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REVIEW

# Longevity and anti-aging effects of curcumin supplementation

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**Abstract** Aging is a gradual and irreversible process that is accompanied by an overall decline in cellular function and a significant increase in the risk of age-associated disorders. Generally, delaying aging is a more effective method than treating diseases associated with aging. Currently, researchers are focused on natural compounds and their therapeutic and health benefits. Curcumin is the main active substance that is present in turmeric, a spice that is made up of the roots and rhizomes of the *Curcuma longa* plant. Curcumin demonstrated a positive impact on slowing down the aging process by postponing age-related changes. This compound may have anti-aging properties by changing levels of proteins involved in the aging process, such as sirtuins and AMPK, and inhibiting pro-aging proteins, such as NF-κB and mTOR. In clinical research, this herbal compound has been extensively examined in terms of safety, efficacy, and pharmacokinetics. There are numerous effects of curcumin on mechanisms related to aging and human diseases, so we discuss many of them in detail in this review.

**Keywords** Curcumin · Aging · Longevity

## Introduction

Generally, human life expectancy has increased. In aging biology studies, biochemical and genetic

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processes that lead to aging are investigated. Now, effective approaches are being examined to combat this. To combat this process, lots of effective approaches are being examined. Aging is an irreversible and natural pathophysiological process associated with the development of many age-related diseases, such as musculoskeletal disorders, neurodegenerative diseases, cardiovascular disease, cancer, and arthritis [1]. The results of recent studies demonstrated that the aging process is manageable and that the rate and quality of aging can be modulated [2]. The biochemical changes that occur in all organisms are hallmarks of aging. These hallmarks are genetic instability, epigenetic changes, telomerase dysfunction, cellular senescence, stem cell exhaustion, and mitochondrial dysfunction [2]. Diets that include anti-oxidants and anti-inflammatory properties have been shown to reduce the risk of age-related cognitive decline and neurodegenerative diseases. In the last few years, the focus of studies has been on curcumin. This natural compound has a positive impact on the treatment of human disorders [3–6].

Curcumin is an orange-yellow pigment that was first isolated from the aromatic rhizomas of turmeric (*Curcuma longa* L.), a plant from the ginger family (Zingiberaceae) [7]. There are many biological and pharmacological properties of curcumin, including anti-oxidant properties, immunomodulatory properties, anti-inflammatory properties, anti-microbic properties, cardio-protective properties, nephroprotective properties, hepato-protective properties, anti-neoplastic properties, and anti-rheumatic and anti-aging properties [8]. Curcumin modulates a wide variety of signaling molecules at the molecular level. Depending on the target structure, it may increase or decrease their activity. Curcumin binding can be activated in two ways: directly or indirectly. An indirect modulator may be an inflammatory mediator, a transcription factor, a protein that regulates drug resistance, enzymes, a cell adhesion molecule, a kinase, a protein that regulates drug resistance, a growth factor, a protein that controls cell survival, or a protein that regulates the cell cycle. Curcumin's direct effect is mediated by inflammation molecules, kinases, reductases, histone acetyltransferases, integrins, DNA methyltransferase 1, carriers, and metal ions [9, 10]. The purpose of this review is to summarize the therapeutic potential of curcumin, especially its potential for preventing and delaying aging.

## The biology of aging process

The biological process of aging is intricate and complex. It is generally accepted that aging refers to a physiological decrease in several biological activities in the organ along with a gradual reduction in the capacity of the cells to adjust to external injuries as well as internal ones [11, 12]. Aging has a highly heterogeneous phenotype. There are several factors that contribute to aging, including random, environmental, genetic, and/or epigenetic factors [13, 14]. A number of premature age-associated diseases can be predicted based on the decline in the physiological function of most living organisms, which is characterized by changes in molecular pathways. As a result of aging, all levels of the human body experience multifaceted changes. It includes cardiovascular disorders, neurodegenerative disorders, musculoskeletal disorders, metabolic disorders, immune system disorders, and cancer [1, 13]. Despite aging's complexity, the basic molecular mechanisms and main pathways are highly conserved and are responsible for maintaining tissue homeostasis. Cellular and molecular changes associated with aging are composed of nine major hallmarks: DNA instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [15] (Fig. 1).

Due to the reduced ability of several stem cells to repair tissues with age, many tissues' regenerative and repair potential declines [16]. There is no definitive evidence of which biological changes (molecular, cellular, or physiological changes) are most important in the aging process and how they interact with each other, despite available research. Oxidative stress is the result of ROS overproduction or insufficient antioxidant defenses in the body. Additionally, ROS are produced as a natural by-product of cellular metabolism and the production of ATP. Oxidative stress plays a key role in the development of age-related conditions. Also, many drugs, alcohol abuse, smoking, radiation, and environmental pollution contribute to the formation of free radicals in the body and oxidative stress [17]. The activation of neutrophils during inflammation increases the production of ROS, an intrinsic immune molecule that modulates the immune response by activating the MAPK pathway [18]. By using physiological signals, dietary

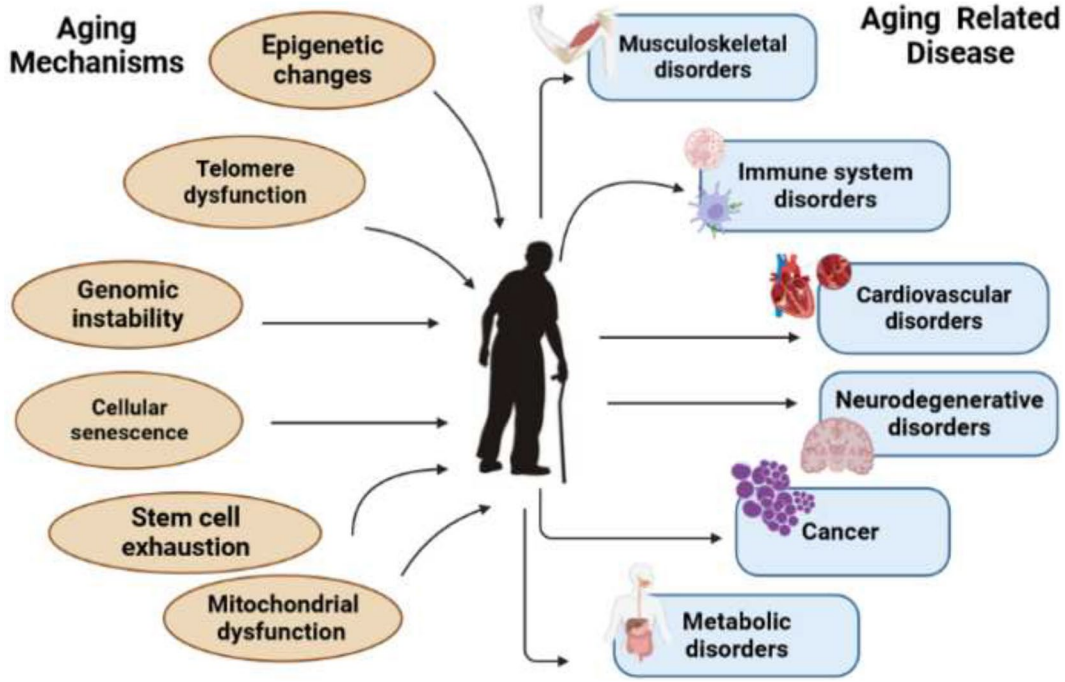


**Fig. 1** Cellular and molecular changes associated with aging are composed of nine major hallmarks: DNA instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication

ingredients, and drugs, the body can scavenge oxidative stressors, including reactive oxygen species. In the process of aging, diet plays a crucial role. From pharmacological and therapeutic points of view, some compounds have been extracted and examined over the years for their anti-aging and therapeutic properties. several natural bioactive products and plant extracts with protective anti-oxidant properties, such as caffeic acid, ginsenosides, blueberry extract, and chayote [19–22]. The successful aging model developed by Rowe and Kahn utilizes three key components: absence of disease and disease-related disability, maintenance of high mental and physical function, and continued engagement with life. According to the study, age, gender, educational level, economic status, heavy drinking, subjective health status, and health screening were the factors that correlated in the individual system; living arrangement, satisfaction with spouse, and frequency of contacting family, siblings, and relatives; and how often you contact neighbors and friends, how many of your neighbors and friends you know, and whether neighborhood facilities are accessible [23].

## Supplements can delay aging

Natural factors that prevent aging have received attention in life span research. Natural compounds that have emerged as anti-aging agents include omega-3 fatty acids (polyunsaturated fatty acid (PUFA)) [24], vitamins (E, D, K, and C) [25, 26], coenzyme $Q_{10}$ (a small, lipid-soluble anti-oxidant molecule) [27], epigallocatechin gallate (EGCG) (a polyphenol compound concentrated in green tea) [28, 29], gingerol (an active component of ginger) [30], collagen (a protein that helps maintain skin structure and slows down the aging process, preventing wrinkles) [31], and curcumin (derived from turmeric) [32].

These compounds offer improved cardiovascular health, reduced inflammation, and enhanced cognitive function. They may reduce the risk of age-related diseases, such as dementia and cancer. Some foods and dietary supplements have been the subject of scientific studies regarding the presence of certain compounds [33]. We will look at the current research to explore how curcumin, as a natural product, may prevent aging-related changes.

## Curcumin

### Chemistry

Curcumin was extracted from the rhizomes of *C. longa* in 1815 by Vogel and Pelletier. After two centuries, more efficient and advanced extraction methods have been reported [34]. The molecule curcumin is symmetrical, also called diferuloyl methane. The chemical formula of curcumin is C21H20O6, and its molecular weight is 368.38 [35]. The most common method for separating curcumin from turmeric is solvent extraction, followed by column chromatography [36].

In addition to its keto form, curcumin also exists in an enol form. While the keto form is predominant, in alkaline conditions, the enol tautomer is exclusively present, which can be rationalized by intramolecular hydrogen bonding in the enol form [37, 38]. Under both neutral and alkaline conditions, curcumin degrades rapidly, but its solubility increases under alkaline conditions. In methanol, curcumin absorbs most efficiently at 430 nm, and in acetone, it absorbs most efficiently at 415–420 nm. The maximum absorbance of curcumin at 467 nm occurs in alkaline conditions [39, 40].

### The metabolism

It is important to understand the metabolism of curcumin in order to fully benefit from its bioactive properties as well as the health benefits it provides [41]. It is suggested that curcumin is primarily metabolized in the liver, along with the intestines and gut microbiota [42]. In oral administration, curcumin is primarily metabolized to glucuronates and glucuronate/sulfate conjugates. In particular, the finding indicates that the gastrointestinal tracts play an important role in the glucuronidation of curcuminoids, which may have significant implications for their pharmacokinetics [43]. After administration of curcumin, a small amount of free and intact curcumin can be detected in plasma [44]. The metabolism of curcuminoids, however, mainly results in reductive metabolites, for example, hexahydrocurcuminoids [45]. Since hexahydrocurcuminoids do not contain olefinic double bonds, they are more stable at pH 7.4 than curcumin [46]. Furthermore, secondary biliary metabolism involves dihydroferulic acid and ferulic acid [35, 47]. In addition, microbiota such as *Escherichia coli* and *Blautia* sp. also metabolize curcumin alternatively. In a two-step reduction pathway from curcumin to dihydrocurcumin and then to tetrahydrocurcumin, *Escherichia coli* was found to be active by an NADPH-dependent reductase [48]. In *Blautia* sp., curcumin is demethylated into demethylcurcumin and bis-demethylcurcumin. Curcumin's polypharmacology is attributed to its metabolites, which have been identified as anti-oxidants, anti-inflammatory, anti-tumor, cardioprotective, and anti-diabetic [49–52].

### Bioavailability and new formulation

Pure curcumin crystals typically have low bioaccessibility due to their high melting point and low water solubility under acidic and neutral conditions [53]. For example, at 37 °C and pH 7.2, curcumin $t_{1/2}$ was reported as less than 10 min [54]. Since curcumin does not degrade under acidic conditions, it should be stable in the stomach [49]. A number of attempts have been made over the years to improve curcumin's bioavailability due to its broad spectrum of potential health benefits. Increasing curcumin's bioaccessibility, retarding its metabolism, and/or enhancing its absorption can enhance its bioavailability. Consequently, by trapping curcumin inside hydrophobic phases, such as micellar, liposomal, microemulsions, emulsions, solid fats, or biopolymers, the metabolism of curcumin can be inhibited [55, 56]. There are three main types of curcumin formulations available, which are either bioavailable or bioenhanced. The first-generation formulation of curcumin included adjuvants that inhibited essential detoxification enzymes like piperine from black pepper or turmeric oils. The absorption of curcumin is enhanced through these adjuvants that delay its metabolism [57–59]. The second-generation curcumin supplements such as BioCurc, Cavacurcmin, CurcuWIN, Hydrocurc, Meriva, Nanocurcumin, Novasol, Theracurmin, and Turmipure Gold use emulsifiers like polysorbates, lipid complexes, and water-dispersible nanopreparations to increase solubility [59]. The conjugated metabolites of curcuminoid (glucuronides and sulfates) are vital in increasing plasma curcuminoid levels. However, according to several studies, these metabolites do not have any significant biological effects due to their large size, quick renal elimination, limited membrane permeability, and limited blood brain barrier

(BBB) permeability [59–61]. Therefore, to maximize curcumin's therapeutic effects, delivering it in its free form (without conjugation) is crucial. Thanks to third-generation curcumin formulations such as Longvida and CurQfen, the issue of "free" curcuminoids is no longer a problem. These formulations have improved bioavailability, membrane permeability, and cellular uptake without artificial emulsifiers like polysorbates [59]. One of the well-studied curcumin formulations is the phytosomal formulation of curcumin (Meriva), which is a complex of curcumin and phosphatidylcholine. Compared to uncomplexed curcumin, Meriva has improved bioavailability and pharmacokinetic profiles [56]. Researchers studied theracurmin, another curcumin formulation consisting of dispersed curcumin and nanoparticles, to determine how well it treats osteoarthritis compared to turmeric powder alone [62, 63]. Compared to turmeric powder, theracurmin has a 40-fold higher bioavailability in rats and a 27-fold higher bioavailability in humans. Nakagawa et al. found that theracurmin was effective at decreasing pain without any adverse effects [64].

## Curcumin analogous

In clinical practice, curcumin is one of the most difficult compounds to administer due to its low solubility in water, low oral bioavailability, and rapid degradation under physiological conditions [65]. A series of curcumin analogs have thus been developed, such as EF24, HO-3867, 2-HBA, and dimethoxy curcumin, in order to improve its biological activity, bioavailability, and therapeutic efficacy. These compounds are more effective than curcumin in preventing and treating a wide range of diseases and reducing age-associated disorders. It is still not clear how these compounds act as anti-aging agents [66–69]. The process of cellular senescence occurs when normal cells stop dividing after they have multiplied extensively or have been exposed to a lot of stress [2]. As a result of senescent cells (SCs) accumulating in various tissues with aging, it can be described as a hallmark of aging. Immune senescence decreases the ability of the body to clear SCs [70]. Despite the fact that cellular senescence is a tumor-suppressing mechanism, SCs can also play a causal role in aging and diseases due to aging by accumulating over time [71–73]. By considering that the pharmacological clearance of SCs may have the capacity to increase healthy life span and postpone the onset of age-related disorders, researchers hypothesized that curcumin and its analogs may also increase health span in part by functioning as novel senolytic agents. EF24, one of the synthetic analogs of curcumin, shows a tenfold greater potential for inducing cancer cell death than curcumin. Furthermore, EF24 is more effective against several cancer cells, and it has less toxicity against normal cells in comparison to cisplatin [74]. In addition, studies have shown that HO-3867, 2-HBA, and DIMC, which are other representative curcumin analogs, have also been reported to have improved anti-cancer activity compared to curcumin itself. Because curcumin has anti-aging activities, curcumin analogs can be used as a rich resource for the discovery of novel senolytic agents [67, 68, 75]. The result from the Wen Li et al. study shows that EF24 selectively induces SC apoptosis via increases in the proteasome degradation of the Bcl-2 anti-apoptotic protein. As a result of this study, curcumin analogs have the potential to function as anti-aging agents and may be useful for treating age-related diseases [76].

## Bioactivity

The wide range of beneficial biological functions of curcumin makes it a unique molecule that is able to affect multiple biological targets. It has been shown that this molecule can be effective against several disorders, such as cancer, cardiovascular dysfunction, neurological diseases, and autoimmune diseases [9, 34, 77]. A variety of studies have shown curcumin to have anti-oxidant, anti-inflammatory, and immunomodulatory effects in lung tissue, as well as anti-fibrotic and lung protective properties [78, 79]. Many biological targets, such as transcription factors, inflammatory mediators, growth factors, cytokines, cell cycle proteins, enzymes, protein kinases, and apoptotic proteins, as well as cellular pathways, can be modulated by curcumin [34, 80, 81]. According to research, it could regulate multiple cell signaling pathways, including tumor suppressor, cell survival caspase pathways, protein kinase, and death receptors, to modulate tumor growth [77, 80].

## Curcumin and its anti-ageing role

Curcumin has various roles in preventing aging and diseases related to it, among which are its effects on oxidative stress, inflammation, telomere length, signaling pathways, and proteins such as sirtuin. These are discussed in detail below and illustrated in Fig. 2.

### Curcumin effect on oxidative stress

There is evidence that elevated reactive oxygen species (ROS) levels can cause oxidative stress and severe damage to the organelle membranes, proteins, DNA, and lipids. This damage results in mitochondrial dysfunction, cell death, and an aging phenotype. Aging is associated with a decline in the production of ATP and ROS and a decline in anti-oxidant defense [82]. According to research, curcumin may be an effective anti-oxidant that reduces the effects of oxidative stress. The ability of curcumin to interact with various molecular mechanisms results in a reduction of oxidative stress, which is related to, among other things, its ability to chelate heavy metals and regulate enzyme activity [83]. Potential therapies to promote healthy aging can be developed using this approach. The anti-oxidant activity of curcumin has been demonstrated both in vitro and in vivo. Multiple cellular and animal models have shown that curcumin protects against oxidative and nitrosative stress. Researchers found that curcumin inhibited lipid and protein oxidation by reducing MDA, as well as protein carbonyls, thiols, and nitrotyrosine levels [84]. It has been demonstrated in several studies that heart tolerance to oxidative stress decreases as we age due to a decrease in anti-oxidant enzyme concentrations (GSH-Px and SOD), contributing to CV alterations [85]. Curcumin also stimulates the activity of the key anti-oxidant enzymes (superoxide dismutase (SOD) and catalase) of the defense mechanisms against free radicals produced during metabolic reactions [86]. One of the

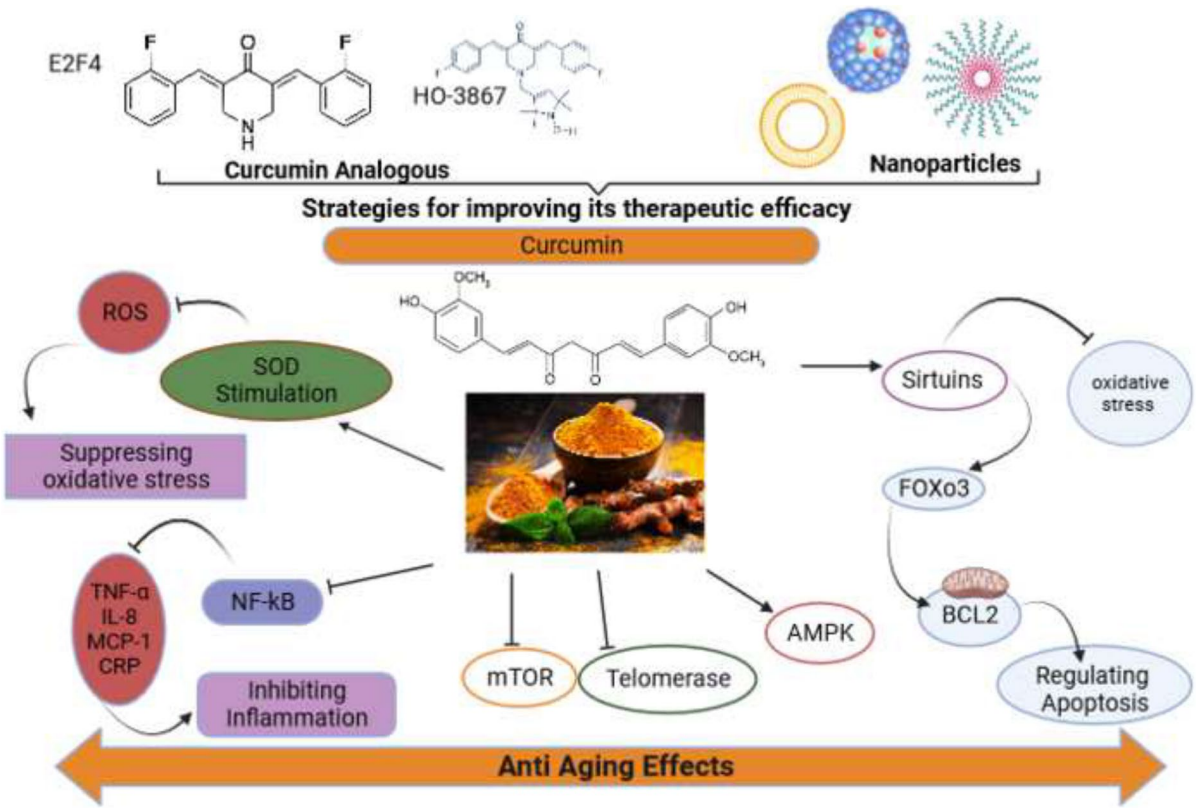


**Fig. 2** Curcumin has various roles in preventing aging and diseases related to it, among which are its effects on oxidative stress, inflammation, telomere length, signaling pathways, and proteins such as sirtuin

best strategies to reduce oxidative stress is to increase levels of endogenous and exogenous anti-oxidants. There are two ways to reduce endogenous oxidative stress: to prevent ROS formation or to quench it with anti-oxidants [87]. The chemical structure of curcumin makes it an excellent scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [88]. Combined, these findings confirm curcumin's anti-oxidant potential for organ health function as we age. Researchers need to investigate further the molecular targets and signaling pathways responsible for curcumin's anti-oxidant effects.

### Curcumin effect on inflammation

With age, inflammation-regulating mechanisms can become impaired, which may contribute to older people's susceptibility to infection and chronic diseases. Chronic pro-inflammatory status is a hallmark of aging [89]. The presence of chronic low-grade inflammation in the elderly without overt infection has been termed "inflammaging" and represents a significant health risk [90]. This low-grade, chronic inflammation develops with age and is characterized by high serum levels of mediators and inflammatory cytokines such as C-reactive protein (CRP), IL-8, IL-6, and tumor necrosis factor (TNF). There is an association between this pleiotropic cytokine and atherosclerosis, osteoporosis, and sarcopenia, as well as disability development and all-cause mortality [91]. Improved immune function in older adults is being explored in various ways. One of the low-tech strategies to combat inflammation is dietary intervention, including curcumin supplementation and healthy nutrition. Different cellular and animal models have illustrated curcumin's age-modulating properties and healthful effects [92]. A recent study demonstrated that curcumin may influence NF-κB (nuclear factor κB) activation due to its anti-oxidant properties. The NF-κB is involved in the response of the cell to the activation of free radicals, heavy metals, radiation, and the oxidation of low-density lipoproteins (LDL) [93]. Inflammation is triggered by all of these factors through the activation of NF-κB. Curcumin, by blocking the most relevant proinflammatory pathway, NF-kB, helps reduce inflammation and cellular damage. Therefore, this effect is useful for preventing aging-related cellular damage. In addition, results from studies have shown treatment with a low dose of curcumin leads to a decrease in the level of secreted pro-inflammatory cytokines such as IL-8 in normal young cells [94]. Inflammaging markers include not only cytokines but also acute-phase proteins such as CRP and mannose-binding lectins [95]. The results of a randomized clinical trial found that 80 mg/day of curcumin nanomicelles resulted in a statistically significant improvement in plasma levels of C-reactive protein [96]. A recent study has shown that the plasma level of circulating monocyte chemoattractant protein-1 (MCP-1) is associated with chronologic age in humans and can be considered a potential age marker [97, 98]. In vitro and in vivo studies demonstrated that curcumin significantly reduced the expression as well as production of inflammatory cytokines, such as monocyte chemoattractant/chemotactic protein-1 (MCP-1), and could be an effective and therapeutic agent for various inflammatory diseases by targeting multiple molecules [99]. Overall, curcumin is an important biochemical compound for reversing inflammation and enhancing immune system performance, both of which are essential factors in improving health and thereby slowing down aging.

### Curcumin effect on lengthens telomeres

The telomeres are highly conserved repetitive DNA sequences that undergo shortening with every division of a cell as well as with oxidative stress and aging [100, 101]. The catalytic subunit of hTERT (telomerase, human telomerase reverse transcriptase) functions during chromosomal replication to stabilize telomere length [102]. Numerous studies have shown that curcumin lengthens telomeres by enhancing telomerase activity [103], while curcumin inhibits telomerase activity in tumor cells, where growth is undesirable, supporting the body's natural anti-tumor response [104].

### Curcumin effect on the mTOR—the aging protein

One of the major evolutionary conserved signaling pathways that influences longevity is the mammalian target of rapamycin (mTOR). The mTOR (mammalian target of rapamycin), a phosphoinositide 3-kinase-related protein kinase, acts as a catalytic subunit in two protein complexes, including mTORC1 and mTORC2 (mTOR complex) [105, 106]. The primary evidence that mTOR modulates

aging comes from studies conducted in *Saccharomyces cerevisiae*, where it was shown that deletion of the Sch9 gene (a functional ortholog of the mammalian S6K gene) leads to an increase in the chronological life span of yeast [107]. In another study in the *Caenorhabditis elegans* model organism, both daf-15 (raptor) and let-363 (Ce TOR) mutants extended adult life spans by shifting metabolism to accumulate fat [108]. In some other aging model organisms, such as fruit flies and yeast, mutations in mTOR and numerous other mTORC1 cascade components are also associated with prolonged life spans [109, 110]. These studies determine that mTORC1 is a major evolutionarily conserved modulator of longevity. Research demonstrated that in RMS cells, curcumin at low concentrations could inhibit the IGF-1-stimulated, mTORC1-mediated phosphorylation of S6K1 and 4E-BP1 and the IGF-1-stimulated, mTORC2-mediated phosphorylation of Akt at higher concentrations [111]. These results were also observed in prostate (DU145), breast (MCF-7), and cervical (HeLa) cancer cell lines [111]. In human colorectal cancer cells (HCT116), curcumin decreased transcriptional and translational expression of mTOR, Raptor, and Rictor [112]. According to Lim et al., curcumin inhibits mTOR signaling by acting as a protonophoric uncoupler and activator of F0F1-ATPase, resulting in AMPK activation and inhibition of mTOR [113].

## Curcumin effect on AMPK

It has been demonstrated in several species that AMPK can exert pro-longevity effects [114]. AMPK is involved in the regulation of cellular metabolism, homeostasis, cell survival and growth, resistance to stress, and cell death, which are all the most important factors in aging and longevity [115]. A variety of indirect AMPK activators are currently being studied in clinical trials for their effects on aging-related characteristics, tissue homeostasis, and metabolic dysfunction in humans [116, 117]. A recent study showed that curcumin enhances AMPK phosphorylation by acting as an AMP-activated protein kinase (AMPK) agonist [118]. In addition, curcumin increased the phosphorylation of AMP-activated protein kinase (AMPK) in H4IIE and Hep3B cells [116].

## Curcumin effect on sirtuins

Sirtuins (nicotine adenine dinucleotide (NAD)-dependent deacetylases) are one of the most promising potential targets for delaying aging and increasing life span. In order to protect cells from DNA damage, efficient repair systems are sufficient to prevent it from accumulating. They play an essential role in maintaining the stability of genomes and the structure of telomeres. In addition, the function of these proteins is to assist in DNA repair as well as in epigenetic modification of histones [119]. In several studies, pretreatment with curcumin significantly increased Sirt1 activation and reduced oxidative stress [120]. Research has shown that curcumin can increase *Caenorhabditis elegans*' life span when sirtuin 2 (the homolog of mammalian sirtuin 1) is not mutated [94]. In primary cortical neurons, curcumin's neuroprotective effects are also mediated by sirtuin-1 induction. Neuronal injuries can result from the accumulation of extracellular glutamate. It is involved in cognitive functions such as synaptic plasticity, learning, and memory. In cortical neurons, curcumin inhibited glutamate excitotoxicity by deacetylating PGC-1α through Sirt1 and preserving mitochondrial functioning [121, 122]. Through synergetic activation of SIRT1 and PI3K/Akt signaling, as a result of enhancing FOXO3 phosphorylation, resveratrol improves the effects of exercise in elderly rat hearts [123]. According to studies, curcumin supplementation has similar effects. A combination of curcumin and physical performance can upregulate SIRT1 more effectively than dietary curcumin alone [124]. In conjunction with exercise, curcumin supplementation may increase AMPK phosphorylation, NAD/NADH ratio, and SIRT1 expression in muscles, as well as affect the time of exhaustion, improve exercise tolerance, and enhance the effect of exercise [125]. Due to increased resistance to stress conditions, improved exercise performance and fatigue prevention were observed in mice [126].

## Curcumin protects brain aging

Aging has a significant impact on the nervous system because of oxidative stress, mitochondrial dysfunction, and cell death [127]. In the CNS, microglial cells support the normal functioning of neurons and monitor their health in homeostasis, the resting

state. In normal conditions, microglia display protective effects. The activation of microglia plays a pivotal role in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, or injuries or infections to the brain by inducing oxidative stress and neuroinflammation in the brain. Various brain diseases and disorders cause microglia to transform into M1 phenotypes, which release cytokines, chemokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS) that promote inflammation. As a result of the overproduction of these inflammatory mediators, neuronal damage and death can occur. In previous studies, microglial activation and neuroinflammation have been shown to reduce the severity of neurodegenerative disorders [128–130]. There is a possibility that curcumin is a therapeutic molecule in the brain, as it inhibits microglial transformation, modulates inflammatory mediators, and counteracts neuroinflammation, which is the first step in neurodegenerative diseases [131]. In microglial cells, curcumin interacts with multiple molecular targets, including NF-κB. This may reduce the levels of pro-inflammatory markers and, therefore, the process of inflammation. The study demonstrated that curcumin blocked the LPS-mediated induction of COX2 by inhibiting NF-κB and activator protein 1 (AP1) in BV2 microglial cells [132]. Further, curcumin also promotes the development of the M2 microglial phenotype in an HO-1-dependent manner, thereby inhibiting the induction of iNOS and therefore reducing oxidative stress in microglia [133]. It has also been shown that curcumin inhibits microglial activation in the retinas of rd1 mice with retinal degeneration [134].

## Evidence from clinical trials

According to both in vitro and in vivo pre-clinical studies, curcumin has shown promise in reducing inflammation associated with chronic disease and infection, as well as limiting cancer proliferation [135–138]. There is still a question as to whether these benefits also apply to humans. Curcuminoid bioactivity has been demonstrated in rodent models, but concerns have been raised about curcuminoid bioavailability in humans. Curcuminoids undergo hepatic conjugation and circulate primarily as inactive glucuronides when ingested by humans and rodents [135, 139, 140]. Thus far, curcumin has been shown to be effective against a wide range of human diseases in clinical trials. It has also been shown that it can protect against hepatic conditions, chronic exposure to arsenic, and alcohol poisoning. These clinical trials tested curcumin in combination with quercetin, gemcitabine, piperine, docetaxel, isoflavone forms, bioperine, sulfasalazine, mesalamine, prednisone, lactoferrin, pantoprazole, and N-acetylcysteine [55]. There is no doubt that curcumin is efficacious against a wide range of human ailments [47]. We describe several clinical trials using curcumin in the following part of this article (Table 1).

### Psoriasis

About 3% of the world's population suffers from psoriasis (PsO), a chronic inflammatory, multifactorial disease. A thick, silvery plaque is the result of the uncontrolled proliferation of keratinocytes. Psoriasis pathogenesis begins with the activation of mature and inflammatory dendritic cells (DC), which leads to the release of cytokines, chemokines, and anti-microbial peptides. This is the first step in the pathogenesis of psoriasis [141]. Studies show that psoriasis patients have an increased number of Th22 cells. It is known that IL-22 is the prototypical cytokine secreted by Th22 cells, a subpopulation of T cells that produce IL-22 exclusively but not IL-17 or IFN-γ [142]. So, IL-22 plays a major role in several steps of the disease's pathogenesis, including inflammation and keratinocyte proliferation [143]. The clinical trial was conducted by Emiliano Antiga et al. and consisted of a randomized, double-blind, placebo-controlled design in patients with psoriasis vulgaris to assess the effectiveness of a bioavailable oral curcumin. In a study conducted by our team, 63 patients with mild-to-moderate psoriasis vulgaris were randomly divided into two groups. One group received topical steroids and Meriva, a commercially available curcumin delivery system based on lecithin, at a dose of 2 g per day (arm 1), and the other group received topical steroids alone. Clinical assessment and immunoenzymatic analysis show that curcumin has been demonstrated to be effective as an adjuvant therapy for the treatment of psoriasis vulgaris and to significantly reduce serum levels of IL-22. In addition, a study by Bahraini et al. highlighted that, compared to the placebo, turmeric tonic could lead to an improvement

**Table 1** Several clinical trials of curcumin

| Disease | Dose | Outcome | Ref |
|---|---|---|---|
| Obese and overweight | 500 mg | Curcumin had beneficial effects on body mass index, high-density lipoprotein levels, and triglyceride/high-density lipoprotein ratio | [163] |
| Solid tumors | 180 mg | Curcumin could suppress systemic inflammation by reducing TNF-α, CGRP, substance P, MCP-1, IL-6, and CRP | [164] |
| COVID-19 | 160 mg | Significant decrease in IL-6 and IL-1β gene expression and secretion level in serum and supernatant occurred | [165] |
| Fatty liver | 70 mg | Reduced liver fat content, body mass index, low-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, glucose, and glycated hemoglobin levels | [166] |
| Knee osteoarthritis | 500 mg | There was a significant reduction in flatulence episodes and anti-ulcer effect | [167] |
| Diabetes | 2 tablets (each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) | There was a significant improvement in the venoarteriolar response, as well as a decrease in the score of peripheral edema (a sign associated with failure of the venoarteriolar response) | [168] |
| Chronic kidney | Meriva® 500 mg/tablet | Curcumin caused a significant reduction in plasma proinflammatory mediators including CCL-2, IFN-γ, and IL-4 as well as a reduction in lipid peroxidation | [[169] |
| Diabetes | Two tablets/day (1 g Meriva/day) | Edema score decreased significantly and venoarteriolar response improved correspondingly | [170] |
| Osteoarthritis | 200 mg | CRP levels decreased and osteoarthritis was effectively managed | [171] |
| Lung cancer | 1.5 g | Curcumin caused a significant reduction in the urinary excretion of mutagens in the smokers which are in risk of lung cancer | [172] |
| Inflammatory bowel disease | 550 mg | In all patients with proctitis, symptoms, and inflammatory indices include ESR and CRP decreased significantly | [173] |
| β-Thalassemia | 500 mg | Curcumin causes a reduction in oxidative damage in patients with β-thalassemia | [174] |
| Prostate cancer | 100 mg | The PSA levels of the patients decreased | [175] |

*COVID-19* coronavirus disease, *TNF-α* tumor necrosis factor alpha, *CGRP* calcitonin gene-related peptide, *MCP-1* monocyte chemoattractant protein-1, *IL* interleukin, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IFN-γ* interferon gamma, *PSA* prostate-specific antigen

in psoriasis symptoms by significantly reducing the erythema, scaling, and induration of lesions (PASI score), as well as improving the patients' quality of life index (DLQI) [144].

## Vitiligo

As a result of vitiligo, the cells responsible for producing pigment (color) in the skin (melanocytes) are destroyed, resulting in white patches on the surface of the skin. It has been suggested that oxidative stress plays an important role in the pathogenesis of this disease [145]. In order to treat vitiligo effectively, narrowband ultraviolet B radiation (NB-UVB) is often prescribed. NB-UVB emits light of wavelengths between 311 and 312 nm, which belongs to the UVB spectrum [146]. In view of the anti-oxidant properties of curcumin, it is a potential treatment option for vitiligo patients. There was one study that examined whether the combination of NB-UVB and tetrarchy drocurcuminoid cream could

lead to synergistic therapeutic effects against vitiligo when used together. There were ten patients enrolled in this study who had vitiligo that was focal or generalized. In this study, two similar lesions were treated either with NB-UVB combined with topical tetrahydrocurcuminoid cream or with UVB alone. There was a statistically significant repigmentation in both treatment groups at the end of the study compared with baseline. It should also be noted that the combination group showed a slightly greater degree of repigmentation at 8 and 12 weeks, and the tetrahydrocurcuminoid treatment was well tolerated [147].

### Arthritis

Arthritis is a chronic disease caused by inflammation of the joints. The disorder usually results from a dysregulation of pro-inflammatory cytokines and pro-inflammatory enzymes that lead to the production of prostaglandins (such as COX-2) and leukotrienes (such as lipoxygenase), as well as matrix metalloproteinases and adhesion molecules. Osteoarthritis is typically treated with exercise, lifestyle changes, and NSAIDs. There are, however, numerous adverse effects associated with the use of NSAIDs. Several studies have shown that curcumin improves the symptoms and delays the progression of rheumatoid arthritis by inhibiting several proteins such as extracellular signal-regulated protein kinase (ERK), mitogen-activated protein kinase family (MAPK or MAP kinase), activator protein-1 (AP-1), and nuclear factor-κB (NF-κB) signaling pathways in rheumatoid arthritis patients. In addition, the use of 250–1500 mg/day of turmeric by rheumatoid arthritis patients over 8–12 weeks can increase the function of dysfunctional immune cells (including TH1, TH17, Treg, and B cells) and decrease clinical symptoms.

## Curcumin effect on aging related disease

### Alzheimer's disease

Aging is the most critical risk factor for many noninfectious diseases, including Alzheimer's disease (AD). Alzheimer's disease is generally a progressive neurological disease that affects mostly people over the age of 65. There are three phases involved in the pathogenesis of Alzheimer's disease: fibril formation, amyloid plaque formation, and plaque deposition in the brain. Patients with Alzheimer's disease are believed to lose cholinergic neurons in the basal forebrain due to these plaques [148]. It is evident that alternative treatments are needed for this disease because the currently available treatments have numerous adverse effects. The study was conducted as a randomized, double-blind, placebo-controlled study by Baum et al. on 34 patients with Alzheimer's disease. Curcumin was administered at two different doses (1 or 4 g) or placebo (4 g). After curcumin treatment, the Mini-Mental State Examination (MMSE) score did not improve [149]. Curcumin can help slow the progression of disease and modulate cognitive function and biomarker levels. Clinical trials may have failed due to the poor bioavailability of curcumin, the selection of cohorts at an advanced stage of AD, and biological differences between rodent models and AD patients. Despite being successful in animal models, many interventions have failed in clinical trials [150].

### Cardiovascular disease

With aging, the cardiovascular system is significantly affected, which can lead to atherosclerosis, hypertension, myocardial infarction, and strokes. A number of pathological changes may occur in aging cardiovascular tissues, including hypertrophy, altered diastolic function of the left ventricular (LV), diminished reverse systolic capacity of the LV, increased arterial stiffness, and impaired endothelial function [151]. There has been much attention focused on unraveling the mechanisms and optimizing treatment regimens for cardiovascular diseases (CVDs), which cause the highest mortality rates worldwide [152]. Numerous studies have demonstrated the cardiovascular-protective properties of curcumin. Randomized clinical trial study results by Jessica R. et al. show that curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults, corroborated by murine studies [153]. Further, curcumin consumption positively correlates with improved central arterial hemodynamics and reduced endothelial dysfunction in postmenopausal women [154, 155]. An additional randomized placebo-controlled study of 45 postmenopausal women found that endurance exercise in combination with curcumin significantly reduced left ventricular afterload. Those who received endurance exercise and curcumin together also experienced a decrease in systolic blood pressure [154]. Moreover, in another

study, after 7 days of curcuminoid supplementation, serum triglyceride concentrations were significantly reduced [156]. According to a randomized controlled trial conducted on 87 non-alcoholic fatty liver disease patients, 1-g curcumin supplements for 8 weeks significantly reduced total cholesterol, non-high-density lipoprotein cholesterol (*non*-HDL-C), uric acid, and triglycerides [157]. The effects of curcumin on the well-being of 38 healthy volunteers were investigated using a lower dose of curcumin (80 mg/day). According to the results, curcumin significantly lowered the plasma level of triglyceride and some other relevant parameters, such as plasma beta-amyloid protein and salivary amylase [158].

## Side effects of curcumin

Several clinical trials have demonstrated curcumin's efficacy and safety. Despite the safety of this product, some side effects have been reported. Some mild adverse effects have been reported with high doses of curcumin, including diarrhea, headache, rash, and yellow stool [159]. Also, nausea and diarrhea and increased serum alkaline phosphatase and lactate dehydrogenase contents were experienced in patients who took low doses of curcumin [160]. Studies have shown that taking turmeric supplements of up to 8000 mg per day for 8 months is safe and does not harm humans. Up to 8000 mg of curcumin daily has been safely administered for 3 months [161]. When consumed with piperine, curcumin enhances bioavailability, which in turn may impact its safety profile [162]. Unfortunately, curcumin's inadequate bioavailability and delivery render it ineffective for medicinal purposes. This review presents practical strategies to comprehensively enhance curcumin bioavailability.

## Conclusions and future perspective

Modern aging research focuses on discovering new agents and strategies to fight aging and age-related diseases. To current knowledge, curcumin is one of the most promising candidates to achieve this purpose. It has powerful anti-inflammatory effects and is a very strong anti-oxidant with great potential to impact on age-related cellular proteins. Despite this, evidence from clinical studies on curcumin's long-term effects on age-related pathology remains largely unexplored. Several strategies have been proposed to increase the systemic bioavailability of curcumin, but the long-term effects of such preparations are unknown, and higher concentrations may even have the opposite effect. However, curcumin's poor bioavailability limits its clinical use against cancer. The list above includes some strategies that can help address the issue of curcumin's poor bioavailability. Furthermore, any method that enhances curcumin's bioavailability can boost its efficacy while increasing the risk of side effects. For instance, nanoparticles or carriers used in drug delivery can reduce the required dosage by releasing the drug slowly in tumor sites, thereby minimizing curcumin's toxicity. Additionally, curcumin should be studied as a synergistic treatment for age-related disorders with other existing drugs. In addition, in the future, further studies are warranted to clarify the mechanisms of curcumin function and determine the possibility of applying it in clinical settings.

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