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Review

The role of curcumin in aging and senescence: Molecular mechanisms

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ABSTRACT

Healthy aging and human longevity are intricate phenotypes affected by environmental factors such as physical exercise, diet, health habits, and psychosocial situations as well as genetic factors. Diet and caloric restriction have a crucial role in healthy aging. Curcumin, a polyphenolic compound isolated from the *Curcuma longa*, has been shown to exert anti-aging characteristics. Recently, investigations on curcumin with regard to aging and age-associated disease in model organisms has described that curcumin and its metabolites, prolong the mean lifespan of some aging model organisms such as *C. elegans*, *D. melanogaster*, yeast, and mouse. It has been proposed to have several biological activities, such as antioxidative, anti-inflammatory, anticancer, chemopreventive, and anti-neurodegenerative characteristics. In several studies on various model organisms it has been shown that the lifespan extension via curcumin treatment was connected with enhanced superoxide dismutase (SOD) activity, and also declined malondialdehyde (MDA) and lipofuscin levels. As well as the pivotal role of curcumin on the modulating of major signaling pathways that influence longevity of organisms like IIS, mTOR, PKA, and FOXO signaling pathways. This review defines the use of curcumin in traditional and modern medicine, its biochemistry and biological functions, such as curcumin's anti-aging, anti-cancer, anti-microbial, anti-inflammatory, and anti-oxidant characteristics. Also, the review further describes the role of curcumin in a pharmacological context and new insights on its therapeutic capacity and restrictions. Particularly, the review emphasizes in-depth on the efficiency of curcumin and its mechanism of action as an anti-aging compound and also treating age-related disease.

1. Introduction

Aging is one of the most complex and intricate phenomenon in the biological context. Aging is described as a physiological decrease of several biological activities in the organ with a gradual reduction of cellular adjustment to external and internal injuries [1,2]. The senescence that is known also as cellular aging is the hallmark of aging, and includes the reduction of the regenerative capacity of cells. In this regard, cellular senescence seems to be harmful because it consists of a defect of tissue renewal and functionality. Cellular senescence is an irreversible growth arrest by which cells cease to replicate; it occurs in somatic cells and limits their proliferative life span [3,4]. Thorough knowledge of aging needs a comprehensive approach to all biochemical and physiological systems. The aging phenotype of humans is highly heterogeneous and can be defined as an intricate mosaic that is a consequence of the interaction of numerous environmental and stochastic events, and also genetic, and epigenetic modifications that are accumulated during the lifetime. Although it's huge intricacy, the basic molecular mechanism and main pathways of aging are restricted to a few biochemical mechanisms and pathways that are also highly conserved and are responsible for maintaining tissue homeostasis [5–7]. Diet has been indicated to play a pivotal role in the process of aging. Several dietary compounds, that are in fruits, vegetables, and spices, have been extracted and assessed through several years for their anti-aging and therapeutic capacity [8,9]. Dietary phenolic compounds like phenolic acids and flavonoids are useful for longevity via decline of oxidative stress, modulating signal transduction, and gene expression [10,11]. Curcumin (diferuloylmethane), is a main bioactive

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polyphenolic compound (Fig. 1) that is extracted from the Curcuma longa (Tumeric) rhizomes, which belongs to Zingiberaceae family and is broadly cultivated in Southeast Asia and India [12,13]. Curcumin is a yellowish compound, which has been broadly used as a food additive, dietary spice, and herbal remedy in Asia. Several investigations have revealed that curcumin possesses potent biochemical and biological activities, including anti-inflammatory, anti-viral, anti-bacterial anti-oxidant, and anticancer activities. Curcumin has strong antioxidative effects and maintains the cells against protein carbonylation, lipid peroxidation, and also mitochondrial permeability transition [12,14]. In traditional herbal medicine, curcumin is used to improve the immune system and as a treatment for various respiratory disorders like allergy and asthma. Curcumin has also been traditionally used for the treatment of numerous diseases including ulcers, dysentery, jaundice, upset stomach, flatulence, sprains, arthritis, acne, wounds, and eye and skin infections. It has broadly been approved from ancient times that this polyphenolic compound has anti-inflammatory characteristics. Numerous advances in modern medicine have exhibited several unknown medicinal characteristics of curcumin which include anti-cancer, antioxidant, anti-mutagenic, anti-cardiovascular, and anti-microbial activities. In recent years, several clinical investigations revealed that curcumin has therapeutic capacity against numerous chronic disorders, such as pulmonary, cardiovascular, neurological, neoplastic, psychological, and metabolic diseases [15,16]. The therapeutic impacts of curcumin were further enhanced in some epidemiological studies in the populations that consume curcumin such as India by which long-term curcumin consumption revealed a considerably lower incidence rate of neurodegenerative disease cases. As well as the epidemiological evidence suggested that, curcumin is responsible for the remarkably diminished (4.4-fold) prevalence of Alzheimer's disease (AD) in India compared to the United States [17,18].

This review describes the effect of curcumin in aging and longevity of various invertebrate model organisms and mammals and also last progresses in the investigation of signaling pathways and regulation of longevity, assuming that the metabolic and endocrine adaptations detected in these organisms through diet and caloric restriction might be a physiological measurement for prolonging the lifespan via a decline in metabolic rate, better regulation in signal transduction and functional reserve capacity of cells, tissues and organ systems.

2. Replicative senescence and aging

The Hayflick demonstrated that the human cell population is limited in the number of times it can divide or repair during its progress of living. In 1961, Dr. Hayflick theorized that the human cell's capability to divide and repair is limited to approximately between 40 and 60 times in cell culture before reaching senescence, which is known as "Hayflick limit'' [19]. Cellular senescence is an irremediable growth arrest by which cells cease to replicate; it takes place in somatic cells and restricts their proliferative life span [20]. Cellular senescence is commonly divided into the following two major forms: an intrinsic form that is telomere-dependent and is known as replicative senescence (RS), and also an extrinsic form that is telomere-independent and is known as stress-induced premature senescence (SIPS) [21,22]. The cells that go through RS exhibit a flattened and enlarged morphology, RS was described as a process that can restrict the life span of cells by decreasing their proliferation capacity. Remarkable progress has been done in discovering the core regulatory pathways that modulate this physiologic program. While replicative senescence is modulated via a biological clock that is linked to the progressive shortening of repetitive DNA sequences (TTAGGG), which is known as telomeres and cap the chromosome ends, the latter phenomenon is not programmed but is biological evidence of senescent characteristics applied through stress. The role of SIPS is now gaining broad prominence due to the fact that it is a relative extension to the concept of exogenous harm to a cell. SIPS is induced via different stressors, including ROS, oncogenic Ras activation, DNA damage/mutation, mitochondrial injury, and chemotherapeutic regimens and radiation. These stresses cause the activation of the premature senescence process independent of telomere length [21–23].

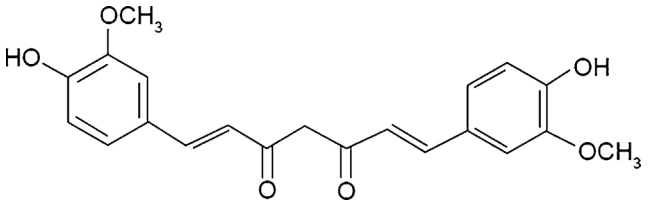

Fig. 1. Chemical structural formula of curcumin.

Senescent cells exhibit a flattened and enlarged morphology and also different biomarkers of the senescent phenotype such as G0/G1 cell cycle arrest, senescence-associated β-gal activity, lipofuscin accumulation, and mitochondrial dehydration or senescence-associated gene expression verified the homogeneity of these permanent, premature cell cycle arrests and replicative senescence [22,23]. Identification of the distinctions between SIPS and RS senescence is essential for the progression of anti-aging therapeutic methods and treatment of age-related diseases that also don't induce tumor formation.

3. Antioxidant effect of curcumin

Among several theories of aging, the most popular aging theory is oxidative stress theory of aging [24]. It describes that aging and age-related disease are caused by oxidative damage to macromolecules such as DNA, lipid, and proteins. An enhanced lifespan is firmly connected with increased survival under oxidative stress or heat conditions [25].

Diet is an essential factor in the process of aging [8,9]. Dietary phenolics are advantageous for healthy aging and longevity via decreasing oxidative stress and modulating age-related signaling pathways [10,11]. Curcumin possesses antioxidant characteristics, and function as a biochemical antioxidant, and also improves cellular antioxidant defenses [13,14]. Antioxidant activity of curcumin was detected to be about 10 times higher than vitamin E [26]. Curcumin is one of the potent antioxidants with great potential to reduce age-related cellular damage induced by the generation of reactive oxygen species (ROS). Due to the presence of phenolic groups at the chemical structure of curcumin, it shows a powerful hydrogen-donating antioxidant activity [12–14]. As well as, it was shown that curcumin is a hormetic agent that stabilizes nuclear factor-erythroid-2-related factor 2 (Nrf2) and enhances expression of heme oxygenase-1 (HO- 1). It triggers the Nrf2 pathway which has a pivotal role in activating antioxidative enzymes, including thioredoxin reductase, Hsp70, heme oxygenase and sirtuins (Fig. 2). Therefore curcumin is proposed as hormetin [27–29].

Several investigations have shown that curcumin prevents lipid peroxidation, and increases the antioxidants activities, including glutathione-s-transferase (GST), glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in a different type of cancers in the various organs [30,31]. In another study was shown that curcumin inhibits rat liver microsomal lipid peroxidation [32], also in rat brain homogenates, where curcuminoids revealed more potent antioxidant activity than vitamin E (alpha-tocopherol). One of the major metabolites of curcumin is tetrahydro curcumin that was reported to remove the ROS formed through hyperglycemia and enhance the concentration of GSH in the cultured rat lens [33]. As well as, Goel et al. [34] has described the effects of curcumin on various target molecules indirectly or even directly that are connected with different metabolic functions, and also some clinical experiments with curcumin in patients have shown these powerful effects. Interestingly in one study by Saghir et al. was reported that after feeding the rats with curcumin for seven days before treatment with cyclophosphamide (CP) to stimulate lung injury, revealed an enhancement in cellular antioxidant defenses [35].

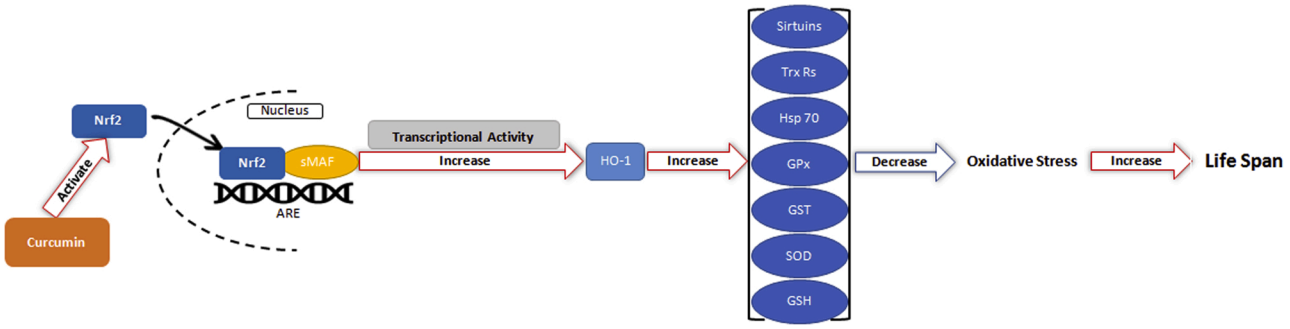

Fig. 2. Curcumin effect on oxidative stress pathway and lifespan.
Curcumin activates Nrf2/HO- 1 signaling pathway. It triggers the Nrf2/ARE signaling pathway which resulting in activating Hsp70, thioredoxin reductase (Trx Rs) sirtuins, and antioxidant enzymes which inhibit oxidative stress and increase life span.

The interest in health benefits linked with anti-oxidants consumption resulted in experiments investigating the possibility that diets rich in anti-oxidants promote lifespan extension. Investigations using the *D. melanogaster* as an aging model organism have reported that the antioxidants vitamin E and N-acetyl cysteine extend lifespan [36,37]. The study that was reported by Suckow [38], described that the lifespan extension by curcumin can be the consequence of enhanced SOD activity. Also, they used disulfiram that can eliminate the lifespan extension via inhibition of SOD. Their results suggested that increased activity of dismutase is connected with increased lifespan by curcumin. In another study, Lee et al. [39] measured whether curcumin can prolong lifespan in flies, also maintains flies against nutritional and oxidative stresses by subjecting curcumin-fed flies to starvation and hydrogen peroxide. A remarkable enhancement in the percentage of survivors was detected in the flies that were pretreated with curcumin and then treated to H2O2. However, the activity of SOD was not measured in this study. Interestingly, Shen et al. [40] investigated the effect of curcumin on longevity in *D. melanogaster* and clarified its connection with curcumin-mediated SOD activities. They found that after increasing the concentration of curcumin in diets supplement it was associated with enhanced SOD activity in males and females Drosophila. Also, the level of MDA as an end product of lipid peroxidation was decreased in both males and female fruit fly. As well as there is another investigation in the role of curcumin to extend the lifespan in *D. melanogaster* [41–43]. Interestingly in another study, Liao et al. [44] was shown that curcumin can enhance the resistance of *C. elegans* to oxidative and thermal stresses. As well as, they found that curcumin can extend the lifespan in mev-1 mutants. MEV-1 is a subunit of complex II of mitochondrial respiratory chain, and the deletion mutant of mev-1 was very susceptible to ROS and showed a decreased lifespan, mainly according to mev-1 mutant overproducing ROS from electron transport complex II of *C. elegans*. In addition, they found that curcumin-treated skn-1 mutants did not exhibit a lifespan extension, which demonstrates that SKN-1 has an essential role in curcumin-mediated lifespan. The SKN-1 protein is homologous to the vertebrate Nrf proteins, which stimulate the defend mechanisms against oxidative stress and acts in different longevity pathways. In 2019 for the first time, Stepien et al. [45] reported the anti-oxidative and anti-aging effects of curcumin on the S. cerevisiae as an aging model organism. They reported that curcumin remarkably promotes chronological and replicative aging of yeast cells lacking antioxidative enzymes (gene deletion of SOD1 and SOD2) and DNA repair mechanisms (RAD52). Fascinating, they found that curcumin can delay aging in the wild-type strain BY4741, through hormesis effect.

4. Effect of curcumin on cellular senescence and telomere

The telomere theory of aging and cellular senescence proposes an elucidation of the mechanism by which cells evaluate the number of divisions and define when termination of replication is suitable [46]. Telomeres are the specific DNA–protein structures found at both ends of each linear chromosome, maintain the genome from unnecessary recombination, nucleolytic degradation, and chromosomal end fusion. Telomeres do not contain active genes, but instead, act to maintain the chromosome ends from damage and to inhibit the end of chromosome from fusing with each other or with other DNA molecules inside the cell. Therefore, telomeres play a pivotal role in preventing the loss of genomic information. In normal cells that lack telomerase, according to the shortening of telomeres at each cell division stage, the cells undergo senescence and/or apoptosis. Telomere length also acts as a biological clock to define cellular and organismal aging [47–49]. Besides the telomeric DNA loss with replication, the oxidized telomeric DNA is a crucial cause of the telomere shortening in a normal human cell. Interestingly increased production of ROS was demonstrated to increase telomere shortening in fibroblast cells [50,51]. In another study, human fibroblasts were treated with α-phenyl-t-butyl-nitrone, as a free radical scavenger that slows the shortening of telomere and also elongates the replicative lifespan [52]. After the exposure of the cells by irradiation and free radicals, these agents induce the genomic DNA damage and lead to a DNA damage response [53,54]. Some investigations have exhibited that telomeric DNA is a special aim of oxidative damage. ROS causes telomere shortening through augmentation of telomeric single-strand breaks induction and telomere dysfunction [55,56]. Nutrition seemed to have an effect on the rate of cell division, in which cell replication in overfed cells is faster than under fed cells [57,58]. Better choice of diet and physical exercise has a great effect to decrease the telomere shortening rate or at least inhibit more telomere attrition, resulting in the delayed onset of age-related disorders and also can prolong the lifespan [59,60]. Several functions of curcumin can be also described via its capability to suppress acute and chronic inflammation through scavenging ROS and increasing antioxidant defense. The ability of ROS scavenging and prevention of lipid peroxidation, related to the electron-donating group on the phenolic rings of curcumin [12–14,30,31]. Interestingly Cui et al. [61] measured the effects of curcumin on telomerase activity and cell proliferation in some human tumor cell lines including, SGC7901, HL60 and Bel7402. They found Curcumin inhibits cell growth in these tumor cell lines in a concentration-dependent manner, also anti-cancer effects of curcumin were shown when it was administered to nude mice transplanted with the human tumor cells. After treatment of the cells with 1 μM of curcumin for 120 h, apoptotic cells were detected. Also, after treatment of extracted cells with 1 μM of curcumin, the suppression of telomerase activity was detected. In another study, Khaw et al. [62] showed telomerase-positive human glioblastoma and medulloblastoma cell lines exhibited higher sensitivity to curcumin compared to the normal human fibroblasts. Inhibition of telomerase activity was seen in all the telomerase-positive cell lines tested following treatment with curcumin.

Telomere uncapping causes cellular senescence. Age-associated telomeric DNA damage may cause t-loop uncapping and induce

double-stranded DNA break (DSB) response, leading to phosphorylation of histone 2A.X (p-H2A.X) molecules in telomeric chromatin-associated p53 (p53) activation. Activated p53 binds to cyclin-dependent kinase inhibitor 1 (p21), resulting in cellular senescence [63]. One of the most indirect anti-aging activity of curcumin is its anti-tumor effect which is mediated by uncapping telomere. Curcumin can inhibit tumorigenesis through induction of apoptosis and senescence [64]. Besides the effects of curcumin in down-regulating hTERT mRNA and inhibiting telomerase activity, it can also lead to significant or moderate telomere shortening in different cells. In some studies, long-term treatment with a high dose of curcumin could induce senescence via telomere uncapping in tumor cells [62,65]. Accordingly, Khaw et al. [62] reported that following long-term treatment with curcumin, brain tumor cells exhibit a reduction in the mean telomere length. This reduction was associated with curcumin-induced telomerase inhibition. The ONS76 and KNS60 cells, which had inherently longer telomeres, showed significant telomere shortening after the long-term treatment. The U251MG and A172 cells which had shorter basal telomere lengths exhibited modest telomere shortening at the end of long-term curcumin treatment. As well, they found that the curcumin-induced remarkable increase in DNA damage and cell death in brain tumor cells. The curcumin down-regulated E2F1, CCNE1, CDK2, and up-regulated PTEN genes and also increased the activity of caspase-3/7, which indicating that brain tumor cells treated with curcumin may undergo cell cycle arrest and apoptosis.

5. Effect of curcumin on major signaling cascades in aging

Among various signaling cascades through aging, the major evolutionary conserve signaling pathways that are known to influence longevity of organism are the insulin/insulin-like growth factor (IGF) signaling (IIS), the serine/ threonine kinase mechanistic target of rapamycin complex (mTORC), and the protein kinase A (PKA) pathways [66]. During recent years, one of the main reviewed subjects in aging is about the pivotal role of the IIS pathway in the modulation of longevity. Cumulative data proposes that this signaling cascade has a pivotal role in the pathogenesis of numerous disorders of elderly such as, cardiovascular, dementia, cancer, and metabolic disorders. In animal model organisms it was exhibited that down-regulation of the IIS pathway remarkably extends the lifespan. However, the data about humans is counteractive [67,68]. In invertebrates, the IIS pathway is modulated by numerous peptides that can interact with insulin/IGF-1receptor. In the model organism *C. elegans* the IIS pathway consists of numerous proteins encoded by some genes, such as age-1 (PI3K homologue), daf-2 (homologue of mammalian insulin/IGF-1 receptor), daf-18 (encoding the homologue of the human tumor suppressor PTEN), and akt-1 (serine-threonine protein kinases). The decreased activity of age-1, akt-1, and daf-2 genes was exhibited to down-regulate this signaling cascade, and the worms with mutations in these genes were shown to have an enhanced lifespan. Whereas, the induction of the IIS pathway reduces the nematode's lifespan [69,70]. In the *D. melanogaster* the IIS pathway consists of the Dp110/p60 (PI3K), DAkt1 (the PI3K target PKB), CHICO (insulin receptor substrate), and the DInR (homologue of Insulin /IGF-1 receptor). The fruit flies with mutations in these genes were shown to have remarkably enhanced longevity [71,72]. Fig. 3 indicates the molecular mechanisms of longevity effects of curcumin in invertebrate species.

Interestingly in another study, Holzenberger et al. [73] was reported, IGF-1 receptor knockout mice (IGF-1R+/−), which is heterozygous in a mutated allele, exhibited very low levels of IGF-1, around 16 percent enhanced lifespan in males and also 33 percent in females. Whereas the majority of IGF-1 receptor knockdown mice (IGF-1R−/−) died at birth. In another investigation using Lit/lit mice that are GHRHR (growth hormone-releasing hormone receptor) deficient, these mice were dwarfs, exhibited lower tumor incidence, enhanced adiposity, and an increased lifespan [74]. Interestingly, Sun et al. [75] was shown that GHRH (growth hormone-releasing hormone) knockout mice live 51 percent (in males) and 43 percent (in females) more than wild-type controls and show several phenotypic features like Ames dwarf mice, such as a decrease in plasma cholesterol and triglyceride levels, increased insulin sensitivity, increase in plasma adiponectin and leptin levels and adiposity. Furthermore, one of the key proteins that is recognized to modulate aging in mice is p66Shc. It is a protein that negatively regulates IIS pathway via MAPK pathway activation. It was reported that P66shc knockout mice had normal phenotype, but lived 28 percent more than wild-type animals [76].

The Mammalian target of rapamycin (mTOR) is a protein-related to the PI3K-related protein kinase (PIKK) that acts as a catalytic subunit in two protein complexes, including mTOR complex 1 (mTORC1) and mTORC2 [77]. One of the major intracellular targets of IIS is mTORC, which is activated in response to ample nutrient supplies and growth factor signals. It has been exhibited that suppression of the mTOR pathway through pharmacological inhibitors or genetic interventions is associated with longevity among invertebrates and human species [78,79]. The primary evidence that the mTOR signaling pathway could modulate aging relates to investigations in S. cerevisiae, in which it was reported that gene deletion of Sch9 (functional ortholog of mammalian S6K), increases yeast chronological lifespan [80]. As well as, in *C. elegans* model organism, both daf-15 (raptor) and let-363 (Ce TOR) mutants, shift metabolism to accumulate fat and extend adult lifespan [81,82]. More investigations in some another aging model organisms such as fruit fly and also yeast, illustrating that mutations in mTOR and numerous other parts of the mTORC1 cascade also enhance lifespan [83,84].

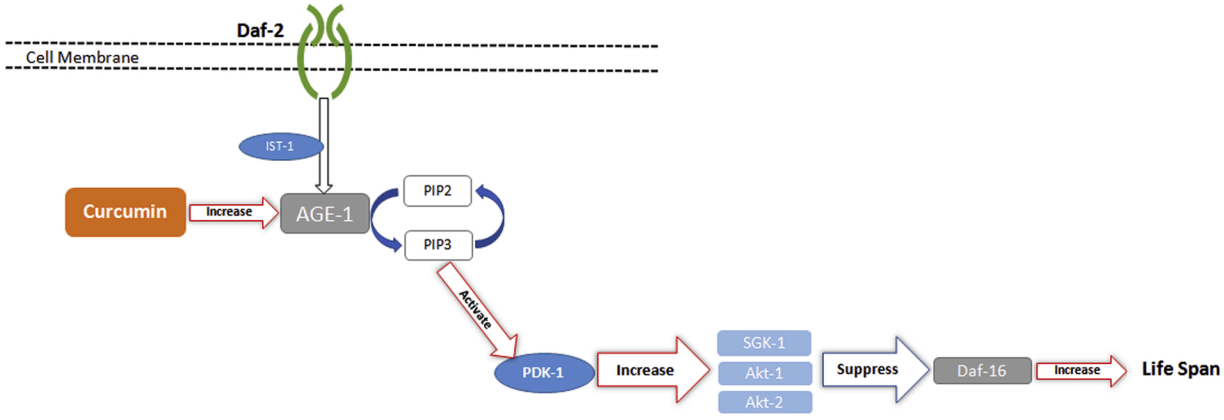

Fig. 3. Longevity effects of Curcumin in Invertebrate Species.
The stimulatory effect of curcumin on AGE-1/PDK-1 activity increases the expression of SCK-1, AKT-1 and AKT-2 and consequently decreases Daf-16 expression. DAF-16 is one of the most important factors that can increase life span in invertebrate.

Additionally, some investigations exhibited that rapamycin prolonged lifespan in yeast [85,86], nematodes [87], fruit flies [88], and mice [89–91] profoundly determining mTORC1 as a major evolutionarily conserved modulator of longevity. A decrease in the intake of nutrients in the absence of dietary restriction or malnutrition extends lifespan in several various organisms [92]. In fact, in addition to mTORC1 inhibition, dietary restriction is now a common strategy to prolong lifespan in some aging model organisms such as yeast, flies, worms, and mice. Thus, the mTORC1 pathway has a pivotal role in modulating longevity as a consequence of dietary restriction, which its action is in responding to growth and nutrient signals. Caloric restriction decreases mTORC1 activity in some mammalian tissues and invertebrate model organisms, and also through non-caloric restriction conditions, genetic or pharmacological disturbance of mTORC1 is adequate to prolong lifespan in both mice and invertebrates [93]. Interestingly, Anisimov et al. [91] reported the mice that were treated with rapamycin, mean lifespan extension was about 10 percent in males, and 18 percent in females. In another study by Selman et al. [94] reported that knockout of the S6K gene in mouse was shown to enhance lifespan in females, but without any longevity benefits in males.

PKA is one of the most crucial mediators of signaling pathway downstream of G-protein-coupled receptors (GPCRs) and has a pivotal role in the modulation of triglyceride storage and metabolism. [95]. PKA is a cAMP-dependent kinase, which requires cAMP for its activation. There are two catalytic and also two regulatory subunits in PKA. cAMP can bind to the regulatory subunits of PKA, after that release the catalytic subunits which then can interact with and phosphorylate downstream targets. There are three types of catalytic subunits (Cα, Cβ, Cγ), and also regulatory subunit consist of four isoforms (RIα, RIβ, RIIα, RIIβ), each one of them represents various patterns of tissue expression and subcellular localization [96,97]. It has been reported that disruption of regulatory RIIβ subunit of PKA extended lifespan in C57/BL6J male mice and are also resistant to age-associated diseases such as cardiac decline. As well as, there was no lifespan advantage seen in PKA RIIβ females [98].

The FOXO family consist of evolutionarily conserved isoforms that in mammals include, FOXO1, FOXO3, FOXO4, and FOXO6, in *C. elegans*, DAF-16, and DFOXO in *D. melanogaster*. The activity of FOXO proteins is associated with different cellular processes including cell differentiation, glucose metabolism, cellular detoxification, DNA repair, and apoptosis [99–101]. The insulin/ IGF-1 pathway initiates intracellular signaling mediated by AKT, enabling phosphorylation of three conserved residues within the FOXO transcription factors. The phosphorylation of FOXO by AKT results in the export of proteins to the cytosol and thus suppresses the expression of FOXO-dependent genes. However, upon cellular stress or in the lack of growth factor signaling, FOXOs transfer into the nucleus and result in the expression of FOXO-dependent gene [102,103]. Numerous mechanisms of how FOXO proteins promote the longevity of model organisms have been proposed. Forkhead proteins modulate lifespan in some of the simple invertebrate organisms including C. elegans [104]. The homologue of Forkhead protein in worms is DAF-16 that is connected to longevity [105]. Interestingly, in one study Liao el al [44]. showed treatment of curcumin can prolong the lifespan in daf-16 mutants of *C. elegans*, proposing that curcumin might function independently of DAF-16. However, curcumin in age-1 mutants that are oxidative stress-resistant, did not extend the lifespan, proposing that AGE-1 might be engaged in curcumin-mediated longevity. AGE-1, as homologue of PI3K, plays a pivotal role in the IIS cascade which prevents DAF-16 activity. The investigation about that AGE-1 is engaged in curcumin-mediated lifespan extension, whilst DAF-16 was also showed in a quercetin-mediated longevity experiment [106]. Considering that DAF-16 is not necessary for the modulation of lifespan by curcumin, probably another members of the IIS pathway are engaged in curcumin-mediated longevity. Also, Xiang et al. [107] found that tetrahydrocurcumin (THC) one of the active metabolites of curcumin, is linked with the antioxidative stress response and also life span extension in *D. melanogaster* via the FOXO transcription factor. In the beginning, they used a mammalian cell culture system and they detected that THC could regulate the nuclear translocation of FOXO4. Also, they considered that Akt might be engaged in this effect since after treatment of cells with THC caused Akt dephosphorylation. The Phosphorylation of Akt normally prevents the FOXO nuclear translocation. To further support this hypothesis, they detected that THC prolonged the life span of *D. melanogaster* under oxidative stress and it was foxo-dependent. Interestingly in one study on mammal Kitani et al. [108] showed that mice treated with THC survive for an enhanced period of time. Fascinating, it was reported that also the mean life span of the mouse, but not the maximum life span, was prolonged via THC treatment. Fig. 4 indicates the effect of curcumin on signaling cascades in the aging process.

The p53 protein acts as a tumor suppressor and regulates the expression of a large number of target genes involved in cell cycle arrest, DNA repair, senescence, and apoptosis [109]. The non-functional or mutated p53 has been reported in most human cancers result in apoptotic resistance and continued proliferation [110]. The p53/p21 pathway has a pivotal role in the initiation of senescence and the p16/Rb pathway seems to have a key role in the maintenance of senescence [111,112]. Some tumor suppressor microRNAs can regulate senescence by controlling the p53 and Retinoblastoma (Rb) network [113]. It was found that curcumin could affect p53/Rb network, leading to control of the progression of cancer by inducing senescence in cancerous cells. In this regard, curcumin inhibited the progression of mouse fibroblast L929 cells through inducing the proapoptotic protein p53 and its effector protein p21 and down-regulating of cell cycle regulatory proteins including Rb and cyclin D1 and D3 [114]. Curcumin also affected the p53/Rb pathway in the core signaling pathways of glioblastoma, [115]. Curcumin induced senescence in human gastric cancer cells by activating DNA demethylation mediated by p53-p21/GADD45A-cyclin /CDK-Rb/E2F-DNMT1 axis [116].

6. Effect of curcumin on inflammation

The immune system is a host defense system that consists of a complex network of cells and proteins that defends the organism against infections. It possesses numerous interactions with other physiological systems and it has been shown that the immune system is able to function as a neuroendocrine organ [117,118]. Among various physiological systems, the immune system shows marked changes during aging. Most investigations on immune alterations through aging exhibit a decrease in numerous aspects of immune system when compared to young people [119,120]. The collection of these alterations is defined as immunosenescence. Immunosenescence enhances our susceptibility to autoimmune reactions, infections, and cancer while decreasing our response to disrupting wound healing and vaccinations. Immunosenescence may also be deteriorated and accelerated by persistent infections, such as HIV, CMV, and Epstein–Barr virus, linking it to microbial burden [121,122]. Immunosenescence is considered a harmful event since it frequently leads to aggregation of pro-inflammatory factors and inflamm-aging. *Inflamm*-aging is a theory of aging according to low-grade chronic systemic inflammation established during physiological aging [123,124]. Collectively, immunosenescence and inflame-aging are proposed to be the main source of age-related disorders, such as cancer, infections, chronic inflammatory diseases, and autoimmune disorders [122–124]. Senescence-associated secretory phenotype (SASP) is a phenotype related to senescent cells wherein those cells secrete high amounts of immune modulators, growth factors, inflammatory cytokines, and proteases. SASP is one of the three main characteristics of senescent cells, the other two characteristics being arrested cell growth, and resistance to apoptosis. SASP expression is induced by a number of transcription factors, the most crucial of which is NF-κB [125,126].

NF-κB relates to the Rel family of transcription factors, including, p65/relA, relB, c-rel, p50, and p52 [127,128]. NF-κB has been described

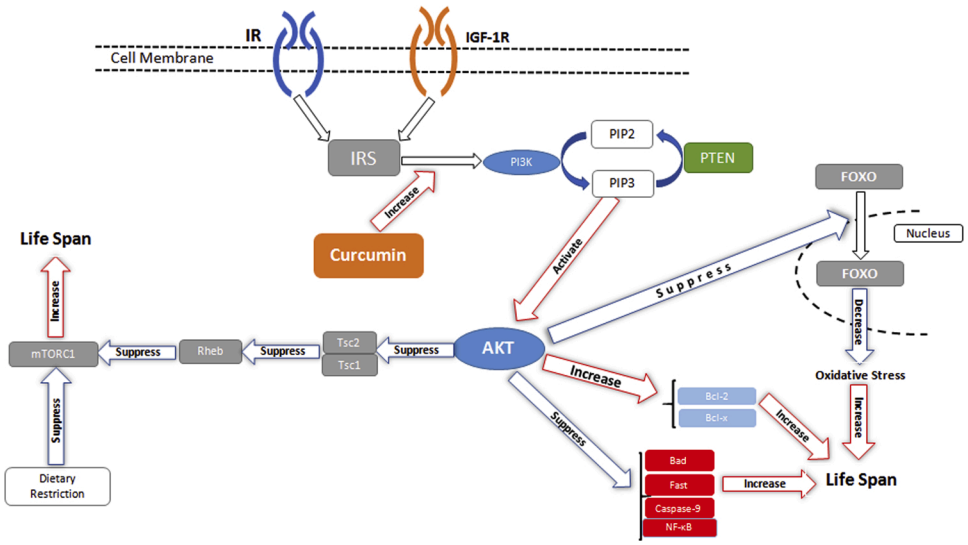

Fig. 4. Effect of curcumin signaling cascades in the aging process.
Curcumin activates PI3K/AKT pathway, leading to transfer of FOXOs into the nucleus and activate FOXO dependent gene expression and decreases oxidative stress and consequently increases life span. Curcumin can also increase life span through modulation of factors involving in inflammation and apoptosis such as NF-κB, Bad, caspase 9, and Fast and also Bcl-2. Inhibition of the mTORC1 pathway is another mechanism by which curcumin increases life span.

as a transcription factor, which has a pivotal role in inflammatory and immune responses, as well as transcriptionally regulation of several chemokines and cytokines. NF-κB stimulates cytokines that modulate the immune response including, IL-1, IL-6, IL-8, and TNFα, which result in the recruitment of leukocytes to targeting sites of inflammation. Besides the role of NF-κB in innate immunity, it was reported that NF-κB modulates other cellular procedures, such as cell proliferation and apoptosis. In the majority of quiescent cells, NF-κB is bound to inhibitory molecule, IκB (inhibitors of NF-κB) and NF-κB activation happen via release from the IκB [129,130]. As well as, the IκB kinase (IKK) complex binds to some cellular components and interacts with upstream signaling molecules and kinases. The NF-κB /IKK cascade has been suggested to be one of the major modulators of aging. This pathway is induced via inflammatory and oxidative stresses and modulates expression of growth factors, cytokines, and genes that control inflammation, a progression of cell cycle, cellular senescence, and apoptosis [131,132]. The NF-κB transcriptional activity is enhanced in different tissues during aging and is connected to several age-associated degenerative disorders such as diabetes, osteoporosis, and AD [133]. The inhibition of NF-κB signaling in mouse models results in the delayed onset of age-associated pathologies and symptoms [134].

Furthermore, NF-κB activation is associated with several signaling pathways that are known as lifespan regulators including insulin/IGF-1, mTOR, and FOXO, Thus NF-κB can be act as a possible therapeutic target for extending lifespan [133]. The IIS pathway activates PI3K/AKT signaling, which then induces NF-κB by the IKK complex [134,135]. This up-regulation of NF-κB happens via various mechanisms such as induction of p65 transcription, also phosphorylation, and activation of IKKβ. More investigations have been shown that insulin, IGF-1, and growth hormone (GH) induce anti-apoptotic responses via NF-κB and that IGF-1R can stimulate inflammatory and immune responses through NF-κB [136,137]. In addition there is an interaction between NF-κB and FOXO, as a downstream mediator of the IIS pathway. The FOXO3A linked with longevity in humans was detected to prevent the activation of NF-κB [138,139] and FOXO3A knockout mice show overactivation of NF-κB especially in T-cell populations [140]. Among another aging-associated pathways that have been reported, NF-κB and mTOR signaling are connected. IKKα and IKKγ have direct interaction with mTOR, and also, repression of Raptor and mTOR declined NF-κB binding activity. The NF-κB /mTOR pathway takes place downstream of Akt [141–143]. This evidence proposes that there are a cross-talk and co-regulation between NF-κB and the mTOR pathway. Collectively, considering the investigations until now on the action of curcumin on the NF-κB pathway it appears rational to suggest that this chemical compound should modulate the aging procedure. Curcumin's anti-inflammatory characteristics result from the suppression of NF-κB that was reported by Aggarwal's group [144]. It was described that the curcumin inhibits activation of NF-κB via suppression of IKK complex, which prevents the NF-κB translocation to the nucleus. Interestingly, Marquardt et al. [145] reported that curcumin can decrease cell proliferation in hepatocellular carcinoma (HCC) which shows the poor prognosis and treatment is to be most difficult. The patients that were involved in HCC were probably to respond to NF-kB modulation via curcumin. Cumulatively their study described that blocking the NF-kB signaling may be a therapeutic method for adverse HCCs with progenitor characteristics and activated NF-kB pathway. The activity of NF-κB is enhanced not only in activated lymphocytes and other immune cells, but also in most of the tumor cells. Thereby, curcumin as an NF-κB inhibitor can apply its chemo-preventive and anti-tumor function via acting directly on tumor cells and stimulating apoptosis in them more efficiently than in normal cells.

7. Therapeutic impact of curcumin and nano-curcumin in diseases of age models

Aging is correlated with several diseases that threaten the old population worldwide. During recent years, numerous investigations have been focused on the therapeutic effect of curcumin and indicated the health benefits of curcumin in age-related disorders. The therapeutic effect of curcumin in age-related disorders is reviewed below.

7.1. *Neurological diseases*

Several studies indicated that curcumin prevents various age-associated neurological disorders.

Long term administration of curcumin ameliorated motor function and digits of the hand of middle-aged rhesus monkeys [146].

Curcumin supplementation also attenuated motor and cognitive function in healthy middle-aged and older adults [147]. Curcumin in decreasing cellular inflammation-related neurodegenerative and aging processes is associated with increased CISD2 expression. It was found that CISD2 expression decreased in the spinal cord and brain of mice aged P2, 8, 25, and 104 weeks. Curcumin increased CISD2 expression; decreased inflammation in neural cells. Also, Curcumin increased the expression of CISD2 and decreased mitochondrial impairment in LPS-challenged neural cells [148]. Curcumin was also effective against AD in several experimental models. Treatment with curcumin of HT22 cells exposed to acrolein increased metalloprotease and A-disintegrin

and decreased β-secretase, amyloid precursor protein, and receptor for advanced glycation end-products [149]. Binding of curcumin-conjugated magnetic nanoparticles to amyloid plaques in mouse brains was observed via magnetic resonance images and immunohistochemical studies [150]. Novel CUR Formulation (NCF) prevented cognitive function in transgenic AD (APPSwe/PS1deE9) mice model during aging, which was confirmed by an open field, novel objective recognition, Y-maze, and Morris water maze [151].

7.2. Atherosclerosis

The incidence of atherosclerosis in the aging population is related to the diet. Long-term administration of curcumin ameliorated increased oxidative stress, decreased the expression of sirt1 in the aorta, increased inflammation, and senescent cells in the aorta of old mice fed with a high-fat diet (HFD). The findings indicated that curcumin might be effective against arteriosclerotic disease [152].

7.3. Reproductive diseases

Reproductive aging is accompanied by a decrease of ovarian follicles due to apoptosis. Curcumin ameliorated ovarian quality via modulating oxidative status, anti-aging-related (sirtuin 1 (SIRT-1), and SIRT-3) and ovulation-related (bone morphogenetic protein 15 (BMP-15) and growth differentiation factor 9 (GDF-9)) genes in NMRI 21-day-old mice. Curcumin treatment up increased ovarian volume and number of follicles related to increased anti-Müllerian hormone and estrogen and decreased FSH serum levels. Curcumin also potentiated oocyte maturation and embryo development with decreased oxidative stress. In addition, curcumin elevated the SIRT-1, SIRT-3, BMP-15 and GDF-9 genes expression [153].

7.4. Skin disorders

Downregulation of β1-integrin plays the main role in skin aging. Nano-formulated curcumin can increase increased β1-integrin gene expression, and increased Bcl2/Bax ratio, and also NFκB expression in fibroblast cells. It was suggested that nanoformulation of curcumin may act as anti-aging and wound-healing formulations [154].

7.5. Skeletal muscle

Curcumin inhibited aging processes in skeletal muscle through the up-regulation of antioxidant enzymes and directly scavenging ROS. Curcumin treatment improved muscle mass and function of aged rats. Curcumin treatment increased plantar mass and force production in aged rats [155].

8. Conclusion

Curcumin as dietary phenolic compounds is useful for longevity via declining of oxidative stress, modulating signal transduction, and gene expression. Curcumin can extend lifespan via inhibition of lipid peroxidation, and also increases the antioxidants activities. Curcumin has antioxidant characteristics and functions as a biochemical antioxidant or as a regulator of cellular defenses. One of these anti-oxidant defend mechanism is the Nrf2/ARE signaling pathway that curcumin has hormetic effects via stabilizing Nrf2 and enhance the expression of HO-1, which thus curcumin is proposed as hormetic. Curcumin with the ability of free radical scavenging has an essential role in telomere maintenance. As well as different investigations on the various model have shown the pivotal role of curcumin and its analog on the modulating of major signaling pathways that influence the longevity of organism Curcumin inhibits activation of NF-κB via suppression of IKK, which prevents the NF-κB translocation to the nucleus. Also, it was has been reported that curcumin as an inhibitor of NF-κB can act as a chemo-preventive and anti-tumor agent via acting directly on tumor cells and stimulating apoptosis in them.

Collection of data across investigations using different aging model organisms has described a wide range of information and reasonable visions for prospective clinical experiments and also for pharmacological interventions through aging and age-related disease in humans. In addition, more clinical experiments are now required to measure completely the capacity of curcumin in the route of administration, choice of optimal dose, and also possible drug interactions.

Author contribution

Study conception and design: A. Z. and S. S. Acquisition of data: A. Z. and A.M.P.S. Drafting of the manuscript: A. Z., T. F. Critical revision: S. S.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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