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Anti-aging natural supplements: the main players in promoting healthy lifespan

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Abstract

Aging is an inevitable biological process accompanied by various physiological changes, and researchers have long sought interventions to promote healthy aging. This article explores the effects of four natural compounds—Omega-3 fatty acids, Coenzyme Q10, Gingerol, and Curcumin—on the aging process. We delve into the scientific literature to examine the potential benefits and mechanisms behind these substances in mitigating age-related conditions. Omega-3's anti-inflammatory properties, Coenzyme Q10's cellular energy support, Gingerol's antioxidant effects, and Curcumin's anti-aging properties are all discussed. By shedding light on the impact of these compounds, this review aims to contribute to a better understanding of how natural substances may play a role in promoting longevity and enhancing the quality of life during the aging journey.

Keywords: Aging, Omega-3, Coenzyme Q10, Gingerol, Curcumin

1. Introduction

Aging is a natural biological process that impacts every living organism, affecting various aspects of physical, mental, and emotional health due to intricate physiological changes over time. It is a physiological and dynamic process that occurs over time. Most gerontologists assert that it starts in the fourth decade of life and leads to death. this complex and individual process that takes place on a biological, psychological, and social level. The biological process of aging causes progressive changes in metabolism and physicochemical properties of cells, resulting in impaired self-regulation, regeneration, as well as structural and functional changes. This is a natural, irreversible process that can be successful, typical, or pathological. The biological changes due to aging affect moods, attitudes towards the environment, physical conditions, and social activity, as well as seniors' position in their families and communities. A person's psychological ageing is determined by his awareness and his ability to adapt to the aging process. The following adaptation attitudes can be distinguished: constructive, dependent, hostile, and self-centered. A person's ability to adjust to a new situation deteriorates with age, cognitive and intellectual changes occur, perception processes deteriorate, perceived sensations and information are lowered, and thinking processes change. Cultural conditioning limits the role of an old person to that of old people, and customs may change over time. Social ageing refers to the way a human being perceives and experiences the aging process (1). Researchers have long been fascinated by aging, leading to a search for interventions that not only extend lifespan but also maintain health and vitality in old age. To explore potential interventions for healthy aging, it's essential to understand the aging process itself, which is governed by genetic and cellular mechanisms (2). At the genetic level, aging is driven by accumulated DNA damage, (3) resulting from environmental pollutants, radiation, and errors in DNA replication over time. These mutations impair cellular function and contribute to aging (4). Telomere shortening is another key factor in aging (5). Telomeres protect chromosome ends during cell division, but as they shorten, cells lose their ability to divide effectively, leading to cellular senescence and a decline in tissue regeneration (6). Oxidative stress, caused by the accumulation of reactive oxygen species (ROS), plays a major role in aging (7, 8). by damaging proteins, DNA, and lipids, leading to aging-related changes in tissues and organs (9). Various tissues and organs show aging-related changes as a result of oxidative stress (10). As

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mitochondria, the cell's energy producers, become less efficient with age, they generate more ROS, further contributing to cellular damage (11). Aging is also influenced by chronic inflammation (12). Chronic inflammation, resulting from persistent immune system activation, also influences aging and is closely linked with age-related diseases (13). Age-related changes in gene expression further accelerate aging, with genes responsible for repair and maintenance becoming less active, while those associated with inflammation and stress responses become more active (14). By changing gene expression, aging can be accelerated. Another hallmark of aging is protein misfolding and aggregation (15). Protein misfolding and aggregation, which interfere with cellular function, are also hallmarks of aging and are implicated in neurodegenerative diseases like Alzheimer's and Parkinson's. In Alzheimer's disease, beta-amyloid and tau proteins are misfolded in the brain. Typically, Parkinson's disease is characterized by brain accumulations of alpha-synuclein protein (16). Hormonal changes, such as declining levels of insulin-like growth factor (IGF-1), growth hormone (GH), and sex hormones, also contribute to the aging process (17). The **table.1.** summarizes aging factors.

Research into lifespan and healthy aging has increasingly focused on natural preventative factors. Compounds like Omega-3 fatty acids, Coenzyme Q10, Gingerol (from ginger), and Curcumin (from turmeric) have emerged as potential anti-aging agents, (**Fig.1.**) offering benefits such as reduced inflammation, improved cardiovascular health, and enhanced cognitive function. The selection of these supplements was based on their well-documented effects on the aging process, particularly in mitigating oxidative stress, inflammation, and mitochondrial dysfunction, which are common contributors to aging. While each compound acts through different molecular mechanisms, they share a unifying link in promoting cellular health and longevity. For instance, Omega-3s and Coenzyme Q10 support cardiovascular and cognitive health, while Gingerol and Curcumin are powerful anti-inflammatory and antioxidant agents. These compounds may also lower the risk of cancer and dementia associated with aging. By examining current scientific studies, we can explore how these natural substances contribute to healthy aging and longevity through their complex molecular mechanisms, providing valuable insights into their potential as preventative factors. Research has been undertaken on the compounds present in certain foods through scientific studies. In foods, bioactive compounds are extra nutritional components found

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in small quantities. A number of bioactive compounds appear to be beneficial to health. For example, there is evidence that consuming foods rich in flavanones (naringenin) and flavanols (quercetin) reduces cardiovascular damage and tumor growth (18-20). Oxidative stress contributes to several disorders such as cancers, metabolic disorders, inflammatory condition, cardiovascular diseases, and brain disorders (21-24). There are several epidemiological studies suggesting that polyphenol compounds in foods, such as flavonoids, phenolic acids, lignans, stilbenes, tannins, and anthocyanins, may delay the onset of degenerative diseases (25, 26). We will look at the current research to explore how these natural substances may serve as preventative factors. This review explores the role of Omega-3, Coenzyme Q10, Gingerol, and Curcumin in aging through a scientific exploration of the scientific literature. Furthermore, we will investigate how these substances exert their effects through complex molecular mechanisms. As a result, we hope to provide comprehensive insights into the potential for healthy aging and longevity using these natural compounds.

2. Omega-3

Many health benefits can be attributed to omega-3 fatty acids, which are polyunsaturated fatty acids (PUFAs). They can help reduce inflammation (27) the risk of heart disease, stroke (28, 29), certain types of cancer (30, 31), rheumatoid arthritis (32), depression (33) and asthma (34). Omega-3 fatty acids are also essential for brain health (35), helping to maintain cognitive function (36) and reduce the risk of dementia (37). They play an important role in human physiology, but the body cannot synthesize them, so it must obtain them from food or supplements. Table 2 summarizes the adequate amount of omega-3. **Table.2.** Summarize the adequate amount of Omega3. Omega-3 fatty acids come in three forms: eicosapentaenoic acid (EPA), alpha-linolenic acid (ALA), and docosahexaenoic acid (DHA) (38). Plant sources of ALA include canola, soybean, flaxseed, and walnut oils, as well as dark green leafy vegetables, soy, chia seeds, and walnuts. Fish and fish oil contain DHA and EPA, especially cold-water fish like tuna, salmon, trout, mackerel, whitefish, and herring (39). In addition to triacylglycerols, omega-3 fatty acids are available as phospholipids, acylglycerols, and ethyl esters (40). Gastric lipases digest omega-3 fatty acids and convert them into diacylglycerol and fatty acids in the stomach (40, 41). In the small intestine, pancreatic lipases and bile salts further break them

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down. Pancreatic carboxylic acid ester lipase breaks down omega-3 ethyl esters into FFAs-EPA and FFA-DHA (40). Micelles are absorbed by enterocytes and transported by fatty acid transport proteins. Following re-esterification, they are converted into triacylglycerols and enter the circulatory system as chylomicrons (42, 43). Beta-oxidation is the primary pathway for the metabolism of DHA and EPA, with cytochrome P450 (CYP) playing a minor role (44). Omega-3 fatty acids are bioavailable based on several factors, including their form and meal content. As a general guideline, bioavailability is ranked from highest to lowest based on lipid structure (re-esterified triacylglycerols, free fatty acids, ethyl esters, phospholipids, triacylglycerols etc.) (45). Phospholipids have higher bioavailability than other forms, and krill oil has high bioavailability compared to other marine sources (42). There is debate on how the chemical positioning of omega-3 fatty acids in oils affects bioavailability, with some studies suggesting different positions may be more effective (45). The average American diet is significantly below recommended levels of EPA and DHA. EPA and DHA can be obtained from dietary supplements, but many of these products contain ethyl ester formulations that are not well absorbed without a meal containing fat. The in-situ emulsification of EPA and DHA enhances their absorption, thereby improving their bioavailability regardless of the presence of fats in the meal. Omega-3 fatty acid supplements containing absorption enhancers have been shown to significantly increase the bioavailability of EPA and DHA in randomized controlled trials (46).

To maintain good health, adults should consume 250-500 mg of combined EPA and DHA per day. There is no official recommended daily allowance for DHA and EPA (47, 48). Some health conditions, however, require higher amounts. AHA recommends omega-3 supplements containing EPA and DHA daily to people with coronary heart disease or heart failure and the AHA recommends 4,000 mg a day of omega-3 supplements for people with high triglycerides (49, 50).

Omega-3 supplements are generally considered safe. The FDA recommends consuming no more than 5 grams of EPA and DHA combined per day from dietary supplements (51). Some omega-3 supplements may cause minor side effects, such as an odorous breath, nausea, fishy aftertaste, diarrhea, and stomach cramps (52, 53). Omega-3 deficiencies can lead to rough, scaly skin and dermatitis (54). A variety of inflammatory pathways have been shown to be influenced by omega-3 fatty acids (55-58), including restricting the movement of white blood cells towards

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inflammation sites (leukocyte chemotaxis inhibition) (59), reducing the expression of adhesion molecules, particularly those involved in interactions between white blood cells and blood vessel walls (leukocyte-endothelial adhesive interactions) (60)v suppressing the activity of cyclooxygenase (COX) and the subsequent production of eicosanoids such as leukotrienes and prostaglandins derived from arachidonic acid (61, 62); reducing the levels of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6 (63); increasing the production of compounds that resolve inflammation, such as maresins, protectins, resolvins, and lipoxins (64); inhibiting NF-kB, a transcription factor that promotes inflammation (57); activating the anti-inflammatory transcription factor NR1C3 (57) ; activating PPARs (peroxisome proliferator-activated receptors) that have anti-inflammatory effects (61); inducing anti-inflammatory effects by activating GPR120; a G protein-coupled receptor (65); and disrupting lipid rafts in cell membranes and altering phospholipid composition (66-68). Normal brain function and aging depend on omega-3 fatty acids. They can reduce inflammation and protect against cognitive decline and dementia. Omega-3 has been studied extensively in relation to aging and longevity. Several studies have shown that it is capable of slowing the aging process and extending life. Several studies suggest omega-3 may protect against dementia and cognitive decline associated with aging. Observational studies and clinical trials have provided conflicting results regarding the efficacy of omega-3 fatty acid supplementation for preventing cognitive decline, dementia, or Alzheimer's. According to prospective studies, individuals with higher omega-3 fatty acid intakes are less likely to develop AD (69), and erythrocyte DHA levels may be inversely associated with the risk of AD and dementia of any cause (70). In comparison with cognitively healthy individuals, patients with AD have lower serum omega-3 fatty acid concentrations, plasma phospholipids, and erythrocyte membrane omega-3 fatty acid concentrations (71, 72). The effects of omega-3 fatty acid supplementation on cognitive decline and probable AD, on the other hand, have been limited in randomized clinical trials (73). It is also possible that the genotype of apolipoprotein 4 (APOE ε4) might influence the relationship between omega-3 fatty acid supplementation and dementia, or cognitive decline and AD (74, 75). The APOE ε4 allele, the major genetic risk factor for AD, could induce abnormal cholesterol metabolism as part of the AD-associated pathology (76). There is still a lack of information about how APOE ε4 interacts with omega-3 fatty acids to affect dementia risk and cognitive decline. A study found an association between omega-3 fatty acid consumption and APOE ε4 carriers, but not APOE ε4

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noncarriers, experiencing slower cognitive decline (74). According to other studies, omega-3 fatty acids are only beneficial for APOE ε4 noncarriers (72, 77). A possible explanation for this may be that APOE is reducing DHA and EPA delivery to the brain (78). However, findings from the meta-analysis suggest that (1) long-term omega-3 fatty acid supplementation may reduce the risk of Alzheimer's disease (AD); (2) dietary intake of omega-3 fatty acids, particularly DHA, may reduce dementia and cognitive decline risks; and (3) peripheral biomarkers of omega-3 fatty acids may be able to predict cognitive decline (37). Nevertheless, additional research is needed to explore the gene-environment interactions associated with omega-3 fatty acid intake. According to the research by Wenbo Qi et al., consuming polyunsaturated fatty acids reduces the risk of aging-related diseases, especially cardiovascular disease and stroke. Researchers employed long-lived *Caenorhabditis elegans* glp-1 germ line-less mutants, which revealed alterations in lipid metabolism, specifically an increase in ALA synthesis. In *C. elegans*, ALA extends lifespan in a dose-dependent manner. Additionally, the extended longevity observed in the glp-1 mutant animals relies on two crucial transcription factors, NHR-49/PPARα and SKN-1/Nrf2, though the exact mechanisms are not fully understood. Both NHR-49 and SKN-1 transcription factors are required for ALA treatment to prolong the lifespan of wild-type worms. ALA activates NHR-49 and upregulates genes involved in lipid β-oxidation. ALA does not directly activate SKN-1; however, exposure to air results in the formation of oxylipins. In addition to extending lifespan, ALA treatment activates one of these oxylipins. Several studies have documented the anti-aging effects of omega-3 fatty acids and their oxylipin metabolites. In addition, oxylipins may contribute to the health benefits associated with consuming omega-3 fatty acids. There are differences between observational and interventional clinical trials regarding the effects of omega-3 fatty acid intake on human health due to variations in oxylipin conversion (79).

Another study in 2023 found that a structured triglyceride form of DHA (DHA-TG) had a positive impact on the health span of aged *C. elegans*, focusing on cognitive health. DHA-TG improved the nematodes' mobility at various stages of adulthood without affecting their overall lifespan. The treatment also activated superoxide dismutase in the nematodes, increasing their antioxidant capability. This study suggests that the DAF-16/FOXO transcription factor might be involved in DHA-TG's beneficial effects, suggesting an intermediary in DHA's mechanism of

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action. DHA-TG bolstered antioxidant defenses and significantly increased physical fitness in aging *C. elegans*, which could have implications for cognitive function (80).

A study conducted by Kamil M. and his colleagues on *Drosophila* demonstrated that dietary supplements containing monoacylglyceride n-3 PUFA have the ability to prolong the lifespan of male *Drosophila* flies. These supplements not only affect mitochondrial oxidative capacity but also influence thoracic muscle markers related to oxidative stress (81).

The omega-3 fatty acid EPA was studied in 2017 in response to saturated fat and inflammation in mouse skeletal muscle cells. The study found that adding EPA under cytotoxic stress partially rescued differentiation, with increased expression of MyoD, myogenin, IGF-II, and IGFBP-5 associated with enhanced myotube formation. In simpler terms, the study showed that EPA can improve the ability of muscle cells to regenerate even when exposed to harmful conditions such as inflammation and saturated fat (82).

The hippocampus, a region crucial to memory and learning, has been shown to reverse age-related changes when supplemented with n-3 fatty acids, specifically DHA. GluR2 and NR2B, two glutamate receptor subunits, decrease in aging rats. However, when aged rats are given n-3 fatty acid supplementation, these levels return to those seen in young adult rats (83). ish oil supplementation has been shown to extend the lifespan of female mice prone to autoimmune disorders by more than 40% (84, 85). Several cardiac dysfunctions have been attenuated by fish oil rich in omega-3 fatty acids in aging mice, including hypertrophy of the ventricular wall and remodeling of the cardiac muscle (86). It has been shown that omega-3 PUFAs EPA and DHA can reverse the decline in retinoid receptors and PPARg in aged animals and may improve neurogenesis (87). The research conducted by Qureshi and his team found that middle-aged and older rats were inhibited or prevented from releasing senescent microvesicles (SMVs) when administered EPA at a ratio of 6:1, which are associated with pro-senescent, pro-thrombotic, and pro-inflammatory effects on endothelial cells. The local angiotensin system likely facilitates this influence. Endothelial dysfunction may be delayed by maintaining an EPA ratio of 6:1 (88). Specific and relevant changes in glutamatergic transmission underlie the potent neuroprotective effects of omega-3 PUFAs during aging in the central nervous system. Through improved glutamatergic transmission, omega-3 can protect the central nervous system during aging (89).

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Telomere length is one of the important hallmarks of aging (90, 91). Various doses of omega-3 fatty acids were administered to male mice over two months in one study, and it was found that both high-dose and low-dose DHA reduced hepatic telomere shortening, while fish oil and low-dose DHA inhibited the attrition of testicular telomeres (92). Research suggests that PUFAs may promote telomere length by counteracting age-related increases in TRF-1 expression, as observed in pigs supplemented with linseed oil for 9 weeks (93). Having omega-3 fatty acids in the diet reduced the rate of telomere attrition and elongated the telomeres of rats in another study (94). Comparative studies on telomere length showed that fish oil containing 60% omega-3 PUFAs had a positive effect compared to control fish oil (95). Another study examined the role of fish oil, DHA, and arachidonic acid in mice whose aging was induced by D-galactose. In this study, fish oil, DHA, and arachidonic acid were linked to aging via a redox-telomere-antioncogene axis. In addition to improving redox balance, reducing oxidative stress, and protecting against telomere shortening, omega-3 and fish oil appear to be beneficial. Interestingly, n-3 PUFAs, particularly DHA, suppress cellular senescence pathways, demonstrating their anti-aging potential (96).

In conclusion, the research presented here highlights the significant positive effects of ω-3 polyunsaturated fatty acids, particularly α-linolenic acid (ALA) and DHA, on various aspects of health and aging. These studies demonstrate that ALA can extend lifespan, potentially through NHR-49/PPARα and SKN-1/Nrf2 transcription factors, and that DHA, especially in structured triglyceride form (DHA-TG), can improve health span by enhancing mobility and antioxidant defenses (79). It has been demonstrated that omega-3 fatty acids, such as EPA, support muscle cell regeneration even when harmful factors are present. Additionally, omega-3 PUFA supplementation promotes neuroprotection by reversing age-related changes in the hippocampus and improving glutamatergic transmission. According to these findings, omega-3 fatty acids may play an important role in promoting health and longevity through a variety of molecular mechanisms.

Extensive research has explored the role of omega-3 fatty acids in aging and age-related diseases in humans. A significant amount of research has been conducted in the field of aging and longevity concerning telomeres, the protective caps at the ends of chromosomes. Often

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considered markers of biological aging, these structures are crucial for cellular division. One area of interest to researchers has been the possible impact of omega-3 fatty acids on telomere length. Many studies have investigated the relationship between omega-3 fatty acid intake and telomere length to discover whether these essential fatty acids maintain telomere health (97). The telomere length of coronary heart disease patients may be protected by marine omega-3 fatty acids, according to a study (98). According to Liu et al. (2021), preschool children with obesity who consumed more omega-3 fatty acids had longer telomeres and lower levels of telomerase methylation (99). Omega-3 fatty acids may protect telomere length from oxidative stress, according to a randomized controlled trial (100). Researchers have found that omega-3 fatty acids may play a protective role in maintaining the length of the telomeres of leukocytes in patients with chronic kidney disease (101). Among older individuals with mild cognitive impairment, omega-3 fatty acid supplementation reduced the shortening of telomeres by 23% in a preliminary study conducted by O'Callaghan et al. in 2014 (102). Ongoing research continues to explore the exact mechanisms and implications of omega-3 fatty acids and telomere length, although these studies collectively suggest a link.

Sedentary, overweight, middle-aged participants in a 2021 study were assessed for cellular aging-related biomarkers following the omega-3 supplementation. Using the Trier Social Stress Test, participants were randomly assigned to receive 2.5 grams of omega-3 every day, 1.25 grams of omega-3 every day, or a placebo for a 4-month period. Telomerase and interleukin-10 stress reactivity were influenced by omega-3 supplementation. In both supplementation groups, telomerase and interleukin-10 levels were protected from declines following stress. Omega-3 at 2.5 g/d reduced overall cortisol and interleukin-6 levels, showing a significant decrease compared to the placebo group. By reducing inflammation and cortisol levels during stress and enhancing repair mechanisms during recovery, omega-3 may be able to slow down the aging process and lower depression risk (103). EPA, DPA, and DHA were found to increase the chances of older individuals experiencing a robust and healthy aging process, according to a prospective cohort study conducted by Heidi TM Lai and colleagues (104). Harris et al. found that higher circulating levels of marine omega-3, including eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids, were associated with a significant reduction in premature mortality, as confirmed by an analysis of data from 17 prospective cohort studies (105).

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Studies conducted in 2013 found lower total mortality, particularly cardiovascular mortality, in people with higher plasma levels of omega-3 polyunsaturated fatty acid biomarkers (106). Over a 3-year period, PUFA levels in the blood, likely reflecting dietary intake, were associated with better physical performance maintenance and a reduced risk of decline in the InCHIANTI study in older Italians. Alternatively, higher levels of n-6 PUFA were associated with poor physical performance and slowed walking speed. Physical performance can be preserved as individuals age through dietary fatty acids, especially n-3 PUFAs (107).

There is growing evidence that PUFAs and their compounds can help combat cognitive decline related to aging. Fish oil supplements totaling 0.4 grams of EPA and 2 grams of DHA significantly improved cognitive processing speed in middle-aged to older adults with obesity (108). EPA and DHA daily doses of 1.86 grams and 1.5 grams were beneficial to patients with coronary artery disease and ischemic risk over 30 months, which led to improved cognitive function (109). A second study found that taking 1.6 grams of EPA and 0.8 grams of DHA daily for 24 weeks reduced cognitive inefficiency in daily activities in older adults with no risk factors but self-perceived cognitive impairment In a double-blind, randomized controlled trial, fish oil was shown to enhance memory function in individuals with Mild Cognitive Impairment (MCI) (110). According to a 2010 study, supplementing with 900 mg of DHA for 24 weeks improved learning and memory in older adults with Age-Related Cognitive Decline (ARCD) (111). According to a meta-analysis by Bao-Zhen et al., omega-3 polyunsaturated fatty acid intake is associated with cognitive impairment, Alzheimer's disease, and dementia (37).

Overall, fish oil supplements with varying EPA and DHA content appear to enhance cognitive function in individuals with diverse conditions, including coronary artery disease, obesity, and age-related cognitive impairments. Age-related macular degeneration (AMD) mainly affects older adults and can cause severe vision loss. The macula is the central component of the retina, responsible for sharp, central vision, which is affected by AMD (112). Due to their potential health benefits for the eyes, omega-3 fatty acids have been a topic of interest in relation to AMD. Researchers found that DHA and EPA consumption significantly reduced the risk of AMD development in 235 AMD patients, following them for 10 years (113). Johanna and Cristina's study supports the recent findings (114, 115). A review of human and animal research suggests omega-3 has numerous health benefits, including slowing the aging process. According to these

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findings, omega-3 fatty acids can promote healthy aging, enhance cognitive function, and protect against age-related diseases. This makes them important dietary components for individuals who want to maintain their health and well-being as they age. Despite these promising findings, further research is required. FDA-approved fatty acid prescriptions (icosapent ethyl, omega-3-acid ethyl esters, omega-3-carboxylic acids, and omega-3-acid ethyl esters A) are generally safe and do not cause adverse reactions such as eructation, dyspepsia, diarrhea, gas, nausea, or arthralgia (116).

3. Coenzyme Q10

Animal cells produce the small, lipid-soluble antioxidant molecule Coenzyme Q, widely located in cell membranes (117). Mevalonic acid and phenylalanine are the main sources of CoQ10. In a healthy individual, synthesis of CoQ10 occurs in all tissues. The synthesis of CoQ10 takes place through a precise sequence of enzymes, specifically complex Q, which is primarily located in the mitochondrial matrix membrane and endoplasmic reticulum. The pathway of mevalonic acid plays a crucial role in cholesterol synthesis by HMG-CoA reductase, which serves as the key regulatory step that is effectively inhibited by statins (Fig.2). The internal biosynthesis of CoQ10 decreases during aging, so it is imperative to obtain CoQ10 through our diet (118). CoQ10 is primarily found in animal meat and vegetables such as lamb, pork, chicken, beef, and fish, as well as broccoli, spinach, peas, and cauliflower, and fruits like oranges, strawberries, and apples. Additionally, CoQ10 can be found in cereals such as rye and wheat (118). Notably, animal organs such as chicken legs, herring, trout, and heart are excellent sources of CoQ10. Since CoQ10 has a large molecular size and low water solubility, its bioavailability is limited. The development of nanoparticle encapsulation, liposomal delivery systems, and emulsified formulations have been used to enhance this effect. Encapsulating CoQ10 in nanoparticles allows the body to more readily absorb it. By encasing CoQ10 in lipid bilayers, lipid delivery enhances its solubility and transport across cell membranes. Droplets of CoQ10 are broken down into smaller, more absorbable ones in emulsified formulations. Through these technological advances, CoQ10's bioavailability has significantly improved, which enhances its therapeutic effects (119). An adequate daily intake is considered to be between 3 and 5 mg. When supplemented externally, plasma CoQ10 levels increase but tissue levels do not (120). The

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presence of tissue uptake and successful treatment in various human diseases proves its efficacy (118, 121). The function of CoQ10 is to facilitate the transfer of electrons between complexes I/II and III in the electron transport chain (118). As a key component of cellular function, it is widely distributed in all cell membranes. As a component of the mitochondrial ETC, ubiquinone plays a crucial role. Complex I (reduced nicotinamide adenine dinucleotide [NADH]-coenzyme Q oxidoreductase) receives electrons from donors, complex II (succinate dehydrogenase), flavin-linked dehydrogenases, which oxidize fatty acids and branched-chain amino acids, and electron transfer factor Q oxidoreductase (ETF-QO) transfers electrons to complex III (ubiquinone-cytochrome C oxidoreductase) (122, 123). CoQ10 exists in three chemical forms: semiquinone, ubiquinone, and ubiquinol. The proton-motive Q cycle within mitochondrial membranes generates a proton motive force for ATP production (124, 125). Various studies have demonstrated that CoQ10 supplementation exerts epigenetic effects on genes associated with different biological processes, including intermediary metabolism, signaling, transcription control, transport and phosphorylation, disease mutation, and embryonic development. The mitochondrial free radical theory of aging asserts that damage to mitochondria is pivotal in cellular aging (126). Activated mitochondrial DNA is a significant target for mitochondrial-derived reactive oxygen species (ROS), according to Eirin et al. (127). OS accumulation in mitochondrial DNA may contribute to aging. Mitochondrial DNA damage is a serious concern because it can lead to a decline in the efficiency of the respiratory chain. DNA lesions and reactive oxygen species (ROS) result from such damage, which, in turn, can hasten the cellular aging process (128). Therefore, it is essential to protect and maintain mitochondrial DNA integrity to prevent cellular aging and associated health problems. By interacting directly with DNA repair enzymes, CoQ10H2 promotes efficient repair of oxidative damage (129). CoQ10 levels decline with age, and inborn errors in its synthesis can further impact these levels (130). Chronic inflammation is a common problem related to aging. CoQ10 can reduce free radicals, decrease NF-κB activation, and lower the release of pro-inflammatory cytokines such as IL-6, TNF-α, and CRP (131). Aging-related reduction in CoQ10 levels is a significant contributor to inflammation. A study has shown that CoQ10 supplementation is effective in reducing inflammation. CRP (C-reactive protein), IL-6, and TNF-α levels were significantly reduced by CoQ10 supplementation (132). CoQ10's epigenetic effects regulate NFkappaB1, thereby effectively reducing inflammation (133). Cardiovascular disease is one of the common aging-

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related concerns. Low levels of CoQ10 in endomyocardial tissues are strongly correlated with heart failure severity, while CoQ10 treatment has been shown to improve cardiac contractility (134). Treatment with CoQ10 has been reported to improve lipid profiles, significantly contributing to the management of cardiovascular disease (135). Clinical studies on CoQ10 supplementation in antiphospholipid syndrome patients have demonstrated a significant reduction in thrombotic markers and pro-inflammatory markers, as well as improved mitochondrial function and endothelial health (136). These findings provide strong evidence in support of CoQ10 as an effective intervention for managing antiphospholipid syndrome. It has been proposed that chronic neuro-inflammatory changes in Down syndrome patients may accelerate Alzheimer's disease (137). Changes in these factors include increased levels of IL-6 and tumor necrosis factor α, as well as decreased levels of CoQ10. In addition, CoQ10 levels are positively correlated with intelligence quotients (138). In human studies, however, inconsistent results have also been found. According to a study conducted in 2003, plasma CoQ10 levels do not correlate with aging in older women (139). According to reports, the levels of plasma and tissue CoQ10 change over time. The pancreas and adrenal glands have the highest levels of CoQ10 by one year of age, and the brain, heart, and lungs reach their peak levels by the age of 20. However, after peak levels, CoQ10 levels decrease over time (140). Other studies have confirmed that, in the brain, CoQ10 levels are decreased (141, 142). As we age, the amount of naturally produced CoQ10 in our heart decreases, and by the age of 80, only 50% of the production remains (143). Furthermore, when comparing centenarians with 76-year-old individuals, ascorbic acid and total CoQ10 levels decreased in serum. It was also found that CoQ10-binding protein prosaposin increased in response to low levels of CoQ10 (144). CoQ10 can be used to treat a number of human disorders and pathologies. Several studies have shown that CoQ10 is a safe and effective treatment for diseases in humans. In randomized, controlled human trials, a daily dose of 1200 mg of CoQ10 is the maximum recommended, although short clinical trials have used doses up to 3000 mg/day (145). older patients with chronic conditions can benefit from this treatment, CoQ10 can serve as an important coadjutant. We describe several clinical trials using CoQ10 in **Table.3.** The human body naturally contains CoQ10. Generally, CoQ10 supplements are well tolerated with only minor and infrequent side effects such as stomach upset, nausea, vomiting, and diarrhea.

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4. Gingerol

Originally from Asia, ginger is now found in tropical environments as a member of the Zingiberaceae family of plants (146). Ginger contains various substances with biological effects, such as 6-gingerol (6-Gingerol), 6-shogaol, gingerdiones, 10-gingerol, paradols, 6-dehydrogingerols, gingerdiols, 3,5-diacetoxy-6-gingerdial, 5-acetoxy-6-gingerol, and 12-gingerol. Various studies have demonstrated that ginger, especially 6-gingerol, has beneficial effects on health, such as reducing oxidative stress (147). Ginger is vital in treating many diseases and has been used for centuries (146). It contains various bioactive substances and components that have demonstrated different therapeutic benefits, such as antibacterial, anti-inflammatory, anticancer, antidiabetic, gastroprotective, neuroprotective, and antioxidant effects (148). It can alleviate the symptoms of some illnesses, such as ulcerative colitis, Crohn's disease, urinary tract inflammatory problems, psoriasis, lupus, rheumatoid arthritis, and cancer (149). Ginger extract could act as an antioxidant by removing excess free radicals (hydrogen peroxide and superoxide radicals). Lung disease-causing oxidative stress can be reduced by ginger, which enhances lung function. Ginger is believed to function by scavenging free radicals and modulating the inflammatory response in the lungs. Ginger can reduce inflammation by blocking the enzyme COX-2 that causes it. It can also lower the levels of IL-β and TNF-α, which are molecules that trigger inflammation. Additionally, ginger contains active substances, such as 6-gingerol and 6-shogaol, that can fight cancer by reducing COX-2 levels, blocking NF-κB activity in DNA, and increasing BAX expression (150, 151). Despite its biological properties, 6-gingerol's low bioavailability limits its application. To overcome these limitations, new encapsulation and solubilization techniques have been introduced, including nanoemulsions, complexations, micelles, and solid dispersions. As a natural antioxidant, preservative, and flavor enhancer, 6-gingerol could be used to maintain food quality and shelf life by combining with various ingredients in a synergistic manner (152).

Ginger is a natural substance that has beneficial effects on health and longevity (Fig. 3). In addition to preventing or delaying age-related diseases, it can improve the quality of life in older adults. Ginger can also enhance the lifespan of healthy individuals by modulating cellular and molecular pathways of aging (153). Oxidative stress occurs when reactive oxygen species (ROS) overwhelm antioxidant defenses in cells. Aging and diseases associated with aging are caused by

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oxidative stress. Oxidative stress and chronic inflammation cause molecular and cellular changes, ranging from genomic instability and epigenetic changes to mitochondrial dysfunction and cellular senescence (154). Physiological functions decline with aging due to the accumulation of oxidative damage, a concept known as the "free radical aging theory" (155). Both Caenorhabditis elegans and mammals are believed to be affected by oxidative stress according to the free radical theory of aging. ROS levels determine the organism's lifespan (156), and free radicals are a major contributor to aging progression (157). When pathological conditions such as infection, inflammation, stress, and exposure to substances that cause ROS—such as NOx pollutants, tobacco smoke, radiation, or drugs like acetaminophen and sunlight—ROS levels increase (158). Based on new findings, some natural products can prevent, reduce, and treat aging and diseases related to aging. It is suggested that ginger modifies molecular targets of the pathogenesis of age-related diseases (155). There is evidence that ginger can fight inflammation and delay the aging process in different organs, according to many studies (159). Ginger possesses strong antioxidant properties, helping to neutralize reactive oxygen species (ROS) and maintain a balance, known as redox balance, between ROS and antioxidants in the body. A high consumption of antioxidants can result in reductive stress. Nevertheless, excessive ginger consumption or improper use could disrupt this balance by overstimulating antioxidant defenses or influencing oxidative stress-related pathways in the body. If ROS levels are not adequately controlled, this imbalance can cause oxidative damage. However, ginger is generally considered beneficial for its antioxidant properties when consumed moderately (160). Studies have shown ginger extract can lower the body's ROS and malondialdehyde (MDA). MDA is a lipid peroxidation marker harmful to cells (161). GPx activity was increased in diabetic rats after ginger treatment, suggesting that antioxidant enzymes are recovering. In addition to lowering caspase-3 activation and the Bax/Bcl-2 ratio, ginger extract also inhibited IL-1 production (162, 163). By blocking the activation of caspase-3, ginger extract may prevent apoptotic signaling that contributes to disease development (164). The level of BDNF, a key molecule for neuronal health, function, learning, and memory, was increased in the brains of mice with SCO-induced cognitive impairment after they received oral ginger extract (165). Ginger extract administration resulted in less oxidative stress in the liver tissue of mice, with enhanced levels of antioxidant enzymes such as SOD, GR, GPx, and CAT (166).

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One of the hallmarks of aging is a persistent pro-inflammatory state. This condition, also known as "inflammaging," involves chronic low-level inflammation. Many diseases affecting older adults are linked to chronic inflammation, including hypertension, atherosclerosis, diabetes, and cancer (167). Higher amounts of inflammatory molecules, such as tumor necrosis factor-α (TNF-α) and IL-6, were detected in older people. These molecules can cause tissue damage and accelerate aging (168). Inflammatory mediators like prostaglandins and leukotrienes are blocked by ginger's anti-inflammatory properties, which include inhibiting their synthesis. Prostaglandin E2 (PGE2), a pro-inflammatory molecule, is suppressed by both fresh and dried ginger extracts when activated by lipopolysaccharide (LPS), a bacterial toxin The results indicated that ginger extract lowered the levels of PGE2, MCP-1, TNF-α, MPO, and IL-6, which are inflammatory mediators. The extract of ginger mainly exerted its anti-inflammatory effect by preventing the migration and activation of inflammatory cells (169). Ginger also has anti-inflammatory properties by reducing the breakdown of IκBα and preventing the movement of p65 into the nucleus, where it activates NF-κB (170).

Genomic damage and instability result from the interrelated pathological processes of chronic inflammation and oxidative stress. The biomarker gamma-H2AX, which is sensitive and reliable, revealed that 6-GN treatment increases DNA damage significantly. P53 is reactivated by intracellular ROS. Due to this, p53 arrests cell cycle progression during G2/M (171). Compared to other supplements, ginger exhibited remarkable activity in protecting DNA at different concentration levels and had the highest overall antioxidant activity (172). In breast cancer cells, 6-SG inhibited NOTCH signaling and induced apoptosis and autophagy (173). The human pancreatic PANC-1 cancer cell line is affected by ginger extract, which inhibits its cell cycle progression and triggers its apoptotic cell death. One possible mechanism by which ginger inhibits cancer growth is by generating ROS in tumor cells (174). 6-GN inhibits the expression of AKT, NF-κB, and Bcl2, and upregulates TNFα, BAX, cytochrome c, PARP, and caspase-3. 6-GN triggers cancer cell death, possibly through caspase-3-dependent apoptosis and autophagy (175). 6-GN has been shown to reduce inflammation by lowering the levels of IL-1β, TNF-α, COX-2, and iNOS, and to suppress cell growth by enhancing the expression of β-catenin, DVL-2, and WNT3a proteins, and, in contrast, diminishing the expression of Ki-67 and cyclin D1 proteins (176).

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Ginger has demonstrated cognitive benefits in older subjects. Taking 400 or 800 mg of ginger daily for two months improved attention and cognitive processing in middle-aged women without adverse effects (177). Cholinesterase breaks down acetylcholine through the action of the active compounds in ginger. Acetylcholine is a neurotransmitter that plays a crucial role in learning and memory processes. As a result, ginger increases acetylcholine levels, thereby enhancing cognitive functions (178).

The prevalence of neurodegenerative diseases increases with aging, with Alzheimer's disease (AD) being a common form of age-related cognitive decline that affects brain structure and function. According to the study, ginger extract enhanced the expression of CAT and SOD enzymes in the brain. It reduced the secretion and expression of IL-1β, NF-κB, and MDA levels, improving behavioral dysfunction (179). Study results show that supplementing middle-aged women with ginger extract at 400-800 mg per day improved their cognitive function (177). One main factor that increases the likelihood of developing cardiovascular diseases is aging. A possible way to reduce blood lipids and blood pressure and inhibit platelet clumping is by using ginger and some of its compounds that have these effects. The blood pressure of rats under anesthesia decreased after they received fresh ginger extract through their veins. The extract seemed to block voltage-dependent calcium channels Three grams per day of ginger supplementation for 45 days significantly lowered serum cholesterol and triglycerides in hyperlipidemic patients (180). [6]-Gingerol inhibited the activation of p38 MAPK, a mitogen-activated protein kinase involved in cardiac remodeling (105). Additionally, 6-gingerol may reduce the accumulation of fat in the liver with age (181).

Sarcopenia is a condition that affects older people and causes them to lose muscle mass, muscle size, and muscle function. This can lead to problems with mobility, balance, and strength. In addition to rejuvenating muscle cells, ginger's antioxidant and anti-inflammatory properties may help prevent and treat sarcopenia (182). Taking ginger supplements may also benefit knee osteoarthritis, a common condition in older adults, by reducing pain and improving joint function (183). one of the most noticeable effects of aging is the alteration of the skin's appearance and structure. Using a body cream containing ginger oil for a month diminished signs of skin aging, possibly due to the plant's ability to scavenge free radicals (184). Ginger has many health benefits that may support healthy aging and longevity. Gingerol is a compound that can improve

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body function and prevent aging-related diseases. Therefore, ginger may be a natural way to support healthy aging and longevity. According to the United States Food and Drug Administration, ginger root is safe in amounts up to 4 grams per day. Higher doses, however, can result in gastrointestinal discomfort, allergic reactions, prolonged preexisting bleeding, depression of the central nervous system, and arrhythmias. Ginger root consumption of more than 6 grams can exacerbate gastrointestinal disturbances such as heartburn, gastrointestinal reflux, and diarrhea, according to studies. A small number of cases have been reported of arrhythmia caused by this spice. Gallstone formation can be aggravated by increased bile acid secretion (185).

5. Curcumin

Curcumin is a potent and effective anti-aging compound that is easily accessible and safe for use. Curcumin, a polyphenol nutraceutical, is derived from the rhizome of *Curcuma longa* (a member of the ginger family) and is found in turmeric (186). Curcumin is a commonly consumed spice and yellow food dye. In aqueous media, curcumin is poorly soluble and stable, leading to poor absorption by intestinal cells, with rapid metabolism by the liver. It is also quickly eliminated from the body (187). Due to its low bioavailability, curcumin's therapeutic potential may be limited. Several approaches have been used to maximize curcumin absorption in the body. One such approach is to take curcumin together with piperine, the active ingredient in black pepper. Using this technique, curcumin can be more readily absorbed into the bloodstream, increasing its concentration by up to 2,000 percent (188). Enhanced aqueous solubility, stability, and cell targeting of curcumin can be achieved by various means, including conjugation with alginate, self-assembling peptide nanofiber carriers, and formulation of curcumin phospholipid complexes, microemulsions, liposomes, polymeric micelles, and nanoparticles (187, 189). Meanwhile, the nano formulation of this compound has been evaluated in various studies and its anti-inflammatory, antioxidant and immunomodulatory effects have been proven. The form of nanocurcumin is recommended as a popular and effective form due to its high stability in the body environment, long half-life and high bioavailability and easier access to different sites (190-192). cytClinical trials have shown that high daily doses of curcumin, up to 12 g/day, are considered safe for patients (193). Curcumin exhibits pleiotropic activity, similar to other

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polyphenols. It can induce cellular responses by interacting with multiple proteins. Curcumin can positively influence cellular processes by regulating miRNAs and influencing epigenetic changes in cells (194). As we age, persistent low-grade inflammation often occurs (195). There is no doubt that polyphenol-rich foods can effectively alleviate symptoms of aging due to their potent anti-inflammatory and antioxidant properties. There is substantial evidence that curcumin has anti-aging properties (**Fig.4.**) (196, 197). Extensive clinical trials have shown that curcumin can reduce symptoms of age-related diseases, including atherosclerosis, diabetes, and cancer (198, 199). Curcumin activated SIRT1 and protected HUVECs from peroxide-induced senescence (200). Bis-demetoxycurcumin, a curcumin analog, protected Wi38 fibroblasts from oxidative stress-induced senescence (201). These findings suggest that curcumin and its analogs show potential for therapeutic use in combating cellular aging and related diseases. Curcumin's anti-tumor activity is another important function (202). Aging is one of the most significant risk factors for tumor development (203). Older adults are more susceptible to cancer than younger individuals. Half of all cancers diagnosed in older adults are prostate, lung, or colon cancers. Breast, colon, lung, and stomach cancers account for 48% of all cases among older women. Curcumin has been shown to protect against tumorigenesis by reducing toxicity, potentially inducing cancer cell apoptosis, and inhibiting metastasis through its anti-angiogenic properties (197). Curcumin helps slow the aging process by targeting multiple pathways involved in age-related diseases (204). The pathogenesis of multiple age-related diseases involves oxidative stress-induced damage, a hallmark of aging (205). Cells and tissues that accumulate ROS can cause oxidative stress when detoxification mechanisms are overwhelmed (206). Curcumin effectively inhibits cyclooxygenase/lipoxygenase and xanthine dehydrogenase/oxidase enzymes, significantly reducing ROS production. It boosts the activity of antioxidant enzymes SOD and POD, which serve as primary defenses against free radicals. Topical application of curcumin can inhibit H2O2 production induced by TPA in the epidermis (207). According to studies, curcumin significantly enhanced the levels of antioxidant enzymes SOD and CAT, along with glutathione, in rats with diabetes (208). Oyetayo et al. (2020) demonstrated that the induction of Al3+ metal ions in *Drosophila melanogaster* resulted in a significant decrease in antioxidants such as catalase, glutathione-S-transferase, and glutathione, while simultaneously caused a notable increase in free radical precursors like H2O2 and NO. Curcumin reduced oxidative damage induced by Al3+ ions in a dose-dependent manner (209). Curcumin inhibits the production of

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inflammatory mediators by regulating signaling pathways. Specifically, curcumin targets Toll-like receptor-4 (TLR-4), influencing inflammation modulation. It contributes to the treatment of inflammatory diseases by regulating downstream signaling pathways, including nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPKs), and Activator Protein 1 (AP-1) (210). NF-κB, a pivotal transcription factor in inflammation, orchestrates the expression of various pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (211). Moreover, it promotes the production of critical proteins like TNF-α, activating NF-κB, particularly in chronic inflammation. NF-κB regulates intracellular immunity in aging and age-related diseases (212). Additionally, elevated levels of MCP-1 in circulation have been identified as a reliable biomarker for aging, indicating that as individuals age, the levels of MCP-1 tend to increase, making it a valuable biomarker for age-related studies (213). Curcumin has been shown to inhibit MCP-1, an inflammatory mediator (214). Extensive research on model organisms, ranging from yeast to mice, highlights the crucial role of autophagy in the aging process. The ATG gene family is crucial for lifespan extension, and increasing the expression of specific autophagy proteins has been shown to further extend lifespan (215). The key regulators of autophagy are mTOR kinase and AMPK. In some model organisms, extending lifespan and health span was achieved by inhibiting the mTOR pathway and activating the AMPK pathway (215). These signaling pathways also regulate nutrient sensing, similar to the insulin/IGF1 pathway. Studies have shown that inhibiting the insulin/IGF1 pathway can effectively postpone aging in animal models (216). Curcumin's impact on autophagy is indicated by its ability to modulate AMPK levels and activity while inhibiting mTOR (217, 218). The dysregulation of the autophagy process is one of the leading causes of neurodegenerative diseases. The accumulation of mutated huntingtin and misfolded Aβ proteins has been established as crucial factors in the pathogenesis of Huntington's and Alzheimer's diseases. Through various mechanisms, curcumin is capable of effectively inducing the degradation of misfolded proteins and damaged organelles. Curcumin activates TFEB (219), inducing lysosome (220) biogenesis and restoring HSP70 levels for proper cargo loading. Additionally, curcumin triggers the process of mitophagy (221), which reduces oxidative stress levels, leading to an improvement in the survival of neurons (222). Recent randomized clinical trials show curcumin's positive impact on aging-related disorders. Osteoarthritis (OA) is a chronic joint condition strongly associated with both chronic and acute inflammation (223). Curcumin has been shown to have anti-arthritic effects in humans with

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osteoarthritis (OA) and rheumatoid arthritis (RA) (224, 225). Two groups of 40 participants with mild-to-moderate knee osteoarthritis were randomized over six weeks. A 500 mg dose of curcuminoid was given to one group (supplemented with 5 mg of piperine per dose), while a placebo was given to the other group. In comparison with the placebo group, the treatment group showed notable reductions in the VAS, WOMAC, and LPFI scores. The pain and physical function scores based on the WOMAC subscales were significantly improved (p-value < 0.001), but stiffness scores did not show significant improvements (226). Curcumin supplementation has been studied in several randomized controlled trials over a four-week period. In particular, the studies assessed glutathione peroxidase activity (GPX) in erythrocytes, malondialdehyde concentrations (MDA), and superoxide dismutase activity (SOD). Supplementing with curcumin at daily doses of 600 mg effectively decreases circulating MDA levels and enhances SOD activity, according to these studies (227). The attenuation of systemic inflammation by curcumin has implications for numerous conditions affecting various systems beyond arthritis. Metabolic syndrome (MetS) is characterized by insulin resistance, hyperglycemia, hypertension, low HDL cholesterol, high LDL cholesterol, elevated triglyceride levels, and visceral obesity. It has been shown that curcumin improves insulin sensitivity (228), suppress adipogenesis (229), reduce elevated blood pressure (230), inflammation (231), and oxidative stress associated with MetS (232). Thirty-four patients with Alzheimer's disease were studied in a randomized, double-blind, placebo-controlled study by Baum et al. There were two different doses of curcumin (1 or 4 g) and a placebo group receiving 4 g. The Mini-Mental State Examination (MMSE) score did not improve after curcumin treatment (233). urcumin delays disease progression and modulates cognitive function as well as biomarker levels. Clinical trials may have been unsuccessful due to curcumin’s poor bioavailability, the selection of cohorts at an advanced stage of AD, and biological differences between rodent models and AD patients. Many interventions have failed in clinical trials despite their success in animal models (234). Curcumin's safety and efficacy have been demonstrated in numerous clinical trials involving healthy individuals. However, it has been associated with some adverse effects. Researchers showed that side effects such as diarrhea, headache, rash, and yellow stools were reported in a dose-response study using 500–12,000 mg of curcumin over 72 hours. Another study noted nausea, diarrhea, and elevated levels of serum alkaline phosphatase and lactate dehydrogenase following daily doses ranging from 0.45 to 3.6 g/day (235).

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5. Potential synergistic effects of supplements

In addition to their complementary roles in enhancing health, omega-3 fatty acids, coenzyme Q10, gingerol, and curcumin may have synergistic effects. The combined effects of omega-3 fatty acids and coenzyme Q10 might further improve cardiovascular health and energy metabolism. A study confirmed that omega-3 and coenzyme Q10 combined significantly prevented the progression of hypercholesterolemia-induced atherosclerosis. This study investigated the effects of omega-3 and/or coenzyme Q10 (CoQ10) on hypercholesterolemia-induced atherosclerosis in rats. The study assessed lipid profiles, cardiovascular risk indices, serum levels of adiponectin and creatine kinase, oxidative stress markers, and histopathological changes in the heart and aorta. Results showed that hypercholesterolemic rats had elevated lipid levels and oxidative stress, along with decreased adiponectin levels and increased levels of creatine kinase. Treatment with omega-3 and/or CoQ10 improved lipid profiles, reduced oxidative stress, and ameliorated histopathological damage. The combination of omega-3 and coenzyme Q10 provided the most significant benefits, suggesting their effective anti-hyperlipidemic, cardioprotective, and atheroprotective effects, supporting their use in managing cardiovascular disorders in obese individuals (236). A synergistic approach to combination therapy is emerging as a method for treating complex diseases, including inflammation (237). Turmeric and ginger are known to exert anti-inflammatory actions through many common signaling pathways, including Nrf2 activation (238, 239). Gingerol and curcumin have antioxidant and anti-inflammatory properties, which may help reduce both inflammation and oxidative stress. When combined, these compounds might provide a more robust defense against age-related conditions (240-242) . One study evaluated the combined analgesic, anti-inflammatory, and hemolytic effects of ethanolic extracts from turmeric (Curcuma longa) and ginger (Zingiber officinale) through in vitro and in vivo experiments using albino mice and Wistar rats. Results showed that all doses significantly reduced inflammation within 1 to 4 hours, with the combination of ginger (200 mg/kg) and turmeric (60 mg/kg) showing the greatest inhibition at the 4-hour mark (243). Another study investigated the effects of curcumin and long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) supplementation on glycemic control and blood lipid levels in individuals at high risk for type 2 diabetes (T2D). In a 12-week, double-blinded, placebo-controlled trial with 64 participants, subjects were randomly assigned to four

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groups: double placebo (PL), curcumin plus placebo (CC), LCn-3PUFA plus placebo (FO), or a combination of curcumin and LCn-3PUFA (CC-FO). The primary outcomes included HbA1c, fasting glucose, and insulin sensitivity. Results showed that while HbA1c and fasting glucose levels did not change significantly, insulin sensitivity improved significantly in the CC group compared to PL. FO and CC-FO also improved insulin sensitivity, though not significantly. Triglyceride levels increased in the PL group but decreased with CC and CC-FO supplementation, with FO showing the greatest reduction. The study concludes that while curcumin and LCn-3PUFA supplementation may reduce insulin resistance and triglycerides, they did not show complementary benefits for glycemic control (244). Research into their combined effects is still evolving, but preliminary findings suggest that this synergy could contribute to more effective strategies for promoting overall health and combating age-related conditions.

6. Concluding remarks

Various factors, primarily environmental and genetic, influence the process of aging. In recent decades, molecular studies have contributed to our understanding of aging mechanisms, particularly genes such as sir-2.1, ctl-1, daf-16, and sod-3. Additionally, oxidative enzymes have been optimized to perform antiaging functions, such as enhanced expression of FOXO3a and Akt proteins, along with increased activity of SOD and CAT. Although our understanding of the biological mechanisms underlying aging has made significant progress, preventing and delaying aging-related diseases remains a challenge. In recent years, anti-aging agents derived from natural active ingredients have been extensively studied. They offer significant benefits to patients by improving quality of life and extending survival. These agents not only eliminate free radicals, inhibit inflammation, and enhance the activity of various oxidative enzymes, but also arrest the cell cycle, regulate oncogenes, prevent diabetes, reduce adipocyte formation, and interact with multiple signaling pathways involved in disease pathogenesis. Additionally, older adults often consume these natural dietary supplements, indicating they may help promote healthy aging and reduce the adverse effects associated with aging. In this study, nutrient-sensing pathways are emphasized as a potential pathway to extend longevity by natural supplements by treating aging-related diseases. A growing burden of aging-related diseases presents a major global health challenge, and natural supplements may help treat these conditions. In addition to providing a theoretical background for the use of natural products as potential anti-aging agents, this study also provides several practical applications. Several recently identified natural supplements with potential anti-aging properties are identified in the study, which summarizes the current understanding of nutrient-sensing pathways involved in the longevity-extending effects of natural supplements. Numerous animal models and clinical studies have showcased the positive effects of Omega-3 fatty acids, Coenzyme Q10, Gingerol, and Curcumin in slowing down the aging process. we identified several key research gaps that warrant further investigation. First, while these supplements have shown potential in mitigating age-related conditions, the long-term effects and optimal dosages for sustained health benefits in humans remain unclear. Additionally, the interactions between these compounds and other medications commonly taken by older adults have not been thoroughly studied. Another critical gap is the need for more large-scale, randomized clinical trials that explore the effects of these compounds on specific aging-related conditions such as neurodegenerative diseases and cardiovascular decline. However, further research is essential to unravel the mechanisms of action of these agents and assess their suitability for clinical application.

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Consent for publication

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Availability of data and material

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Competing interests

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Authors' contributions

Mehran Izadi, Nariman Sadri, and Amirhossein Abdi contributed to hypothesis, data gathering, and writing the main text of the manuscript. Mohammad Mahdi Raeis Zadeh, Mohammad Mahdi Ghazimoradi, Sara Shouri, and Dorsa Jalaei contributed to hypothesis, data gathering, designing figure and tables, as well as final editing. Safa Tahmasebi contributed to the writing, scientific, and structural editing, hypothesis, correspondence, and verifying the manuscript before submission.

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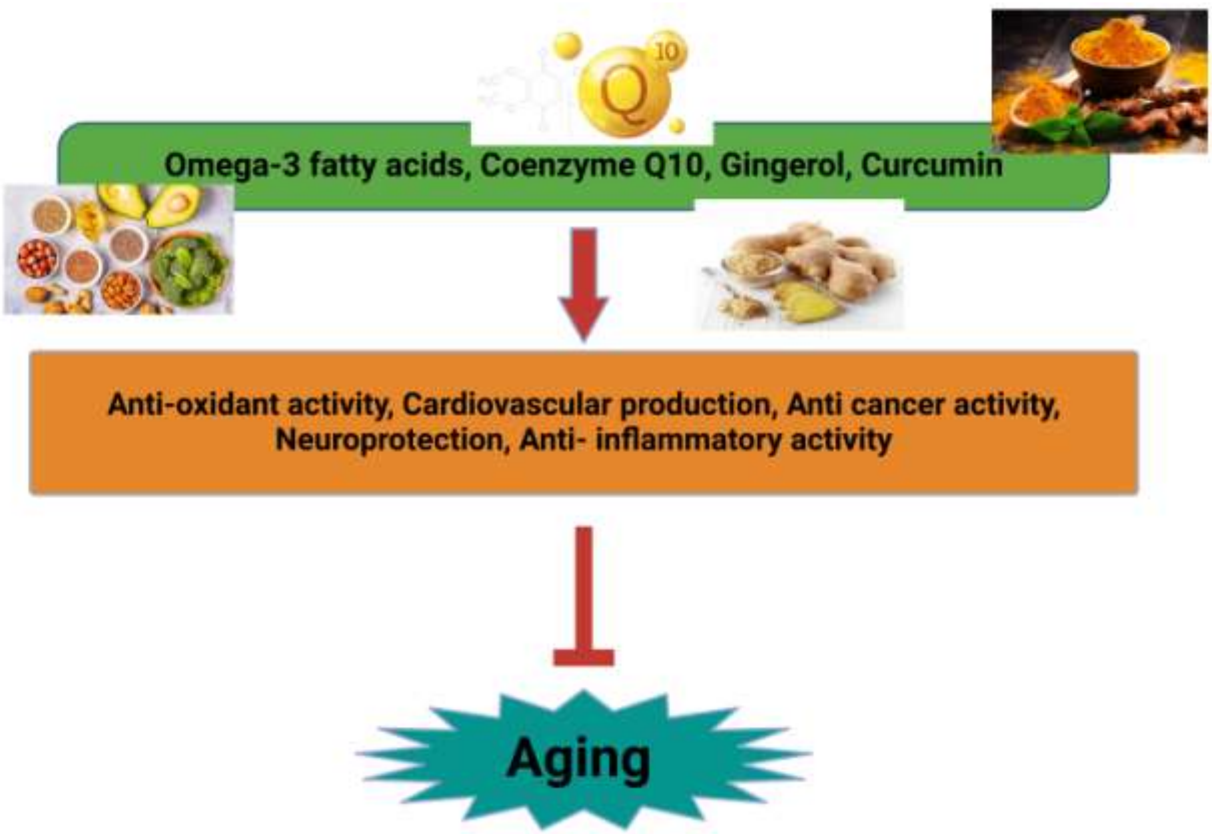

Figure 1. A schematic represents anti-aging effects of Omega-3, Coenzyme Q10, Gingerol, and Curcumin.

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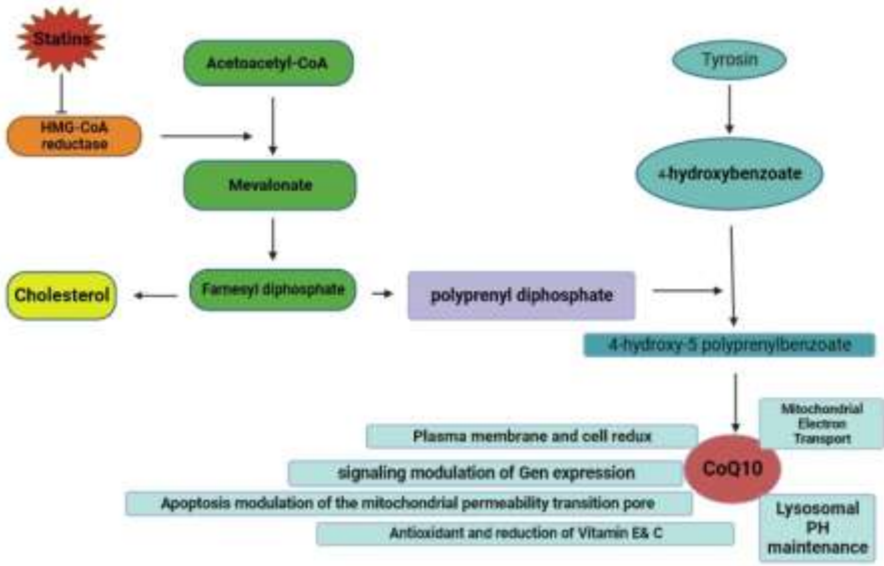

Figure 2. The potential of ginger substance for the antioxidant and anti-inflammatory action: By translocating Nrf2 into the nucleus, it can increase the expression of Nrf2 target genes, modify Keap1, and prevent Nrf2 from proteasomal degradation. This results in an increase in GSH and a decrease in ROS. Chronic inflammation may be mediated by overexpression of COX-2 and iNOS. The ginger extract reduces inflammation by suppressing NF-κB activity through stabilizing inhibitory IκBα and degrading IκBα kinase (IKK) activity. Therefore, the expression of COX-2 and iNOS down-regulate.

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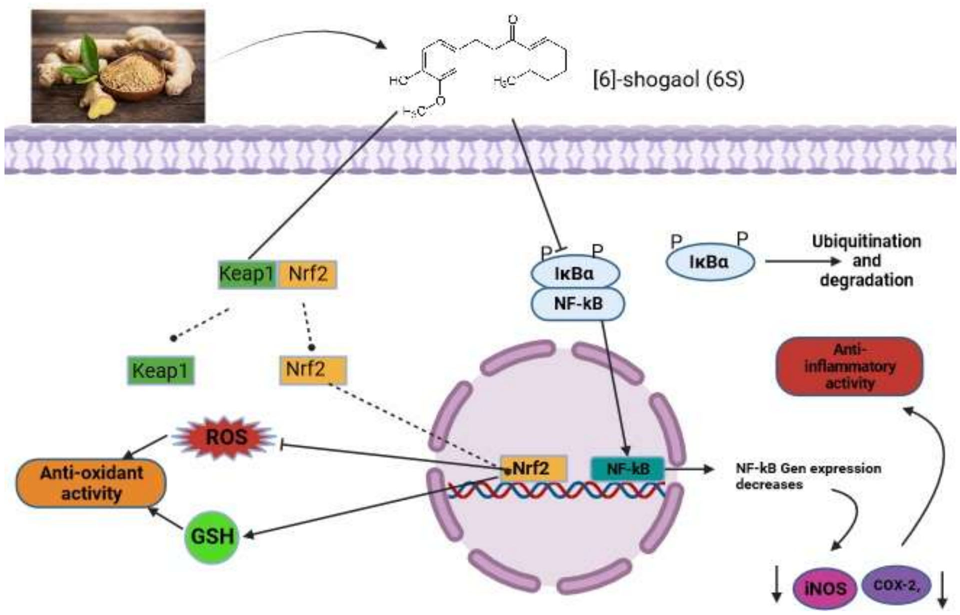

Figure 3. Function and Metabolic pathway for the biosynthesis of CoQ10. The mevalonic acid pathway is responsible for cholesterol and Coenzyme Q10 biosynthesis. *Statins* are drugs that inhibit the enzyme hydroxy-methylglutaryl-Coenzyme A (HMG-CoA) reductase. This interference prevents the conversion of HMG-CoA to mevalonate, which in turn blocks the production of farnesyl pyrophosphate (PP). Farnesyl pyrophosphate is an intermediate in synthesizing Coenzyme Q10 and other vital compounds. Also, main function of Coenzyme Q10 represented.

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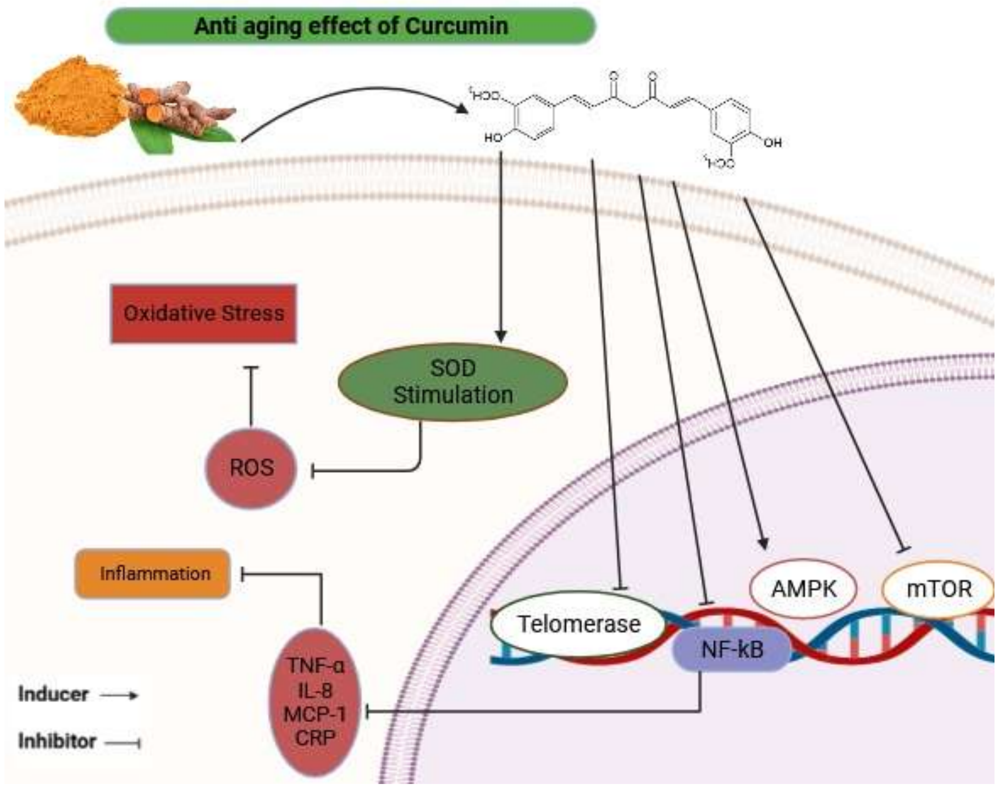

Figure 4. Anti-aging effects of curcumin. Curcumin is a substance that has been found to have broad anti-aging effects. At the cellular level, it can increase the level or activity of anti-aging factors such as AMPK while suppressing pro-aging factors such as NF-κB, mTOR, and Telomerase. Curcumin can also help to reduce oxidative stress by decreasing ROS levels. Additionally, it can modulate inflammation by inhibiting or reducing the levels of anti-inflammatory cytokines, which can help to delay the aging process.

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Table 1. Factors associated with aging

Hallmark	Mechanism	Reference
Genomic instability	Accumulation of damage to the DNA and chromosomes over time	(245-248)
Telomere attrition	Shortening of telomeres, which are the protective caps at the ends of chromosomes	(249-252)
Epigenetic alterations	Changes in gene expression that occur without changes to the underlying DNA sequence	(253, 254)
Loss of proteostasis	Imbalance in the production, function, and degradation of proteins	(255-257)
Deregulated nutrient sensing	Disruption in the ability of cells to sense and respond to nutrients	(258, 259)
Mitochondrial dysfunction	Decline in the function of mitochondria and produce increasing amounts of ROS	(260-262)
Cellular senescence	State where cells lose their ability to divide and function properly	(263, 264)
Stem cell exhaustion	Decrease in the number and function of stem cells, which are responsible for repairing and regenerating tissues	(265, 266)
Altered intercellular communication	Changes in the signaling between cells that can lead to chronic inflammation and other problems	(267, 268)

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Table 2. The Adequate Intakes of Omega-3 (269)

Age	**Male**	**Female**	**Pregnancy**	**Lactation**
Birth to 6 months	0.5 g	0.5 g		
7–12 months	0.5 g	0.5 g		
1–3 years	0.7 g	0.7 g		
4–8 years	0.9 g	0.9 g		
14–18 years	1.6 g	1.1 g	1.4 g	1.3 g
19-50 years	1.6 g	1.1 g	1.4 g	1.3 g
51+ years	1.6 g	1.1 g		

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Table 3. Summary of several clinical trials by CQ10

Disease	Dose	Outcome	Ref
early-stage Huntington disease (HD)	2,400 mg/day	Generally safe and well-tolerated	(270)
cardiovascular disease (CVD)	100 mg/day	Improvement in left ventricular ejection fraction in patients suffering from heart failure	(271)
Swedish healthy elderly population	200 mg/day	Significant reduction in cardiovascular mortality	(272, 273)
Type 2 diabetic patients	260 mg/day	Reduce fasting plasma glucose levels without changes in fasting insulin and glycated hemoglobin (HbA1c)	(274)
Rheumatoid arthritis	100 mg/day	Lower TFN-α plasma levels	(275)
Alzheimer's Disease	400 mg/day	No difference	
Hemodialysis	1200 mg/day	lowered F2-isoprostane plasma levels indicative of a reduction in oxidative stress	(276)
Diabetic Nephropathy	100 mg/day	Significantly improved gene expression of peroxisome proliferator-activated receptor-γ, interleukin-1, and tumor necrosis factor-α.	(277)

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