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

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Review Article

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Abstract

Ageing is an inevitable biological process accompanied by various physiological changes, and researchers have long sought interventions to promote healthy ageing. This article explores the effects of four natural compounds – omega-3 fatty acids, coenzyme Q10, gingerol and curcumin – on the ageing 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-ageing properties are 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 ageing journey.

Introduction

Ageing is a natural biological process that impacts every living organism, affecting various aspects of physical, mental and emotional health owing to intricate physiological and dynamic changes over time. Most gerontologists assert that it starts in the fourth decade of life and leads to death. This complex and individual process takes place on a biological, psychological and social level. The biological process of ageing causes progressive changes in metabolism and physico-chemical properties of cells, resulting in impaired self-regulation, regeneration and structural and functional changes. This is a natural, irreversible process that can be successful, typical or pathological. The biological changes due to ageing 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 their awareness and their ability to adapt to the ageing process. The following adaptation attitudes can be distinguished: constructive, dependent, hostile and self-centred. 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. Social conditioning constrains the function of the elderly to that of senior citizens, and traditions may evolve over time. Social ageing refers to the way a human being perceives and experiences the ageing process[(1)].

Researchers have long been fascinated by ageing, 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 ageing, it is essential to understand the ageing process itself, which is governed by genetic and cellular mechanisms[(2)]. At the genetic level, ageing 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 ageing[(4)]. Telomere shortening is another key factor in ageing[(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 ageing[(7,8)]. by damaging proteins, DNA and lipids, leading to ageing-related changes in tissues and organs[(9)]. Various tissues and organs show ageing-related changes as a result of oxidative stress[(10)]. As mitochondria, the cell's energy producers, become less efficient with age, they generate more ROS, further contributing to cellular damage[(11)]. Ageing is also influenced by chronic inflammation[(12)]. Chronic inflammation, resulting from persistent immune system activation, is

Table 1. Factors associated with ageing

Hallmark	Mechanism	Reference
Genomic instability	Accumulation of damage to the DNA and chromosomes over time	(243–246)
Telomere attrition	Shortening of telomeres, which are the protective caps at the ends of chromosomes	(247–250)
Epigenetic alterations	Changes in gene expression that occur without changes to the underlying DNA sequence	(251,252)
Loss of proteostasis	Imbalance in the production, function, and degradation of proteins	(253–255)
Deregulated nutrient sensing	Disruption in the ability of cells to sense and respond to nutrients	(256,257)
Mitochondrial dysfunction	Decline in the function of mitochondria and produce increasing amounts of ROS	(258–260)
Cellular senescence	State in which cells lose their ability to divide and function properly	(261,262)
Stem cell exhaustion	Decrease in the number and function of stem cells, which are responsible for repairing and regenerating tissues	(263,264)
Altered intercellular communication	Changes in the signalling between cells that can lead to chronic inflammation and other problems	(265,266)

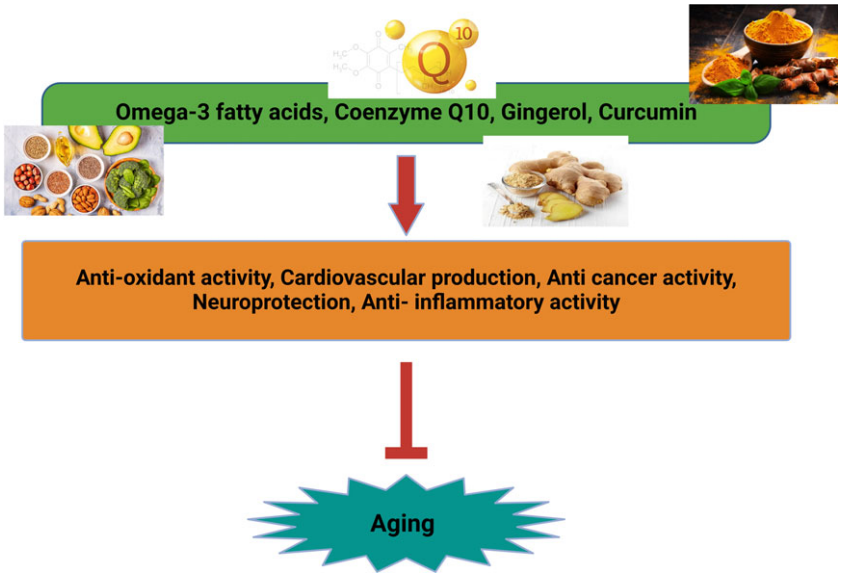

Figure 1. A schematic showing the anti-ageing effects of omega-3, coenzyme Q10, gingerol and curcumin.

closely linked with age-related diseases[13]. Age-related changes in gene expression further accelerate ageing, 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, ageing can be accelerated. Another hallmark of ageing is protein misfolding and aggregation[15]. Protein misfolding and aggregation, which interfere with cellular function, are also hallmarks of ageing and are implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's. In Alzheimer's disease, β-amyloid and tau proteins are misfolded in the brain. Typically, Parkinson's disease is characterised by brain accumulations of α-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 ageing process[17]. Table 1 summarises ageing factors.

Research into lifespan and healthy ageing has increasingly focused on natural preventative factors. Compounds including omega-3 fatty acids, coenzyme Q10, gingerol (from ginger) and curcumin (from turmeric) have emerged as potential anti-ageing 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 ageing process, particularly in mitigating oxidative stress, inflammation and mitochondrial dysfunction, which are common contributors to ageing. Although 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, whereas gingerol and curcumin are powerful anti-inflammatory and antioxidant agents. These compounds may also lower the risk of cancer and dementia associated with ageing. By examining current scientific studies, we can explore how these natural substances contribute to healthy ageing 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 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 tumour growth[18–20]. Oxidative

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Table 2. The Adequate Intakes of Omega-3[267]

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		

stress contributes to various disorders, including 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 ageing 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 ageing and longevity using these natural compounds.

Omega-3

Many health benefits can be attributed to omega-3 fatty acids, which are polyunsaturated fatty acids (PUFA). They can help reduce inflammation[27] as well as 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 synthesise them, so they must be obtained from food or supplements. Table 2 summarises the adequate amount of omega-3. Omega-3 fatty acids come in three forms: eicosapentaenoic acid (EPA), α-linolenic acid (ALA) and docosahexaenoic acid (DHA)[38]. Plant sources of ALA include rapeseed, 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 such as 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 down. Pancreatic carboxylic acid ester lipase breaks down omega-3 ethyl esters into EPA and 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]. β-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, NEFA, ethyl esters, phospholipids, triacylglycerols and so on)[45]. Phospholipids have higher bioavailability than other forms, and krill oil has high bioavailability compared with 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 that different positions may be more effective[45]. The average American diet is significantly below the 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 randomised 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. The American Heart Association recommends omega-3 supplements containing EPA and DHA daily to people with coronary heart disease or heart failure and recommends 4000 mg/d of omega-3 supplements for people with high triacylglycerol[49,50].

Omega-3 supplements are generally considered safe. The Food and Drug Administration (FDA) recommends consuming no more than 5 g of EPA and DHA combined per day from dietary supplements[51]. Some omega-3 supplements may cause minor side effects, such as odorous breath, nausea, fishy aftertaste, diarrhoea 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 leucocytes towards inflammation sites (leucocyte chemotaxis inhibition)[59]; reducing the expression of adhesion molecules, particularly those involved in interactions between leucocytes and blood vessel walls (leucocyte–endothelial adhesive interactions)[60]; suppressing the activity of cyclooxygenase (COX) and the subsequent production of eicosanoids such as leukotrienes and prostaglandins derived from arachidonic acid[59,61]; reducing the levels of proinflammatory cytokines such as IL-1β, TNF-α and IL-6[62]; increasing the production of compounds that resolve inflammation, such as maresins, protectins, resolvins and lipoxins[63]; inhibiting *NF-kB*, a transcription factor that promotes inflammation[57]; activating the anti-inflammatory transcription factor *NR1C3*[57]; activating peroxisome proliferator-activated receptors (PPAR) that have anti-inflammatory effects[59]; inducing anti-inflammatory effects by activating *GPR120*, a G-protein-coupled receptor[64]; and disrupting lipid rafts in cell membranes and altering phospholipid composition[65–67]. Normal brain function and ageing 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 ageing and longevity. Several studies have shown that it can slow down the ageing process and extend life. Several studies suggest that omega-3 may protect against dementia and cognitive decline associated with ageing. 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 disease (AD). According to prospective studies, individuals with higher omega-3 fatty acid intakes are less likely to develop AD[68], and erythrocyte DHA levels may be inversely associated with the risk of AD and dementia of any

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cause[69]. 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[70,71]. The effects of omega-3 fatty acid supplementation on cognitive decline and probable AD, however, have been limited in randomised clinical trials[72]. 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[73,74]. The *APOE ε4* allele, the major genetic risk factor for AD, could induce abnormal cholesterol metabolism as part of the AD-associated pathology[75]. 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* non-carriers, experiencing slower cognitive decline[73]. According to other studies, omega-3 fatty acids are beneficial only for *APOE ε4* non-carriers[71,76]. A possible explanation for this may be that APOE is reducing DHA and EPA delivery to the brain[77]. However, findings from a meta-analysis suggest that (1) long-term omega-3 fatty acid supplementation may reduce the risk of 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 research by Wenbo Qi *et al.*, consuming polyunsaturated fatty acids reduces the risk of ageing-related diseases, especially cardiovascular disease and stroke. Researchers found alterations in lipid metabolism, specifically an increase in ALA synthesis, in long-lived *Caenorhabditis elegans* glp-1 germline-less mutants. In *C. elegans*, ALA extends lifespan in a dose-dependent manner. In addition, the extended longevity observed in the glp-1 mutant animals relies on two crucial transcription factors, *NHR-49/PPARα* and *SKN-1/Nrf2*, although 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-ageing 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[78].

Another study in 2023 found that a structured triacylglycerol 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 action. DHA-TG bolstered antioxidant defences and significantly increased physical fitness in ageing *C. elegans*, which could have implications for cognitive function[79].

A study conducted by Kamil M. and his colleagues on *Drosophila* demonstrated that dietary supplements containing monoacylglycerol n-3 PUFA can 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[80].

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[81].

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. Levels of *GluR2* and *NR2B*, two glutamate receptor subunits, decrease in ageing rats. However, when aged rats are given n-3 fatty acid supplementation, these levels return to those seen in young adult rats[82]. Fish oil supplementation has been shown to extend the lifespan of female mice prone to autoimmune disorders by more than 40%[83,84]. Several cardiac dysfunctions have been attenuated by fish oil rich in omega-3 fatty acids in ageing mice, including hypertrophy of the ventricular wall and remodelling of the cardiac muscle[85]. It has been shown that omega-3 PUFA EPA and DHA can reverse the decline in retinoid receptors and *PPARγ* in aged animals and may improve neurogenesis[86]. The research conducted by Qureshi and his team found that middle-aged and older rats were inhibited or prevented from releasing senescent microvesicles (SMV) 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[87]. Specific and relevant changes in glutamatergic transmission underlie the potent neuroprotective effects of omega-3 PUFAs during ageing in the central nervous system. Through improved glutamatergic transmission, omega-3 can protect the central nervous system during ageing[88]. Telomere length is one of the important hallmarks of ageing[89,90]. Various doses of omega-3 fatty acids were administered to male mice over 2 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[91]. Research suggests that PUFA may promote telomere length by counteracting age-related increases in TRF-1 expression, as observed in pigs supplemented with linseed oil for 9 weeks[92]. Having omega-3 fatty acids in the diet reduced the rate of telomere attrition and elongated the telomeres of rats in another study[93]. Comparative studies on telomere length showed that fish oil containing 60% omega-3 PUFA had a positive effect compared with control fish oil[94]. Another study examined the role of fish oil, DHA and arachidonic acid in mice whose ageing was induced by D-galactose. In this study, fish oil, DHA and arachidonic acid were linked to ageing 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 PUFA, particularly DHA, suppress cellular senescence pathways, demonstrating their anti-ageing potential[95].

In conclusion, the research presented here highlights the significant positive effects of ω-3 polyunsaturated fatty acids, particularly ALA and DHA, on various aspects of health and ageing. These studies demonstrate that ALA can extend lifespan,

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potentially through *NHR-49/PPARα* and *SKN-1/Nrf2* transcription factors, and that DHA, especially in structured triacylglycerol form (DHA-TG), can improve health span by enhancing mobility and antioxidant defences[78]. It has been demonstrated that omega-3 fatty acids, such as EPA, support muscle cell regeneration even when harmful factors are present. In addition, 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 ageing and age-related diseases in humans. A significant amount of research has been conducted in the field of ageing and longevity on telomeres, the protective caps at the ends of chromosomes. Often considered markers of biological ageing, 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[96]. The telomere length of patients with coronary heart disease may be protected by marine omega-3 fatty acids[97]. 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[98]. Omega-3 fatty acids may protect telomere length from oxidative stress, according to a randomised controlled trial[99]. 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[100]. 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[101]. 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 ageing-related biomarkers following omega-3 supplementation. Using the Trier Social Stress Test, participants were randomly assigned to receive 2·5 g of omega-3 every day, 1·25 g 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 with 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 ageing process and lower depression risk[102]. EPA, DPA and DHA were found to increase the chances of older individuals experiencing a robust and healthy ageing process, according to a prospective cohort study conducted by Heidi TM Lai and colleagues[103]. 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 seventeen prospective cohort studies[104].

Studies conducted in 2013 found lower total mortality, particularly cardiovascular mortality, in people with higher plasma levels of omega-3 polyunsaturated fatty acid biomarkers[105]. 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 PUFA[106].

There is growing evidence that PUFA and their compounds can help combat cognitive decline related to ageing. Fish oil supplements totalling 0·4 g of EPA and 2 g of DHA significantly improved cognitive processing speed in middle-aged to older adults with obesity[107]. EPA and DHA daily doses of 1·86 g and 1·5 g were beneficial to patients with coronary artery disease and ischaemic risk over 30 months, leading to improved cognitive function[108]. A second study found that taking 1·6 g of EPA and 0·8 g 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, randomised controlled trial, fish oil was shown to enhance memory function in individuals with mild cognitive impairment (MCI)[109]. 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)[110]. According to a meta-analysis by Bao-Zhen *et al.*, omega-3 polyunsaturated fatty acid intake is associated with cognitive impairment, AD 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[111]. 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 patients with AMD, following them for 10 years[112]. Augood and Seddon's study supports the recent findings[113,114]. A review of human and animal research suggests omega-3 has numerous health benefits, including slowing the ageing process. According to these findings, omega-3 fatty acids can promote healthy ageing, enhance cognitive function and protect against age-related diseases. This makes them important dietary components for individuals who want to maintain their health and wellbeing 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, diarrhoea, gas, nausea or arthralgia[115].

Coenzyme Q10

Animal cells produce the small, lipid-soluble antioxidant molecule coenzyme Q, widely located in cell membranes[116]. 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 ageing, so it is

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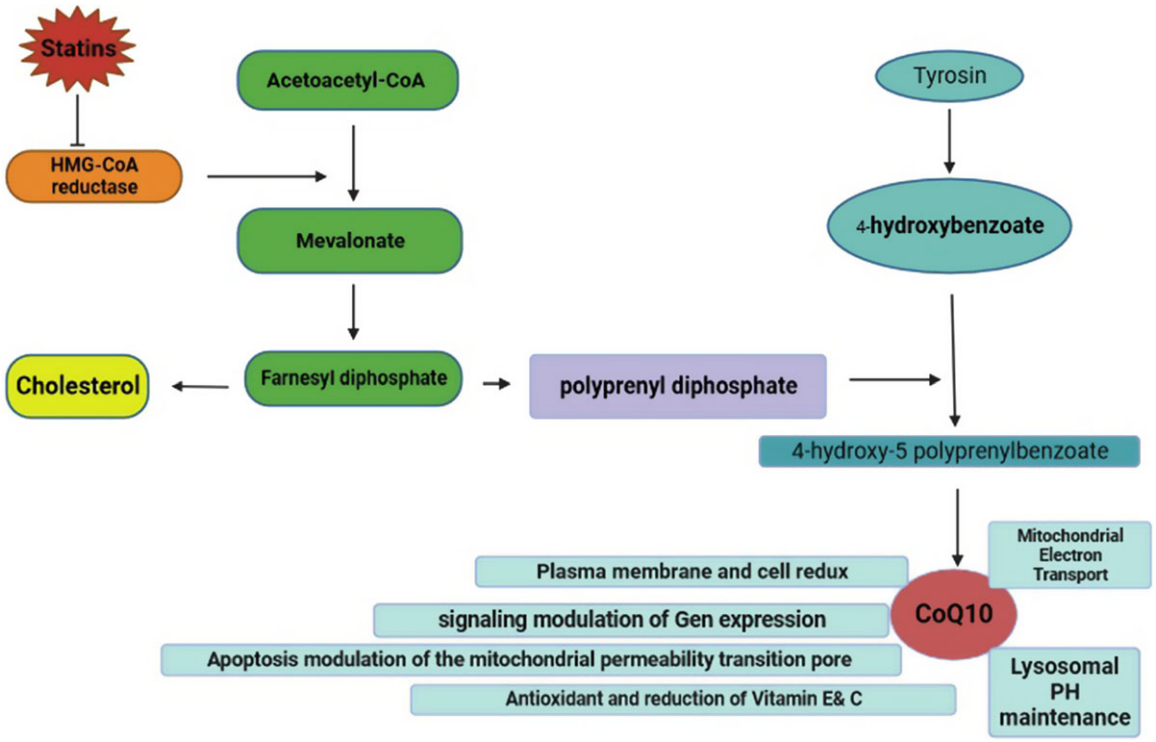

Figure 2. The potential of ginger for antioxidant and anti-inflammatory action: By translocating *Nrf2* into the nucleus, it can increase the expression of *Nrf2* target genes, modify *Keap1* and prevent *Nrf2* from proteasomal degradation. This results in an increase in GSH and a decrease in ROS. Chronic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

imperative to obtain CoQ10 through our diet[117]. 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 such as oranges, strawberries and apples. In addition, CoQ10 can be found in cereals such as rye and wheat[117]. 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 has 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[118]. 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[119]. The presence of tissue uptake and successful treatment in various human diseases proves its efficacy[117,120]. The function of CoQ10 is to facilitate the transfer of electrons between complexes I/II and III in the electron transport chain[117]. As a key component of cellular function, it is widely distributed in all cell membranes. As a component of the mitochondrial electron transport chain, ubiquinone plays a crucial role. Complex I (reduced nicotinamide adenine dinucleotide (NADH)-coenzyme Q oxidoreductase) receives electrons from donors, complex II (succinate dehydrogenase) consists of flavin-linked dehydrogenases, which oxidise fatty acids and branched-chain amino acids, and electron transfer factor Q oxidoreductase (ETF-QO) transfers electrons to complex III (ubiquinone–cytochrome C oxidoreductase)[121,122]. 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[123,124]. Various studies have demonstrated that CoQ10 supplementation exerts epigenetic effects on genes associated with different biological processes, including intermediary metabolism, signalling, transcription control, transport and phosphorylation, disease mutation and embryonic development. The mitochondrial free radical theory of ageing asserts that damage to mitochondria is pivotal in cellular ageing[125]. Activated mitochondrial DNA is a significant target for mitochondrially derived reactive oxygen species (ROS), according to Eirin *et al.*[126]. Overall survival (OS) accumulation in mitochondrial DNA may contribute to ageing. Mitochondrial DNA damage is a serious concern because it can lead to a decline in the efficiency of the respiratory chain. DNA lesions and ROS result from such damage, which, in turn, can hasten the cellular ageing process[127]. Therefore, it is essential to protect and maintain mitochondrial DNA integrity to prevent cellular ageing and associated health problems. By interacting directly with DNA repair enzymes, CoQ10H2 promotes efficient repair of oxidative damage[128]. CoQ10 levels decline with age, and inborn errors in its synthesis can further impact these levels[129]. Chronic inflammation is a common problem related to ageing. CoQ10 can reduce free radicals, decrease *NF-κB* activation and lower the release of pro-inflammatory cytokines such as IL-6, TNF-α and C-reactive protein (CRP)[130]. Ageing-related reduction in CoQ10 levels is a significant contributor to inflammation. A study has shown that CoQ10 supplementation is effective in reducing inflammation. CRP, IL-6 and TNF-α levels were significantly reduced by CoQ10

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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/d	Generally safe and well tolerated	(268)
Cardiovascular disease (CVD)	100 mg/d	Improvement in left ventricular ejection fraction in patients suffering from heart failure	(269)
Swedish healthy elderly population	200 mg/d	Significant reduction in cardiovascular mortality	(270,271)
Type 2 diabetes	260 mg/d	Reduce fasting plasma glucose levels without changes in fasting insulin and glycated haemoglobin (HbA1c)	(272)
Rheumatoid arthritis	100 mg/d	Lower TNF-α plasma levels	(273)
Alzheimer's disease	400 mg/d	No difference	
Haemodialysis	1,200 mg/d	lowered F2-isoprostane plasma levels indicative of a reduction in oxidative stress	(274)
Diabetic nephropathy	100 mg/d	Significantly improved gene expression of PPAR-γ, IL-1 and TNF-α.	(275)

supplementation[131]. CoQ10's epigenetic effects regulate *NF-κB1*, thereby effectively reducing inflammation[132]. Cardiovascular disease is one of the common ageing-related concerns. Low levels of CoQ10 in endomyocardial tissues are strongly correlated with heart failure severity, whereas CoQ10 treatment has been shown to improve cardiac contractility[133]. Treatment with CoQ10 has been reported to improve lipid profiles, significantly contributing to the management of cardiovascular disease[134]. Clinical studies on CoQ10 supplementation in patients with antiphospholipid syndrome have demonstrated a significant reduction in thrombotic markers and pro-inflammatory markers, as well as improved mitochondrial function and endothelial health[135]. 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 patients with Down syndrome may accelerate AD[136]. Changes in these factors include increased levels of IL-6 and TNF-α, as well as decreased levels of CoQ10. In addition, CoQ10 levels are positively correlated with intelligence quotients[137]. In human studies, however, inconsistent results have been found. According to a study conducted in 2003, plasma CoQ10 levels do not correlate with ageing in older women[138]. 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 1 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[139]. Other studies have confirmed that, in the brain, CoQ10 levels are decreased[140,141]. 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[139]. 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[142]. 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 randomised 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/d[143]. 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 diarrhoea.

Gingerol

Originally from Asia, ginger is now found in tropical environments as a member of the Zingiberaceae family of plants[144]. Ginger contains various substances with biological effects, including 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[145]. 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, including antibacterial, anti-inflammatory, anticancer, antidiabetic, gastroprotective, neuroprotective and antioxidant effects[146]. 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[147]. 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. In addition, ginger contains active substances, including 6-gingerol and 6-shogaol, that can fight cancer by reducing COX-2 levels, blocking *NF-κB* activity in DNA and increasing *BAX* expression[148,149]. Despite its biological properties, 6-gingerol's low bioavailability limits its application. To overcome these limitations, new encapsulation and solubilisation techniques have been introduced, including nanoemulsions, complexations, micelles and solid dispersions. As a natural antioxidant, preservative and flavour enhancer, 6-gingerol could be used to maintain food quality and shelf life by combining with various ingredients in a synergistic manner[150].

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

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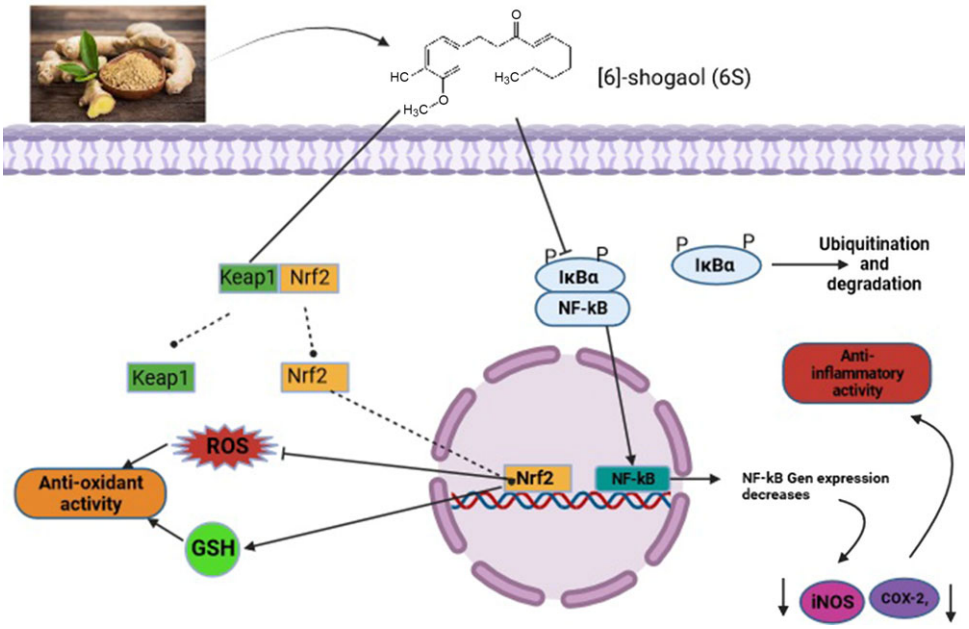

Figure 3. Function and metabolic pathway for the biosynthesis of CoQ10. The mevalonic acid pathway is responsible for cholesterol and coenzyme Q10 biosynthesis. Statins are drugs that inhibit the enzyme hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase. This interference prevents the conversion of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

by modulating cellular and molecular pathways of ageing[151]. Oxidative stress occurs when reactive oxygen species (ROS) overwhelm antioxidant defences in cells. Ageing and diseases associated with ageing are caused by 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[152]. Physiological functions decline with ageing owing to the accumulation of oxidative damage, a concept known as the free radical ageing theory[153]. Both *C. elegans* and mammals are believed to be affected by oxidative stress according to the free radical theory of ageing. ROS levels determine the organism's lifespan[154], and free radicals are a major contributor to ageing progression[155]. ROS levels increase as a result of infection, inflammation, stress and exposure to substances such as NO_x pollutants, tobacco smoke, radiation, drugs (for example, acetaminophen) and sunlight[156]. Based on new findings, some natural products can prevent, reduce and treat ageing and diseases related to ageing. It is suggested that ginger modifies molecular targets of the pathogenesis of age-related diseases[153]. There is evidence that ginger can fight inflammation and delay the ageing process in different organs, according to many studies[157]. Ginger possesses strong antioxidant properties, helping to neutralise 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 defences 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[158]. Studies have shown that ginger extract can lower the body's ROS and malondialdehyde (MDA). MDA is a lipid peroxidation marker harmful to cells[159]. glutathione peroxidase (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[160,161]. By blocking the activation of caspase-3, ginger extract may prevent apoptotic signalling that contributes to disease development[162]. The level of BDNF, a key molecule for neuronal health, function, learning and memory, was increased in the brains of mice with Scopolamine (SCO)-induced cognitive impairment after they received oral ginger extract[163]. Ginger extract administration resulted in less oxidative stress in the liver tissue of mice, with enhanced levels of antioxidant enzymes such as superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx) and catalase (CAT)[164].

One of the hallmarks of ageing 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[165]. Higher amounts of inflammatory molecules, such as TNF-α and IL-6, were detected in older people. These molecules can cause tissue damage and accelerate ageing[166]. Inflammatory mediators such as 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, 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[167]. 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[168].

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Genomic damage and instability result from the interrelated pathological processes of chronic inflammation and oxidative stress. The biomarker γ-H2AX, which is sensitive and reliable, revealed that 6-gingerol (6-GN) treatment increases DNA damage significantly. P53 is reactivated by intracellular ROS. Due to this, p53 arrests cell cycle progression during G2/M[169]. Compared with other supplements, ginger exhibited remarkable activity in protecting DNA at different concentration levels and had the highest overall antioxidant activity[170]. In breast cancer cells, 6-SG inhibited NOTCH signalling and induced apoptosis and autophagy[171]. 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 tumour cells[172]. 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[173]. 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, by contrast, diminishing the expression of Ki-67 and cyclin D1 proteins[174].

Ginger has demonstrated cognitive benefits in older subjects. Taking 400 or 800 mg of ginger daily for 2 months improved attention and cognitive processing in middle-aged women without adverse effects[175]. 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[176].

The prevalence of neurodegenerative diseases increases with ageing, with AD being a common form of age-related cognitive decline that affects brain structure and function. Ginger extract enhanced the expression of CAT and SOD enzymes in the brain and reduced the secretion and expression of *IL-1β, NF-κB* and *MDA* levels, improving behavioural dysfunction[177]. Study results show that supplementing middle-aged women with ginger extract at 400–800 mg/d improved their cognitive function[175]. One main factor that increases the likelihood of developing cardiovascular diseases is ageing. 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 anaesthesia decreased after they received fresh ginger extract through their veins. The extract seemed to block voltage-dependent calcium channels. Ginger supplementation of 3 g/d for 45 d significantly lowered serum cholesterol and triacylglycerol in patients with hyperlipidaemia[178]. 6-Gingerol inhibited the activation of *p38 MAPK*, a mitogen-activated protein kinase involved in cardiac remodelling[103]. In addition, 6-gingerol may reduce the accumulation of fat in the liver with age[179].

Sarcopenia is a condition that affects older people and causes a loss in 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[180]. Taking ginger supplements may also benefit knee osteoarthritis, a common condition in older adults, by reducing pain and improving joint function[181]. One of the most noticeable effects of ageing is the alteration of the skin's appearance and structure. Using a body cream containing ginger oil for a month diminished signs of skin ageing, possibly due to the plant's ability to scavenge free radicals[182]. Ginger has many health benefits that may support healthy ageing and longevity. Gingerol is a compound that can improve body function and prevent ageing-related diseases. Therefore, ginger may be a natural way to support healthy ageing and longevity. According to the US Food and Drug Administration, ginger root is safe in amounts up to 4 g/d. 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 g can exacerbate gastrointestinal disturbances such as heartburn, gastrointestinal reflux and diarrhoea. A small number of cases have been reported of arrhythmia caused by this spice. Gallstone formation can be aggravated by increased bile acid secretion[183].

Curcumin

Curcumin is a potent and effective anti-ageing 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[184]. 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[185]. Due to its low bioavailability, curcumin's therapeutic potential may be limited. Several approaches have been used to maximise 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 2000%[186]. Enhanced aqueous solubility, stability and cell targeting of curcumin can be achieved by various means, including conjugation with alginate, self-assembling peptide nanofibre carriers and formulation of curcumin phospholipid complexes, microemulsions, liposomes, polymeric micelles and nanoparticles[185,187]. Meanwhile, the nanoformulation 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 owing to its high stability in the body environment, long half-life and high bioavailability and easier access to different sites[188–190]. Clinical trials have shown that high daily doses of curcumin, up to 12 g/d, are considered safe for patients[191]. Curcumin exhibits pleiotropic activity, similar to other polyphenols. It can induce cellular responses by interacting with multiple proteins. Curcumin can positively influence cellular processes by regulating microRNAs and influencing epigenetic changes in cells[192]. As we age, persistent low-grade inflammation often occurs[193]. There is no doubt that polyphenol-rich foods can effectively alleviate symptoms of ageing owing to their potent anti-inflammatory and antioxidant properties. There is substantial evidence that curcumin has anti-ageing properties (Fig. 4)[194,195]. Extensive clinical trials have shown that curcumin can reduce symptoms of age-related diseases, including atherosclerosis, diabetes and cancer[196,197]. Curcumin activated *SIRT1* and protected human umbilical vein endothelial cell (HUVEC) from peroxide-induced senescence[198]. Bis-demetoxycurcumin, a curcumin analogue, protected Wi38 fibroblasts from oxidative stress-induced senescence[199]. These findings suggest that curcumin and its analogues show potential for therapeutic use in combatting cellular ageing and related diseases. Curcumin's anti-tumour activity is another important function[200]. Ageing is one of the most significant risk factors for

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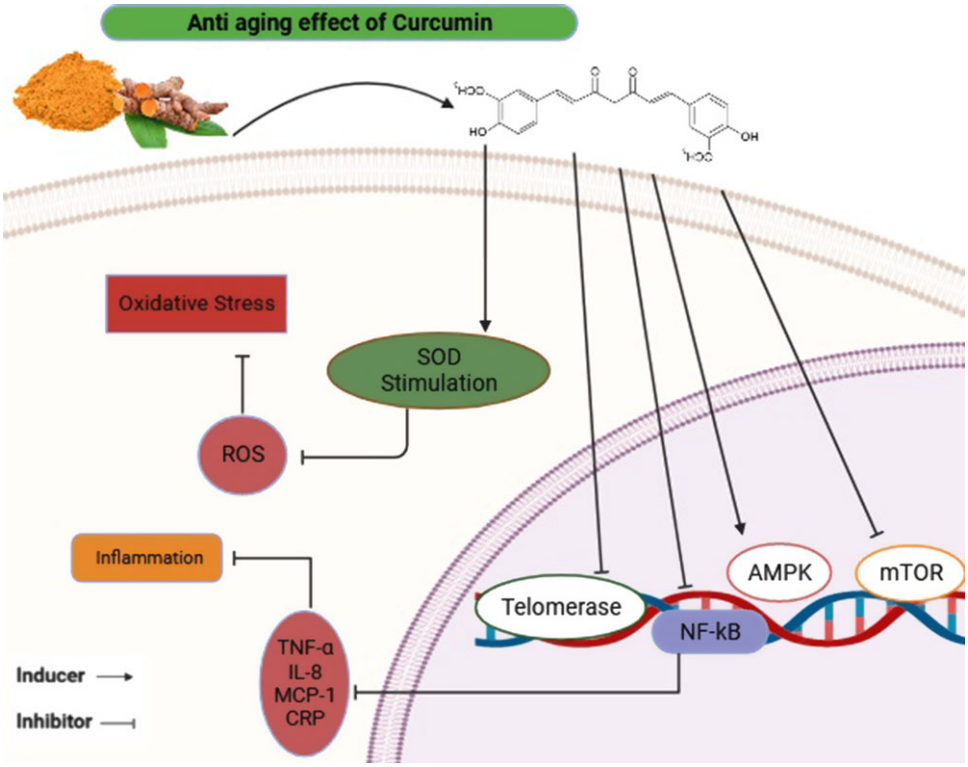

Figure 4. Anti-ageing effects of curcumin. Curcumin is a substance that has been found to have broad anti-ageing effects. At the cellular level, it can increase the level or activity of anti-ageing factors such as *AMPK* while suppressing pro-ageing factors such as *NF-κB, mTOR* and telomerase. Curcumin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

tumour development[201]. 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 tumourigenesis by reducing toxicity, potentially inducing cancer cell apoptosis and inhibiting metastasis through its anti-angiogenic properties[195]. Curcumin helps slow the ageing process by targeting multiple pathways involved in age-related diseases[202]. The pathogenesis of multiple age-related diseases involves oxidative stress-induced damage, a hallmark of ageing[203]. Cells and tissues that accumulate ROS can cause oxidative stress when detoxification mechanisms are overwhelmed[204]. 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 defences against free radicals. Topical application of curcumin can inhibit H_2O_2 production induced by tissue plasminogen activator (TPA) in the epidermis[205]. Curcumin significantly enhanced the levels of antioxidant enzymes SOD and CAT, along with glutathione, in rats with diabetes[206]. Oyetayo *et al.* (2020) demonstrated that the induction of Al^{3+} metal ions in *Drosophila melanogaster* resulted in a significant decrease in antioxidants such as catalase, glutathione-*S*-transferase and glutathione and simultaneously caused a notable increase in free radical precursors such as H_2O_2 and NO. Curcumin reduced oxidative damage induced by Al^{3+} ions in a dose-dependent manner[207]. Curcumin inhibits the production of inflammatory mediators by regulating signalling pathways. Specifically, curcumin targets Toll-like receptor-4 (*TLR-4*), influencing inflammation modulation. It contributes to the treatment of inflammatory diseases by regulating downstream signalling pathways, including *NF-κB*, mitogen-activated protein kinases (*MAPK*) and activator protein 1 (*AP-1*)[208]. *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*[209]. Moreover, it promotes the production of critical proteins such as TNF-α, activating *NF-κB*, particularly in chronic inflammation. *NF-κB* regulates intracellular immunity in ageing and age-related diseases[210]. In addition, elevated levels of *MCP-1* in circulation have been identified as a reliable biomarker for ageing, indicating that, as individuals age, the levels of *MCP-1* tend to increase, making it a valuable biomarker for age-related studies[211]. Curcumin has been shown to inhibit *MCP-1*, an inflammatory mediator[212]. Extensive research on model organisms, ranging from yeast to mice, highlights the crucial role of autophagy in the ageing process. The Autophagy gene family is crucial for lifespan extension, and increasing the expression of specific autophagy proteins has been shown to further extend lifespan[213]. 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[213]. These signalling pathways also regulate nutrient sensing, similar to the insulin/IGF-1 pathway. Studies have shown that inhibiting the insulin/IGF-1 pathway can effectively postpone ageing in animal models[214]. Curcumin's impact on autophagy is indicated by its ability to modulate *AMPK* levels and activity while inhibiting *mTOR*[215,216]. The dysregulation of the autophagy process is one of the leading causes of neurodegenerative diseases. The accumulation of mutated

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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 transcription factor EB (TFEB)[217], inducing lysosome[218] biogenesis and restoring HSP70 levels for proper cargo loading. In addition, curcumin triggers the process of mitophagy[219], which reduces oxidative stress levels, leading to an improvement in the survival of neurons[220]. Recent randomised clinical trials show curcumin's positive impact on ageing-related disorders. Osteoarthritis (OA) is a chronic joint condition strongly associated with both chronic and acute inflammation[221]. Curcumin has been shown to have anti-arthritic effects in humans with OA and rheumatoid arthritis[222,223]. Two groups of forty participants with mild-to-moderate knee osteoarthritis were randomised over 6 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 Visual analogue scales (VAS), WOMAC (It measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation) and Lequesne's pain functional index (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[224]. Curcumin supplementation has been studied in several randomised controlled trials over a 4-week period. In particular, the studies assessed GPx in erythrocytes, MDA concentrations and SOD activity. Supplementing with curcumin at daily doses of 600 mg effectively decreases circulating MDA levels and enhances SOD activity, according to these studies[225]. The attenuation of systemic inflammation by curcumin has implications for numerous conditions affecting various systems beyond arthritis. Metabolic syndrome (MetS) is characterised by insulin resistance, hyperglycaemia, hypertension, low HDL-cholesterol, high LDL-cholesterol, elevated triacylglycerol levels and visceral obesity. It has been shown that curcumin improves insulin sensitivity[226], suppresses adipogenesis[227] and reduces elevated blood pressure[228], inflammation[229] and oxidative stress associated with MetS[230]. Thirty-four patients with AD were studied in a randomised, 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[231]. Curcumin 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 patients with AD. Many interventions have failed in clinical trials despite their success in animal models[232]. 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 diarrhoea, headache, rash and yellow stools were reported in a dose–response study using 500–12 000 mg of curcumin over 72 h. Another study noted nausea, diarrhoea and elevated levels of serum alkaline phosphatase and lactate dehydrogenase following daily doses ranging from 0·45 to 3·6 g/d[233].

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 hypercholesterolaemia-induced atherosclerosis. This study investigated the effects of omega-3 and/or coenzyme Q10 (CoQ10) on hypercholesterolaemia-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 hypercholesterolaemic 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-hyperlipidaemic, cardioprotective and atheroprotective effects, supporting their use in managing cardiovascular disorders in obese individuals[234]. A synergistic approach to combination therapy is emerging as a method for treating complex diseases, including inflammation[235]. Turmeric and ginger are known to exert anti-inflammatory actions through many common signalling pathways, including Nrf2 activation[236,237]. 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 defence against age-related conditions[238–240]. One study evaluated the combined analgesic, anti-inflammatory and haemolytic 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 1–4 h, with the combination of ginger (200 mg/kg) and turmeric (60 mg/kg) showing the greatest inhibition at the 4-h mark[241]. Another study investigated the effects of curcumin and long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) supplementation on glycaemic 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 sixty-four participants, subjects were randomly assigned to four 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 with PL. FO and CC-FO also improved insulin sensitivity, though not significantly. Triacylglycerol 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 triacylglycerol, they did not show complementary benefits for glycaemic control[242]. 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 combatting age-related conditions.

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Concluding remarks

Various factors, primarily environmental and genetic, influence the process of ageing. In recent decades, molecular studies have contributed to our understanding of ageing mechanisms, particularly genes such as *sir-2·1, ctl-1, daf-16* and *sod-3*. In addition, oxidative enzymes have been optimised to perform anti-ageing 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 ageing has made significant progress, preventing and delaying ageing-related diseases remains a challenge. In recent years, anti-ageing 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 signalling pathways involved in disease pathogenesis. In addition, older adults often consume these natural dietary supplements, indicating they may help promote healthy ageing and reduce the adverse effects associated with ageing. In this study, nutrient-sensing pathways are emphasised as a potential pathway to extend longevity by natural supplements by treating ageing-related diseases. A growing burden of ageing-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-ageing agents, this study also provides several practical applications. Several recently identified natural supplements with potential anti-ageing properties are identified in the study, which summarises 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 ageing process. We identified several key research gaps that warrant further investigation. First, although 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. In addition, 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, randomised clinical trials that explore the effects of these compounds on specific ageing-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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References

1. Dziechciaż M & Filip R (2014) Biological psychological and social determinants of old age: bio-psycho-social aspects of human aging. *Ann Agric Environ Med: AAEM* **21**, 835–838.
2. Farr JN & Almeida M (2018) The spectrum of fundamental basic science discoveries contributing to organismal aging. *J Bone Miner Res* **33**, 1568–1584.
3. Sourada L & Kuglík P (2020) Genetic mechanisms of aging. *Cas Lek Cesk* **159**, 81–87.
4. Khrapko K & Turnbull D (2014) Mitochondrial DNA mutations in aging. *Prog Mol Biol Transl Sci* **127**, 29–62.
5. Fathi E, Charoudeh HN, Sanaat Z & Farahzadi R (2019) Telomere shortening as a hallmark of stem cell senescence. *Stem Cell Investig* **6**, 7.
6. Turner KJ, Vasu V & Griffin DK (2019) Telomere biology and human phenotype. *Cells* **8**, 73. doi: 10.3390/cells8010073.
7. Jiang F, Xu XR, Li WM, Xia K, Wang LF & Yang XC (2020) Monotropein alleviates H_2O_2-induced inflammation, oxidative stress and apoptosis via NF-κB/AP-1 signaling. *Mol Med Rep* **22**, 4828–4836.
8. Coluzzi E, Leone S & Sgura A (2019) Oxidative stress induces telomere dysfunction and senescence by replication fork arrest. *Cells* **8**, 19.
9. Lundgren CA, Sjöstrand D, Biner O, Bennett M, Rudling A, Johansson A-L, *et al.* (2018) Scavenging of superoxide by a membrane-bound superoxide oxidase. *Nat Chem Biol* **14**, 788–793.
10. Labunskyy VM & Gladyshev VN (2013) Role of reactive oxygen species-mediated signaling in aging. *Antioxid Redox Signal* **19**, 1362–1372.
11. Giorgi C, Marchi S, Simoes IC, Ren Z, Morciano G, Perrone M, *et al.* (2018) Mitochondria and reactive oxygen species in aging and age-related diseases. *Int Rev Cell Mol Biol* **340**, 209–344.
12. Franceschi C & Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol Ser A: Biomed Sci Med Sci* **69**, Suppl_1, S4–S9.
13. Akazawa H (2017) Aging and homeostasis. Chronic inflammation and aging. *Clin Calcium* **27**, 963–968.
14. Harris SE, Riggio V, Evenden L, Gilchrist T, McCafferty S, Murphy L, *et al.* (2017) Age-related gene expression changes, and transcriptome wide association study of physical and cognitive aging traits, in the Lothian Birth Cohort 1936. *Aging* **9**, 2489.
15. Cuanalo-Contreras K, Mukherjee A & Soto C (2013) Role of protein misfolding and proteostasis deficiency in protein misfolding diseases and aging. *Int J Cell Biol* **2013**, 638083. doi: 10.1155/2013/638083.
16. Forloni G, Terreni L, Bertani I, Fogliarino S, Invernizzi R, Assini A, *et al.* (2002) Protein misfolding in Alzheimer's and Parkinson's disease: genetics and molecular mechanisms. *Neurobiol Aging* **23**, 957–976.
17. Copinschi G & Caufriez A (2013) Sleep and hormonal changes in aging. *Endocrinol Metab Clin* **42**, 371–389.
18. Sánchez Macarro M, Martínez Rodríguez JP, Bernal Morell E, Pérez-Piñero S, Victoria-Montesinos D, García-Muñoz AM, *et al.* (2020) Effect of a combination of citrus flavones and flavanones and olive polyphenols for the reduction of cardiovascular disease risk: an exploratory randomized, double-blind, placebo-controlled study in healthy subjects. *Nutrients* **12**, 1475. doi: 10.3390/nu12051475.
19. Tajaldini M, Samadi F, Khosravi A, Ghasemnejad A & Asadi J (2020) Protective and anticancer effects of orange peel extract and naringin in doxorubicin treated esophageal cancer stem cell xenograft tumor mouse model. *Biomed Pharmacother* **121**, 109594.
20. Asgharian P, Tazekand AP, Hosseini K, Forouhandeh H, Ghasemnejad T, Ranjbar M, *et al.* (2022) Potential mechanisms of quercetin in cancer

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

prevention: focus on cellular and molecular targets. *Cancer Cell Int* **22**, 257.
21. Abdolmohammadi K, Mahmoudi T, Alimohammadi M, Tahmasebi S, Zavvar M & Hashemi SM (2023) Mesenchymal stem cell-based therapy as a new therapeutic approach for acute inflammation. *Life Sci* **312**, 121206.
22. Jafari D, Mousavi MJ, Keshavarz Shahbaz S, Jafarzadeh L, Tahmasebi S, Spoor J, *et al.* (2021) E3 ubiquitin ligase Casitas B lineage lymphoma-b and its potential therapeutic implications for immunotherapy. *Clin Exp Immunol* **204**, 14–31.
23. Marofi F, Azizi R, Motavalli R, Vahedi G, Nasimi M, Yousefi M, *et al.* (2021) COVID-19: our current knowledge of epidemiology, pathology, therapeutic approaches, and diagnostic methods. *Anti-Cancer Agents Med Chem* **21**, 2142–2162.
24. Zare Rafie M, Esmaeilzadeh A, Ghoreishi A, Tahmasebi S, Faghihzadeh E, Elahi R (2021) IL-38 as an early predictor of the ischemic stroke prognosis. *Cytokine* **146**, 155626.
25. Liu RH (2003) Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am J Clin Nutr* **78**, 3 Suppl, 517S–520S.
26. Tressera-Rimbau A, Arranz S, Eder M & Vallverdú-Queralt A (2017) Dietary polyphenols in the prevention of stroke. *Oxid Med Cell Longy* **2017**, 7467962.
27. Calder PC & Grimble RF (2002) Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr* **56**, Suppl 3, S14–S19.
28. Ander BP, Dupasquier CM, Prociuk MA & Pierce GN (2003) Polyunsaturated fatty acids and their effects on cardiovascular disease. *Exp Clin Cardiol* **8**, 164–172.
29. Endo J & Arita M (2016) Cardioprotective mechanism of omega-3 polyunsaturated fatty acids. *J Cardiol* **67**, 22–27.
30. Paixão EMdS, Oliveira ACdM, Pizato N, Muniz-Junqueira MI, Magalhães KG, Nakano EY, *et al.* (2017) The effects of EPA and DHA enriched fish oil on nutritional and immunological markers of treatment naïve breast cancer patients: a randomized double-blind controlled trial. *Nutr J* **16**, 1–11.
31. Chagas TR, Borges D, de Oliveira PF, Mocellin MC, Barbosa AM, Camargo C, *et al.* (2017) Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival: a randomised clinical trial. *J Human Nutr Diet* **30**, 681–692.
32. Simopoulos AP (2002) The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother* **56**, 365–379.
33. Su KP, Tseng PT, Lin PY, Okubo R, Chen TY, Chen YW, *et al.* (2018) Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms: a systematic review and meta-analysis. *JAMA Netw Open* **1**, e182327.
34. Brigham EP, Woo H, McCormack M, Rice J, Koehler K, Vulcain T, *et al.* (2019) Omega-3 and omega-6 intake modifies asthma severity and response to indoor air pollution in children. *Am J Respir Crit Care Med* **199**, 1478–1486.
35. Dighriri IM, Alsubaie AM, Hakami FM, Hamithi DM, Alshekh MM, Khobrani FA, *et al.* (2022) Effects of omega-3 polyunsaturated fatty acids on brain functions: a systematic review. *Cureus* **14**, e30091.
36. Welty FK (2023) Omega-3 fatty acids and cognitive function. *Curr Opin Lipidol* **34**, 12–21.
37. Wei BZ, Li L, Dong CW, Tan CC & Xu W (2023) The relationship of omega-3 fatty acids with dementia and cognitive decline: evidence from prospective cohort studies of supplementation, dietary intake, and blood markers. *Am J Clin Nutr* **117**, 1096–1109.
38. Krupa K, Fritz K & Parmar M (2023) *Omega-3 fatty acids. StatPearls*. Treasure Island, FL: StatPearls Publishing. Copyright ©, StatPearls Publishing LLC.
39. Jacobsen C (2010) Enrichment of foods with omega-3 fatty acids: a multidisciplinary challenge. *Ann N Y Acad Sci* **1190**, 141–150. doi: 10.1111/j.1749-6632.2009.05263.x.
40. Shahidi F & Ambigaipalan P (2018) Omega-3 polyunsaturated fatty acids and their health benefits. *Annu Rev Food Sci Technol* **9**, 345–381.
41. Ito MK (2015) A comparative overview of prescription omega-3 fatty acid products. *P T* **40**, 826–857.
42. Schuchardt JP & Hahn A (2013) Bioavailability of long-chain omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **89**, 1–8.
43. Innis SM (2014) Omega-3 fatty acid biochemistry: perspectives from human nutrition. *Mil Med* **179**, 11 Suppl, 82–87.
44. Yang X, Yi X, Zhang F, Li F, Lang L, Ling M, *et al.* (2022) Cytochrome P450 epoxygenase-derived EPA and DHA oxylipins 17,18-epoxyeicosatetraenoic acid and 19,20-epoxydocosapentaenoic acid promote BAT thermogenesis and WAT browning through the GPR120-AMPKα signaling pathway. *Food Funct* **13**, 1232–1245.
45. Cholewski M, Tomczykowa M & Tomczyk M (2018) A comprehensive review of chemistry, sources and bioavailability of Omega-3 fatty acids. *Nutrients* **10**, 1662. doi: 10.3390/nu10111662.
46. Maki KC & Dicklin MR (2019) Strategies to improve bioavailability of omega-3 fatty acids from ethyl ester concentrates. *Curr Opin Clin Nutr Metab Care* **22**, 116–123.
47. Vannice G & Rasmussen H (2014) Position of the academy of nutrition and dietetics: dietary fatty acids for healthy adults. *J Acad Nutr Diet* **114**, 136–153.
48. EFSA (2012) Panel on Dietetic Products N, Allergies. Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). *EFSA J* **10**, 2815.
49. Medicine Io (2005) *Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington, DC: The National Academies Press, 1358.
50. McDonnell SL, French CB, Baggerly CA & Harris WS (2019) Cross-sectional study of the combined associations of dietary and supplemental eicosapentaenoic acid + docosahexaenoic acid on Omega-3 Index. *Nutr Res* **71**, 43–55.
51. Zhang Z, Fulgoni VL, Kris-Etherton PM & Mitmesser SH (2018) Dietary intakes of EPA and DHA omega-3 fatty acids among US childbearing-age and pregnant women: an analysis of NHANES 2001–2014. *Nutrients* **10**, 416. doi: 10.3390/nu10040416.
52. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W & Herrmann N (2012) Effects of ω-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging* **33**, 1482.e17–1482.e29.
53. Lev-Tzion R, Griffiths AM, Leder O & Turner D (2014) Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* **2014**, Cd006320.
54. Bjerve KS, Fischer S, Wammer F & Egeland T (1989) alpha-Linolenic acid and long-chain omega-3 fatty acid supplementation in three patients with omega-3 fatty acid deficiency: effect on lymphocyte function, plasma and red cell lipids, and prostanoid formation. *Am J Clin Nutr* **49**, 290–300.
55. Sakamoto A, Saotome M, Iguchi K & Maekawa Y (2019) Marine-derived omega-3 polyunsaturated fatty acids and heart failure: current understanding for basic to clinical relevance. *Int J Mol Sci* **20**, 4025. doi: 10.3390/ijms20164025.
56. Calder PC (2017) Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans* **45**, 1105–1115.
57. Calder PC (2013) Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* **75**, 645–662.
58. Krupa K, Fritz K & Parmar M (2023) *Omega-3 fatty acids*. [Updated 2023 Jan 17]. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023 Jan-: NCBI.
59. Calder PC (2015) Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta (BBA) – Mol Cell Biol Lipids* **1851**, 469–484.
60. Sethi S, Ziouzenkova O, Ni H, Wagner DD, Plutzky J & Mayadas TN (2002) Oxidized omega-3 fatty acids in fish oil inhibit leukocyte-endothelial interactions through activation of PPAR alpha. *Blood* **100**, 1340–1346.
61. Calder PC (2020) *n*-3 PUFA and inflammation: from membrane to nucleus and from bench to bedside. *Proc Nutr Soc*, 1–13. doi: 10.1017/S0029665120007077.
62. Nielsen AA, Jørgensen LG, Nielsen JN, Eivindson M, Grønbaek H, Vind I, *et al.* (2005) Omega-3 fatty acids inhibit an increase of proinflammatory cytokines in patients with active Crohn's disease compared with omega-6 fatty acids. *Aliment Pharmacol Ther* **22**, 1121–1128.

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

63. Serhan CN & Levy BD (2018) Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *J Clin Invest* **128**, 2657–2669.
64. Wellhauser L & Belsham DD (2014) Activation of the omega-3 fatty acid receptor GPR120 mediates anti-inflammatory actions in immortalized hypothalamic neurons. *J Neuroinflamm* **11**, 60.
65. Hashimoto M & Hossain S (2018) Fatty acids: from membrane ingredients to signaling molecules. In: Viduranga W (ed.), *Biochemistry and health benefits of fatty acids*. Rijeka: IntechOpen, pp. 1–20.
66. Calder PC (2016) Docosahexaenoic acid. *Ann Nutr Metab* **69**, Suppl. 1, 8–21.
67. de Carvalho C & Caramujo MJ (2018) The various roles of fatty acids. *Molecules* **23**, 2583. doi: 10.3390/molecules23102583.
68. Wood AHR, Chappell HF & Zulyniak MA (2022) Dietary and supplemental long-chain omega-3 fatty acids as moderators of cognitive impairment and Alzheimer's disease. *Eur J Nutr* **61**, 589–604.
69. Sala-Vila A, Satizabal CL, Tintle N, Melo van Lent D, Vasan RS, Beiser AS, *et al.* (2022) Red blood cell DHA is inversely associated with risk of incident Alzheimer's disease and all-cause dementia: Framingham offspring study. *Nutrients* **14**, 2408. doi: 10.3390/nu14122408.
70. Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, *et al.* (2003) Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *Br J Nutr* **89**, 483–489.
71. Whalley LJ, Deary IJ, Starr JM, Wahle KW, Rance KA, Bourne VJ, *et al.* (2008) n-3 Fatty acid erythrocyte membrane content, APOE varepsilon4, and cognitive variation: an observational follow-up study in late adulthood. *Am J Clin Nutr* **87**, 449–454.
72. Phillips MA, Childs CE, Calder PC, Rogers PJ (2015) No effect of omega-3 fatty acid supplementation on cognition and mood in individuals with cognitive impairment and probable Alzheimer's disease: a randomised controlled trial. *Int J Mol Sci* **16**, 24600–24613.
73. van de Rest O, Wang Y, Barnes LL, Tangney C, Bennett DA & Morris MC (2016) APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. *Neurology* **86**, 2063–2070.
74. Li L, Xu W, Tan CC, Cao XP, Wei BZ, Dong CW, *et al.* (2022) A gene-environment interplay between omega-3 supplementation and APOE ε4 provides insights for Alzheimer's disease precise prevention amongst high-genetic-risk population. *Eur J Neurol* **29**, 422–431.
75. Jeong W, Lee H, Cho S & Seo J (2019) ApoE4-induced cholesterol dysregulation and its brain cell type-specific implications in the pathogenesis of Alzheimer's disease. *Mol Cells* **42**, 739–746.
76. Beydoun MA, Kaufman JS, Satia JA, Rosamond W & Folsom AR (2007) Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. *Am J Clin Nutr* **85**, 1103–1111.
77. Barberger-Gateau P, Samieri C, Féart C & Plourde M (2011) Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: interaction with apolipoprotein E genotype. *Curr Alzheimer Res* **8**, 479–491.
78. Qi W, Gutierrez GE, Gao X, Dixon H, McDonough JA, Marini AM, *et al.* (2017) The ω-3 fatty acid α-linolenic acid extends *Caenorhabditis elegans* lifespan via NHR-49/PPARα and oxidation to oxylipins. *Aging Cell* **16**, 1125–1135.
79. Mora I, Pérez-Santamaria A, Tortajada-Pérez J, Vázquez-Manrique RP, Arola L & Puiggròs F (2023) Structured docosahexaenoic acid (DHA) enhances motility and promotes the antioxidant capacity of aged *C. elegans*. *Cells* **12**, 1932. doi: 10.3390/cells12151932.
80. Champigny CM, Cormier RPJ, Simard CJ, St-Coeur PD, Fortin S & Pichaud N (2018) Omega-3 monoacylglyceride effects on longevity, mitochondrial metabolism and oxidative stress: insights from *Drosophila melanogaster*. *Mar Drugs* **16**, 453. doi: 10.3390/md16110453.
81. Saini A, Sharples AP, Al-Shanti N & Stewart CE (2017) Omega-3 fatty acid EPA improves regenerative capacity of mouse skeletal muscle cells exposed to saturated fat and inflammation. *Biogerontology* **18**, 109–129.
82. Su HM (2010) Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance. *J Nutr Biochem* **21**, 364–373.
83. Jolly CA, Muthukumar A, Avula CP, Troyer D & Fernandes G (2001) Life span is prolonged in food-restricted autoimmune-prone (NZB x NZW) F(1) mice fed a diet enriched with (n-3) fatty acids. *J Nutr* **131**, 2753–2760.
84. Fernandes G (2008) Progress in nutritional immunology. *Immunol Res* **40**, 244–261.
85. Halade GV, Williams PJ, Lindsey ML & Fernandes G (2011) Fish oil decreases inflammation and reduces cardiac remodeling in rosiglitazone treated aging mice. *Pharmacol Res* **63**, 300–307.
86. Dyall SC, Michael GJ, Michael-Titus AT (2010) Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. *J Neurosci Res* **88**, 2091–2102.
87. Qureshi AW, Altamimy R, El Habhab A, El Itawi H, Farooq MA, Zobairi F, *et al.* (2020) Ageing enhances the shedding of splenocyte microvesicles with endothelial pro-senescent effect that is prevented by a short-term intake of omega-3 PUFA EPA:DHA 6:1. *Biochem Pharmacol* **173**, 113734.
88. Dyall SC, Michael GJ, Whelpton R, Scott AG, Michael-Titus AT (2007) Dietary enrichment with omega-3 polyunsaturated fatty acids reverses age-related decreases in the GluR2 and NR2B glutamate receptor subunits in rat forebrain. *Neurobiol Aging* **28**, 424–439.
89. Razgonova MP, Zakharenko AM, Golokhvast KS, Thanasoula M, Sarandi E, Nikolouzakis K, *et al.* (2020) Telomerase and telomeres in aging theory and chronographic aging theory (Review). *Mol Med Rep* **22**, 1679–1694.
90. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, *et al.* (2004) Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA* **101**, 17312–17315.
91. Chen J, Wei Y, Chen X, Jiao J & Zhang Y (2017) Polyunsaturated fatty acids ameliorate aging via redox-telomere-antioncogene axis. *Oncotarget* **8**, 7301.
92. Ogłuszka M, Te Pas MFW, Poławska E, Nawrocka A, Stepanow K & Pierzchała M (2020) Omega-3 Alpha-Linolenic fatty acid affects the level of telomere binding protein TRF1 in porcine skeletal muscle. *Animals (Basel)* **10**, 1090. doi: 10.3390/ani10061090.
93. Varela-Lopez A, Pérez-López MP, Ramirez-Tortosa CL, Battino M, Granados-Principal S, del Carmen Ramirez-Tortosa M, *et al.* (2018) Gene pathways associated with mitochondrial function, oxidative stress and telomere length are differentially expressed in the liver of rats fed lifelong on virgin olive, sunflower or fish oils. *J Nutr Biochem* **52**, 36–44.
94. Gao J, Xiao H, Li J, Guo X, Cai W & Li D (2019) N-3 polyunsaturated fatty acids decrease long-term diabetic risk of offspring of gestational diabetes rats by postponing shortening of hepatic telomeres and modulating liver metabolism. *Nutrients* **11**, 1699.
95. Chen J, Wei Y, Chen X, Jiao J & Zhang Y (2016) Polyunsaturated fatty acids ameliorate aging via redox-telomere-antioncogene axis. *Oncotarget* **8**, 7301–7314. doi: 10.18632/oncotarget.14236.
96. Ogłuszka M, Lipiński P & Starzyński RR (2022) Effect of Omega-3 fatty acids on telomeres-are they the elixir of youth? *Nutrients* **14**, 3723. doi: 10.3390/nu14183723.
97. Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH & Whooley MA (2010) Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA* **303**, 250–257.
98. Liu X, Shi Q, Fan X, Chen H, Chen N, Zhao Y, *et al.* (2022) Associations of maternal polyunsaturated fatty acids with telomere length in the cord blood and placenta in Chinese population. *Front Nutr* **8**, 779306.
99. Kiecolt-Glaser JK, Epel ES, Belury MA, Andridge R, Lin J, Glaser R, *et al.* (2013) Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: a randomized controlled trial. *Brain, Behav Immun* **28**, 16–24.
100. Barden A, O'Callaghan N, Burke V, Mas E, Beilin LJ, Fenech M, *et al.* (2016) n-3 fatty acid supplementation and leukocyte telomere length in patients with chronic kidney disease. *Nutrients* **8**, 175.
101. O'Callaghan N, Parletta N, Milte CM, Benassi-Evans B, Fenech M, Howe PR (2014) Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with ω-3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition* **30**, 489–491.
102. Madison AA, Belury MA, Andridge R, Renna ME, Rosie Shrout M, Malarkey WB, *et al.* (2021) Omega-3 supplementation and stress reactivity of cellular aging biomarkers: an ancillary substudy of a randomized, controlled trial in midlife adults. *Mol Psychiatry* **26**, 3034–3042.
103. Lai HT, de Oliveira Otto MC, Lemaitre RN, McKnight B, Song X, King IB, *et al.* (2018) Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study: prospective cohort study. *BMJ* **363**, k4067.

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

104. Harris WS, Tintle NL, Imamura F, Qian F, Korat AVA, Marklund M, *et al.* (2021) Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. *Nat Commun* **12**, 2329.
105. Mozaffarian D, Lemaitre RN, King IB, Song X, Huang H, Sacks FM, *et al.* (2013) Plasma phospholipid long-chain ω-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. *Ann Intern Med* **158**, 515–525.
106. Abbatecola AM, Cherubini A, Guralnik JM, Andres Lacueva C, Ruggiero C, Maggio M, *et al.* (2009) Plasma polyunsaturated fatty acids and age-related physical performance decline. *Rejuvenation Res* **12**, 25–32.
107. Kuszewski JC, Howe PR & Wong RH (2020) Evaluation of cognitive performance following fish-oil and curcumin supplementation in middle-aged and older adults with overweight or obesity. *J Nutr* **150**, 3190–3199.
108. Malik A, Ramadan A, Vemuri B, Siddiq W, Amangurbanova M, Ali A, *et al.* (2021) ω-3 Ethyl ester results in better cognitive function at 12 and 30 months than control in cognitively healthy subjects with coronary artery disease: a secondary analysis of a randomized clinical trial. *Am J Clin Nutr* **113**, 1168–1176.
109. Gillies D, Leach MJ & Algorta GP (2023) Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev* **4**, CD007986. doi: 10.1002/14651858.
110. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, *et al.* (2010) Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement* **6**, 456–464.
111. Iroku-Malize T & Kirsch S (2016) Eye conditions in older adults: age-related macular degeneration. *FP Essent* **445**, 24–28.
112. Christen WG, Schaumberg DA, Glynn RJ & Buring JE (2011) Dietary ω-3 fatty acid and fish intake and incident age-related macular degeneration in women. *Arch Ophthalmol* **129**, 921–929.
113. Augood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, *et al.* (2008) Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. *Am J Clin Nutr* **88**, 398–406.
114. Seddon JM, George S, Rosner B (2006) Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of age-related macular degeneration. *Arch Ophthalmol* **124**, 995–1001.
115. Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, *et al.* (2019) Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. *Circulation* **140**, e673–e691.
116. Laredj LN, Licitra F & Puccio HM (2014) The molecular genetics of coenzyme Q biosynthesis in health and disease. *Biochimie* **100**, 78–87.
117. Gutierrez-Mariscal FM, Yubero-Serrano EM, Villalba JM, Lopez-Miranda J (2019) Coenzyme Q(10): From bench to clinic in aging diseases, a translational review. *Crit Rev Food Sci Nutr* **59**, 2240–2257.
118. Maciejewska-Stupska K, Czarnecka K & Szymański P (2024) Bioavailability enhancement of coenzyme Q(10): An update of novel approaches. *Arch Pharmazie* **357**, e2300676.
119. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, Vega AF, de la Mata M, Pavon AD, *et al.* (2014) Clinical applications of coenzyme Q10. *Front Biosci* **19**, 619–633.
120. Zozina VI, Covantev S, Goroshko OA, Krasnykh LM & Kukes VG (2018) Coenzyme Q10 in cardiovascular and metabolic diseases: current state of the problem. *Curr Cardiol Rev* **14**, 164–174.
121. Lenaz G, Fato R, Di Bernardo S, Jarreta D, Costa A, Genova ML, *et al.* (1999) Localization and mobility of coenzyme Q in lipid bilayers and membranes. *BioFactors* **9**, 87–93.
122. Olson RE & Rudney H (1983) Biosynthesis of ubiquinone. *Vitam Hormones* **40**, 1–43.
123. Alcázar-Fabra M, Navas P & Brea-Calvo G (2016) Coenzyme Q biosynthesis and its role in the respiratory chain structure. *Biochim Biophys Acta* **1857**, 1073–1078.
124. Lenaz G, Fato R, Castelluccio C, Genova ML, Bovina C, Estornell E, *et al.* (1993) The function of coenzyme Q in mitochondria. *Clin Invest* **71**, 8 Suppl, S66–S70.
125. Harman D (1972) The biologic clock: the mitochondria? *J Am Geriatr Soc* **20**, 145–147.
126. Eirin A, Lerman A & Lerman LO (2017) The emerging role of mitochondrial targeting in kidney disease. *Handb Exp Pharmacol* **240**, 229–250. doi: 10.1007/164_2016_6.
127. Poulose N & Raju R (2014) Aging and injury: alterations in cellular energetics and organ function. *Aging Dis* **5**, 101.
128. Schniertshauer D, Gebhard D, van Beek H, Nöth V, Schon J & Bergemann J (2020) The activity of the DNA repair enzyme hOGG1 can be directly modulated by ubiquinol. *DNA Repair* **87**, 102784.
129. Mantle D & Dybring A (2020) Bioavailability of coenzyme Q10: an overview of the absorption process and subsequent metabolism. *Antioxidants* **9**, 386.
130. Olivieri F, Lazzarini R, Babini L, Prattichizzo F, Rippo MR, Tiano L, *et al.* (2013) Anti-inflammatory effect of ubiquinol-10 on young and senescent endothelial cells via miR-146a modulation. *Free Radical Biol Med* **63**, 410–420.
131. Fan L, Feng Y, Chen GC, Qin LQ, Fu CL & Chen LH (2017) Effects of coenzyme Q10 supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* **119**, 128–136.
132. Schmelzer C, Lindner I, Rimbach G, Niklowitz P, Menke T & Döring F (2008) Functions of coenzyme Q10 in inflammation and gene expression. *BioFactors* **32**, 179–183.
133. Sharma A, Fonarow GC, Butler J, Ezekowitz JA & Felker GM (2016) Coenzyme Q10 and heart failure: a state-of-the-art review. *Circ Heart Failure* **9**, e002639.
134. Jorat MV, Tabrizi R, Mirhosseini N, Lankarani KB, Akbari M, Heydari ST, *et al.* (2018) The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis* **17**, 230.
135. Pérez-Sánchez C, Aguirre M, Ruiz-Limón P, Ábalos-Aguilera MC, Jiménez-Gómez Y, Arias-de la Rosa I, *et al.* (2017) Ubiquinol effects on antiphospholipid syndrome prothrombotic profile: a randomized, placebo-controlled trial. *Arterioscler Thromb Vasc Biol* **37**, 1923–1932.
136. Wilcock DM & Griffin WS (2013) Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. *J Neuroinflamm* **10**, 84.
137. Zaki ME, El-Bassyouni HT, Tosson A, Youness E & Hussein J (2017) Coenzyme Q10 and pro-inflammatory markers in children with Down syndrome: clinical and biochemical aspects☆. *J Pediatr* **93**, 100–104.
138. Wolters M & Hahn A (2003) Plasma ubiquinone status and response to six-month supplementation combined with multivitamins in healthy elderly women – results of a randomized, double-blind, placebo-controlled study. *Int J Vitamin Nutr Res* **73**, 207–214.
139. Kalén A, Appelkvist EL & Dallner G (1989) Age-related changes in the lipid compositions of rat and human tissues. *Lipids* **24**, 579–584.
140. Söderberg M, Edlund C, Kristensson K & Dallner G (1990) Lipid compositions of different regions of the human brain during aging. *J Neurochem* **54**, 415–423.
141. Edlund C, Söderberg M, Kristensson K, Dallner G (1992) Ubiquinone, dolichol, and cholesterol metabolism in aging and Alzheimer's disease. *Biochem Cell Biol* **70**, 422–428.
142. Nagase M, Yamamoto Y, Matsumoto N, Arai Y & Hirose N (2018) Increased oxidative stress and coenzyme Q10 deficiency in centenarians. *J Clin Biochem Nutr* **63**, 129–136.
143. Hathcock JN & Shao A (2006) Risk assessment for coenzyme Q10 (ubiquinone). *Regul Toxicol Pharmacol* **45**, 282–288.
144. Singletary K (2010) Ginger: an overview of health benefits. *Nutr Today* **45**, 171–183.
145. Abolaji AO, Ojo M, Afolabi TT, Arowoogun MD, Nwawolor D & Farombi EO (2017) Protective properties of 6-gingerol-rich fraction from *Zingiber officinale* (ginger) on chlorpyrifos-induced oxidative damage and inflammation in the brain, ovary and uterus of rats. *Chem-Biol Interact* **270**, 15–23.
146. Mohd Sahardi NFN & Makpol S (2019) Ginger (*Zingiber officinale* Roscoe) in the prevention of ageing and degenerative diseases: review of current evidence. *Evid-Based Complement Altern Med: eCAM* **2019**, 5054395.

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

147. Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K & Zafrilla P (2022) Effect of ginger on inflammatory diseases. *Molecules* **27**, 7223. doi: 10.3390/molecules27217223.
148. Kim SO, Chun KS, Kundu JK & Surh YJ (2004) Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. *BioFactors* **21**, 27–31.
149. Miyoshi N, Nakamura Y, Ueda Y, Abe M, Ozawa Y, Uchida K, *et al.* (2003) Dietary ginger constituents, galanals A and B, are potent apoptosis inducers in human T lymphoma Jurkat cells. *Cancer Lett* **199**, 113–119.
150. Hu W, Yu A, Wang S, Bai Q, Tang H, Yang B, *et al.* (2023) Extraction, purification, structural characteristics, biological activities, and applications of the polysaccharides from *Zingiber officinale* Roscoe. (Ginger): a review. *Molecules* **28**, 3855. doi: 10.3390/molecules28093855.
151. Butt MS & Sultan MT (2011) Ginger and its health claims: molecular aspects. *Crit Rev Food Sci Nutr* **51**, 383–393.
152. Izadi M, Sadri N, Abdi A, Serajian S, Jalalei D & Tahmasebi S (2024) Epigenetic biomarkers in aging and longevity: current and future application. *Life Sci* **351**, 122842.
153. Ozkur M, Benlier N, Takan I, Vasileiou C, Georgakilas AG, Pavlopoulou A, *et al.* (2022) Ginger for healthy ageing: a systematic review on current evidence of its antioxidant, anti-inflammatory, and anticancer properties. *Oxid Med Cell Longevity* **2022**, 4748447.
154. Arulkumar R, Bang E, Noh S-G, Yokozawa T & Chung HY (2019) Role of garlic and ginger in anti-oxidative and anti-inflammatory effects in aging. *SDRP J Food Sci Technol* **4**, 788–795.
155. Ziada AS, Smith MR & Côté HCF (2020) Updating the free radical theory of aging. *Front Cell Develop Biol* **8**, 575645.
156. Checa J & Aran JM (2020) Reactive oxygen species: drivers of physiological and pathological processes. *J Inflamm Res* **13**, 1057–1073.
157. Ilkhanizadeh B, Shirpoor A, Khadem Ansari MH, Nemati S & Rasmi Y (2016) Protective effects of ginger (*Zingiber officinale*) extract against diabetes-induced heart abnormality in rats. *Diabetes Metab J* **40**, 46–53.
158. Shaukat MN, Nazir A & Fallico B (2023) Ginger bioactives: a comprehensive review of health benefits and potential food applications. *Antioxidants (Basel)* **12**, 2015. doi: 10.3390/antiox12112015.
159. Romero A, Forero M, Sequeda-Castañeda LG, Grismaldo A, Iglesias J, Celis-Zambrano CA, *et al.* (2018) Effect of ginger extract on membrane potential changes and AKT activation on a peroxide-induced oxidative stress cell model. *J King Saud Univ – Sci* **30**, 263–269.
160. Shanmugam KR, Mallikarjuna K, Nishanth K, Kuo CH, Reddy KS (2011) Protective effect of dietary ginger on antioxidant enzymes and oxidative damage in experimental diabetic rat tissues. *Food Chem* **124**, 1436–1442.
161. Thomas CM, Fuller CJ, Whittles CE & Sharif M (2007) Chondrocyte death by apoptosis is associated with cartilage matrix degradation. *Osteoarthritis Cartilage* **15**, 27–34.
162. Asl SS, Pourheydar B, Dabaghian F, Nezhadi A, Roointan A & Mehdizadeh M (2013) Ecstasy-induced caspase expression alters following ginger treatment. *Basic Clin Neurosci* **4**, 329–333.
163. Kim CY, Seo Y, Lee C, Park GH & Jang JH (2018) Neuroprotective effect and molecular mechanism of [6]-gingerol against scopolamine-induced amnesia in C57BL/6 mice. *Evid-Based Complement Altern Med: eCAM* **2018**, 8941564.
164. Al Syaad KM, Elsaid FG, Abdraboh ME & Al-Doaiss AA (2019) Effect of graviola (*Annona muricata* l.) and ginger (*Zingiber officinale* Roscoe) on diabetes mellitus induced in male Wistar albino rats. *Folia Biol* **65**, 275–284.
165. Baechle JJ, Chen N, Makhijani P, Winer S, Furman D & Winer DA (2023) Chronic inflammation and the hallmarks of aging. *Mol Metab* **74**, 101755.
166. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD & Ross OA (2018) Age and age-related diseases: role of inflammation triggers and cytokines. *Front Immunol* **9**, 586.
167. Ezzat SM, Ezzat MI, Okba MM, Menze ET & Abdel-Naim AB (2018) The hidden mechanism beyond ginger (*Zingiber officinale* Rosc.) potent *in vivo* and *in vitro* anti-inflammatory activity. *J Ethnopharmacol* **214**, 113–123.
168. Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, *et al.* (2019) Bioactive compounds and bioactivities of ginger (*Zingiber officinale* Roscoe). *Foods* **8**, 185. doi: 10.3390/foods8060185.
169. Rastogi N, Gara RK, Trivedi R, Singh A, Dixit P, Maurya R, *et al.* (2014) (6)-Gingerolinduced myeloid leukemia cell death is initiated by reactive oxygen species and activation of miR-27b expression. *Free Radical Biol Med* **68**, 288–301.
170. Deorukhkar A, Ahuja N, Mercado AL, Diagaradjane P, Raju U, Patel N, *et al.* (2015) Zerumbone increases oxidative stress in a thiol-dependent ROS-independent manner to increase DNA damage and sensitize colorectal cancer cells to radiation. *Cancer Med* **4**, 278–292.
171. Bawadood AS, Al-Abbasi FA, Anwar F, El-Halawany AM & Al-Abd AM (2020) 6-Shogaol suppresses the growth of breast cancer cells by inducing apoptosis and suppressing autophagy via targeting notch signaling pathway. *Biomed Pharmacother* **128**, 110302.
172. Akimoto M, Iizuka M, Kanematsu R, Yoshida M & Takenaga K (2015) Anticancer effect of ginger extract against pancreatic cancer cells mainly through reactive oxygen species-mediated autotic cell death. *PLoS One* **10**, e0126605.
173. Chakraborty D, Bishayee K, Ghosh S, Biswas R, Mandal SK, Khuda-Bukhsh AR (2012) [6]-Gingerol induces caspase 3 dependent apoptosis and autophagy in cancer cells: drug-DNA interaction and expression of certain signal genes in HeLa cells. *Eur J Pharmacol* **694**, 20–29.
174. Farombi EO, Ajayi BO & Adedara IA (2020) 6-Gingerol delays tumorigenesis in benzo[a]pyrene and dextran sulphate sodium-induced colorectal cancer in mice. *Food Chem Toxicol* **142**, 111483.
175. Saenghong N, Wattanathorn J, Muchimapura S, Tongun T, Piyavhatkul N, Banchonglikitkul C, *et al.* (2012) *Zingiber officinale* improves cognitive function of the middle-aged healthy women. *Evid-Based Complement Altern Med: eCAM* **2012**, 383062.
176. Ghayur MN, Gilani AH, Ahmed T, Khalid A, Nawaz SA, Agbedahunsi JM, *et al.* (2008) Muscarinic, Ca(++) antagonist and specific butyrylcholinesterase inhibitory activity of dried ginger extract might explain its use in dementia. *J Phar Pharmacol* **60**, 1375–1383.
177. Zeng GF, Zhang ZY, Lu L, Xiao DQ, Zong SH & He JM (2013) Protective effects of ginger root extract on Alzheimer disease-induced behavioral dysfunction in rats. *Rejuvenat Res* **16**, 124–133.
178. Zhao Y & Chen ZY (2018) Roles of spicy foods and their bioactive compounds in management of hypercholesterolemia. *J Agric Food Chem* **66**, 8662–8671.
179. Li J, Wang S, Yao L, Ma P, Chen Z, Han TL, *et al.* (2019) 6-gingerol ameliorates age-related hepatic steatosis: association with regulating lipogenesis, fatty acid oxidation, oxidative stress and mitochondrial dysfunction. *Toxicol Appl Pharmacol* **362**, 125–135.
180. Khezri K, Maleki Dizaj S, Rahbar Saadat Y, Sharifi S, Shahi S, Ahmadian E, *et al.* (2021) Osteogenic differentiation of mesenchymal stem cells via curcumin-containing nanoscaffolds. *Stem Cells Int* **2021**, 1520052.
181. Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L & Mofid MR (2013) Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. *Int J Prevent Med* **4**, Suppl 1, S36–S42.
182. Leelapornpisid P, Wickett RR, Chansakaow S & Wongwattananukul N (2015) Potential of native Thai aromatic plant extracts in antiwrinkle body creams. *J Cosmet Sci* **66**, 219–231.
183. Ryan JL & Morrow GR (2010) Ginger. *Oncol Nurse Ed* **24**, 46–49.
184. Tyagi AK, Prasad S, Yuan W, Li S & Aggarwal BB (2015) Identification of a novel compound (β-sesquiphellandrene) from turmeric (*Curcuma longa*) with anticancer potential: comparison with curcumin. *Invest New Drugs* **33**, 1175–1186.
185. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, *et al.* (2016) Oral bioavailability of curcumin: problems and advancements. *J Drug Target* **24**, 694–702.
186. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R & Srinivas PS (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Plant Med* **64**, 353–356.
187. Dey S & Sreenivasan K (2014) Conjugation of curcumin onto alginate enhances aqueous solubility and stability of curcumin. *Carbohydr Polym* **99**, 499–507.
188. Abbaspour-Aghdam S, Hazrati A, Abdolmohammadi-Vahid S, Tahmasebi S, Mohseni J, Valizadeh H, *et al.* (2022) Immunomodulatory role of nanocurcumin in COVID-19 patients with dropped natural killer cells frequency and function. *Eur J Pharmacol* **933**, 175267.

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

189. Esmaeilzadeh A, Jafari D, Tahmasebi S, Elahi R & Khosh E (2021) Immune-based therapy for COVID-19. *Adv Exp Med Biol* **1318**, 449–468.
190. Tahmasebi S, Saeed BQ, Temirgalieva E, Yumashev AV, El-Esawi MA, Navashenaq JG, *et al.* (2021) Nanocurcumin improves Treg cell responses in patients with mild and severe SARS-CoV2. *Life Sci* **276**, 119437.
191. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, *et al.* (2001) Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res* **21**, 2895–2900.
192. Gupta SC, Kismali G & Aggarwal BB (2013) Curcumin, a component of turmeric: from farm to pharmacy. *BioFactors* **39**, 2–13.
193. Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Doré J, *et al.* (2017) Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. *Ageing Res Rev* **40**, 95–119.
194. Sikora E, Scapagnini G & Barbagallo M (2010) Curcumin, inflammation, ageing and age-related diseases. *Immun Ageing: I & A* **7**, 1.
195. Sandur SK, Ichikawa H, Pandey MK, Kunnumakkara AB, Sung B, Sethi G, *et al.* (2007) Role of pro-oxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane). *Free Radical Biol Med* **43**, 568–580.
196. Olszanecki R, Jawień J, Gajda M, Mateuszuk L, Gebska A, Korabiowska M, *et al.* (2005) Effect of curcumin on atherosclerosis in apoE/LDLR-double knockout mice. *J Physiol Pharmacol: Off J Polish Physiol Soc* **56**, 627–635.
197. He Y, Yue Y, Zheng X, Zhang K, Chen S & Du Z (2015) Curcumin, inflammation, and chronic diseases: how are they linked? *Molecules* **20**, 9183–9213.
198. Sun Y, Hu X, Hu G, Xu C & Jiang H (2015) Curcumin attenuates hydrogen peroxide-induced premature senescence via the activation of SIRT1 in human umbilical vein endothelial cells. *Biol Pharm Bull* **38**, 1134–1141.
199. Kitani K, Osawa T & Yokozawa T (2007) The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. *Biogerontology* **8**, 567–573.
200. Bielak-Zmijewska A, Sikora-Polaczek M, Nieznanski K, Mosieniak G, Kolano A, Maleszewski M, *et al.* (2010) Curcumin disrupts meiotic and mitotic divisions via spindle impairment and inhibition of CDK1 activity. *Cell Proliferation* **43**, 354–364.
201. Hansen J (1998) Common cancers in the elderly. *Drugs Aging* **13**, 467–478.
202. Izadi M, Sadri N, Abdi A, Zadeh MMR, Jalaei D, Ghazimoradi MM, *et al.* (2024) Longevity and anti-aging effects of curcumin supplementation. *GeroScience* **46**, 2933–2950.
203. Luo J, Mills K, le Cessie S, Noordam R & van Heemst D (2020) Ageing, age-related diseases and oxidative stress: what to do next? *Ageing Res Rev* **57**, 100982.
204. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, *et al.* (2017) Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev* **2017**, 8416763. doi: 10.1155/2017/8416763.
205. Huang MT (1997). Antioxidant and antitumorigenic properties of curcumin. In Ohigashi H, Osawa T, Terao J, Watanabe S, Yoshikawa T (eds.), *Food Factors for Cancer Prevention*. Tokyo: Springer. doi: 10.1007/978-4-431-67017-9_50.
206. Abo-Salem O, Harisa G, Ali T, El-Sayed E & Abou-Elnour F (2014) Curcumin ameliorates streptozotocin-induced heart injury in rats: Curcumin attenuates diabetic heart injury. *J Biochem Mol Toxicol* **28**, 263–270.
207. Oyetayo BO, Abolaji AO, Fasae KD & Aderibigbe A (2020) Ameliorative role of diets fortified with curcumin in a *Drosophila melanogaster* model of aluminum chloride-induced neurotoxicity. *J Funct Foods* **71**, 104035.
208. Zhang J, Zheng Y, Luo Y, Du Y, Zhang X & Fu J (2019) Curcumin inhibits LPS-induced neuroinflammation by promoting microglial M2 polarization via TREM2/ TLR4/ NF-κB pathways in BV2 cells. *Mol Immunol* **116**, 29–37.
209. Tahmasebi S, Alimohammadi M, Khorasani S & Rezaei N (2022) Pro-tumorigenic and anti-tumorigenic roles of pro-inflammatory cytokines in cancer. In Rezaei N (ed.), *Handbook of cancer and immunology*. Cham: Springer International Publishing, pp. 1–25.
210. Salminen A, Huuskonen J, Ojala J, Kauppinen A, Kaarniranta K & Suuronen T (2008) Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. *Ageing Rese Rev* **7**, 83–105.
211. Yousefzadeh MJ, Schafer MJ, Noren Hooten N, Atkinson EJ, Evans MK, Baker DJ, *et al.* (2018) Circulating levels of monocyte chemoattractant protein-1 as a potential measure of biological age in mice and frailty in humans. *Aging Cell* **17**, e12706.
212. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, *et al.* (2017) Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol* **174**, 1325–1348.
213. Hansen M, Rubinsztein DC & Walker DW (2018) Autophagy as a promoter of longevity: insights from model organisms. *Nat Rev Mol Cell Biol* **19**, 579–593.
214. Brown-Borg HM & Bartke A (2012) GH and IGF1: roles in energy metabolism of long-living GH mutant mice. *J Gerontol Ser A, Biol Sci Med Sci* **67**, 652–660.
215. Sikora E, Bielak-Zmijewska A, Mosieniak G & Piwocka K (2010) The promise of slow down ageing may come from curcumin. *Curr Pharmaceut Design* **16**, 884–892.
216. Jiao D, Wang J, Lu W, Tang X, Chen J, Mou H, *et al.* (2016) Curcumin inhibited HGF-induced EMT and angiogenesis through regulating c-Met dependent PI3K/Akt/mTOR signaling pathways in lung cancer. *Mol Ther Oncolyt* **3**, 16018.
217. Zhang J, Wang J, Xu J, Lu Y, Jiang J, Wang L, *et al.* (2016) Curcumin targets the TFEB-lysosome pathway for induction of autophagy. *Oncotarget* **7**, 75659–75671.
218. Maiti P, Rossignol J & Dunbar GL (2017) Curcumin modulates molecular chaperones and autophagy-lysosomal pathways in vitro after exposure to Aβ42. *J Alzheimers Dis Parkinsonism* **7**, 299. doi: 10.4172/2161-0460.1000299.
219. de Oliveira MR, Jardim FR, Setzer WN, Nabavi SM & Nabavi SF (2016) Curcumin, mitochondrial biogenesis, and mitophagy: Exploring recent data and indicating future needs. *Biotechnol Adv* **34**, 813–826.
220. Giordano S, Darley-Usmar V & Zhang J (2014) Autophagy as an essential cellular antioxidant pathway in neurodegenerative disease. *Redox Biol* **2**, 82–90.
221. Hunter DJ, Schofield D & Callander E (2014) The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* **10**, 437–441.
222. Henrotin Y, Priem F & Mobasheri A (2013) Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management. *SpringerPlus* **2**, 56.
223. Belcaro G, Hosoi M, Pellegrini L, Appendino G, Ippolito E, Ricci A, *et al.* (2014) A controlled study of a lecithinized delivery system of curcumin (Meriva®) to alleviate the adverse effects of cancer treatment. *Phytother Res: PTR* **28**, 444–450.
224. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A & Sahebkar A (2014) Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. *Phytother Res: PTR* **28**, 1625–1631.
225. Qin S, Huang L, Gong J, Shen S, Huang J, Tang Y, *et al.* (2018) Meta-analysis of randomized controlled trials of 4 weeks or longer suggest that curcumin may afford some protection against oxidative stress. *Nutr Res* **60**, 1–12.
226. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, *et al.* (2013) Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. *Mol Nutr Food Res* **57**, 1569–1577.
227. Bradford PG (2013) Curcumin and obesity. *BioFactors* **39**, 78–87.
228. Hlavačková L, Janegová A, Uličná O, Janega P, Cerná A & Babál P (2011) Spice up the hypertension diet – curcumin and piperine prevent remodeling of aorta in experimental L-NAME induced hypertension. *Nutr Metab* **8**, 72.
229. Sahebkar A (2014) Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytother Res: PTR* **28**, 633–642.
230. Ak T & Gülçin I (2008) Antioxidant and radical scavenging properties of curcumin. *Chem-Biol Interact* **174**, 27–37.
231. Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, *et al.* (2008) Six-month randomized, placebo-controlled, double-blind, pilot clinical trial

https://doi.org/10.1017/S0954422424000301 Published online by Cambridge University Press

of curcumin in patients with Alzheimer disease. *J Clin Psychopharmacol* **28**, 110–113.
232. Chen M, Du ZY, Zheng X, Li DL, Zhou RP & Zhang K (2018) Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. *Neural Regenerat Res* **13**, 742–752.
233. Hewlings SJ & Kalman DS (2017) Curcumin: a review of its effects on human health. *Foods* **6**, 92. doi: 10.3390/foods6100092.
234. Ibrahim Fouad G (2020) Synergistic anti-atherosclerotic role of combined treatment of omega-3 and co-enzyme Q10 in hypercholesterolemia-induced obese rats. *Heliyon* **6**, e03659.
235. Xiao B, Zhang Z, Viennois E, Kang Y, Zhang M, Han MK, *et al.* (2016) Combination therapy for ulcerative colitis: orally targeted nanoparticles prevent mucosal damage and relieve inflammation. *Theranostics* **6**, 2250–2266.
236. Muhammad I, Wang X, Li S, Li R & Zhang X (2018) Curcumin confers hepatoprotection against AFB(1)-induced toxicity via activating autophagy and ameliorating inflammation involving Nrf2/HO-1 signaling pathway. *Mol Biol Rep* **45**, 1775–1785.
237. Chen F, Tang Y, Sun Y, Veeraraghavan VP, Mohan SK & Cui C (2019) 6-shogaol, a active constiuents of ginger prevents UVB radiation mediated inflammation and oxidative stress through modulating NrF2 signaling in human epidermal keratinocytes (HaCaT cells). *J Photochem Photobiol B, Biol* **197**, 111518.
238. Zhou X, Afzal S, Wohlmuth H, Münch G, Leach D, Low M, *et al.* (2022) Synergistic anti-inflammatory activity of ginger and turmeric extracts in inhibiting lipopolysaccharide and interferon-γ-induced proinflammatory mediators. *Molecules* **27**, 3877. doi: 10.3390/molecules27123877.
239. Zhou X, Münch G, Wohlmuth H, Afzal S, Kao MT, Al-Khazaleh A, *et al.* (2022) Synergistic Inhibition of pro-inflammatory pathways by ginger and turmeric extracts in RAW 264.7 cells. *Front Pharmacol* **13**, 818166.
240. Bakhtiari Aqmasjed S, Sajjadi MM, Falahatkar B & Safari R (2023) Effects of dietary ginger (Zingiber officinale) extract and curcumin on growth, hematology, immunity, and antioxidant status in rainbow trout (Oncorhynchus mykiss). *Aquacult Rep* **32**, 101714.
241. (2024) Synergistic effect of *Zingiber officinale* (ginger) and *Curcuma longa* L. (curcumin analogs) for anti-inflammatory, anti-nociceptive activity and analgesic potentials. *J Popul Ther Clin Pharmacol* **31**, 1363–1369. https://doi.org/10.53555/jptcp.v31i3.5132
242. Thota RN, Acharya SH & Garg ML (2019) Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: a randomised controlled trial. *Lipids Health Dis* **18**, 31.
243. Hoeijmakers JH (2009) DNA damage, aging, and cancer. *N Engl J Med* **361**, 1475–1485.
244. Burtner CR & Kennedy BK (2010) Progeria syndromes and ageing: what is the connection? *Nat Rev Mol Cell Biol* **11**, 567–578.
245. Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H, *et al.* (2013) The role of DNA damage and repair in aging through the prism of Koch-like criteria. *Ageing Res Rev* **12**, 661–684.
246. Wu H & Roks AJ (2014) Genomic instability and vascular aging: a focus on nucleotide excision repair. *Trends Cardiovasc Med* **24**, 61–68.
247. Fumagalli M, Rossiello F, Clerici M, Barozzi S, Cittaro D, Kaplunov JM, *et al.* (2012) Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nat Cell Biol* **14**, 355–365.
248. Palm W & de Lange T (2008) How shelterin protects mammalian telomeres. *Annu Rev Genet* **42**, 301–334.
249. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu C-P, Morin GB, *et al.* (1998) Extension of life-span by introduction of telomerase into normal human cells. *Science* **279**, 349–352.
250. Blackburn EH, Epel ES & Lin J (2015) Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science* **350**, 1193–1198.
251. Fraga MF & Esteller M (2007) Epigenetics and aging: the targets and the marks. *Trends Genet* **23**, 413–418.
252. Talens RP, Christensen K, Putter H, Willemsen G, Christiansen L, Kremer D, *et al.* (2012) Epigenetic variation during the adult lifespan: cross-sectional and longitudinal data on monozygotic twin pairs. *Aging Cell* **11**, 694–703.
253. van Ham TJ, Holmberg MA, van der Goot AT, Teuling E, Garcia-Arencibia M, Kim H-E, *et al.* (2010) Identification of MOAG-4/SERF as a regulator of age-related proteotoxicity. *Cell* **142**, 601–612.
254. Taylor RC & Dillin A (2011) Aging as an event of proteostasis collapse. *Cold Spring Harb Perspect Biol* **3**, a004440. doi: 10.1101/cshperspect.a004440.
255. Yu G & Hyun S (2021) Proteostasis-associated aging: lessons from a Drosophila model. *Genes Genomics* **43**, 1–9.
256. Barzilai N, Huffman DM, Muzumdar RH & Bartke A (2012) The critical role of metabolic pathways in aging. *Diabetes* **61**, 1315–1322.
257. Fontana L, Partridge L & Longo VD (2010) Extending healthy life span—from yeast to humans. *Science* **328**, 321–326.
258. Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, *et al.* (2005) Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* **309**, 481–484.
259. Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, *et al.* (2004) Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* **429**, 417–423.
260. Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA, *et al.* (2008) DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. *Nature Genet* **40**, 392–394.
261. Matheu A, Maraver A, Collado M, Garcia-Cao I, Cañamero M, Borras C, *et al.* (2009) Anti-aging activity of the Ink4/Arf locus. *Aging Cell* **8**, 152–161.
262. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, Van De Sluis B, *et al.* (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* **479**, 232–236.
263. Rando TA & Chang HY (2012) Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell* **148**, 46–57.
264. Conboy IM & Rando TA (2012) Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. *Cell Cycle* **11**, 2260–2267.
265. da Silva PFL & Schumacher B (2021) Principles of the molecular and cellular mechanisms of aging. *J Invest Dermatol* **141**, 951–960.
266. Chen S, Gan D, Lin S, Zhong Y, Chen M, Zou X, *et al.* (2022) Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. *Theranostics* **12**, 2722–2740.
267. Trumbo P, Schlicker S, Yates AA & Poos M (2002) Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc* **102**, 1621–1630.
268. Andrew M, Michael M, Karl K, Elisabeth AdB, Flint B, Karen M, *et al.* (2017) A randomized, double-blind, placebo-controlled trial of coenzyme Q10 in Huntington disease. *Neurology* **88**, 152.
269. Fotino AD, Thompson-Paul AM & Bazzano LA (2013) Effect of coenzyme Q10 supplementation on heart failure: a meta-analysis. *Am J Clin Nutr* **97**, 268–275.
270. Alehagen U, Aaseth J & Johansson P (2015) Reduced cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years: follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly citizens. *PLoS One* **10**, e0141641.
271. Alehagen U, Alexander J & Aaseth J (2016) Supplementation with selenium and coenzyme Q10 reduces cardiovascular mortality in elderly with low selenium status. A secondary analysis of a randomised clinical trial. *PLoS One* **11**, e0157541.
272. Moradi M, Haghighatdoost F, Feizi A, Larijani B & Azadbakht L (2016) Effect of coenzyme Q10 supplementation on diabetes biomarkers: a systematic review and meta-analysis of randomized controlled clinical trials. *Arch Iran Med* **19**.
273. Abdollahzad H, Aghdashi MA, Jafarabadi MA & Alipour B (2015) Effects of coenzyme Q10 supplementation on inflammatory cytokines (TNF-α, IL-6) and oxidative stress in rheumatoid arthritis patients: a randomized controlled trial. *Arch Med Res* **46**, 527–533.
274. Rivara MB, Yeung CK, Robinson-Cohen C, Phillips BR, Ruzinski J, Rock D, *et al.* (2017) Effect of coenzyme Q10 on biomarkers of oxidative stress and cardiac function in hemodialysis patients: the CoQ10 biomarker trial. *Am J Kidney Dis* **69**, 389–399.
275. Heidari A, Hamidi G, Soleimani A, Aghadavod E & Asemi Z (2018) Effects of Coenzyme Q10 supplementation on gene expressions related to insulin, lipid, and inflammation pathways in patients with diabetic nephropathy. *Iran J Kidney Dis* **12**, 14–21.

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