pH-shifting method's encapsulation efficiency was about 60%, while

the sample generated without the pH-shifting method showed an encapsulation efficiency of 2.53%. Therefore, they proposed the pH-shifting method would shape more binding sites for curcumin complexation with walnut proteins. They also documented strong anti-radical and anti-cancer activity for curcumin-loaded walnut proteins prepared by a pH-shifting approach.[154]

CONCLUSION

Curcumin is a polyphenolic compound. It has been shown that this biologically active molecule has many functional and biological properties, including antioxidant and anticancer activity. Besides use as a food additive, curcumin is also used for treatment. Curcumin uses in food formulations, however, are very restricted due to the low aqueous solubility and poor chemical stability. Different methods such as nanocomplexing, gelation, electrospraying, co-conservation, and pH-shift approaches, and different carriers, enhance curcumin solubility, stability, and bioavailability. This analysis showed that encapsulated curcumin forms are potentially useful bio-products with health-promoting attributes. Further studies will therefore be needed to investigate the applications and characteristics of curcumin-loaded structures in natural food systems and to determine their role under the harsh conditions present in many food items. The lack of *in vivo* studies seems to be a barrier, and more comprehensive studies are also required in this research field.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors were equal contributors in the writing of this review article. All the authors have read and approved the final manuscript.

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