



COMPREHENSIVE STUDY ON PHARMACOLOGICAL BENEFITS OF LYCOPENE IN THE PREVENTION AND TREATMENT OF AGING AND AGE-RELATED AILMENTS

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Abstract

The process of ageing and associated chronic diseases are significant contributors to global death rates. The incidence of these disorders is steadily and universally rising. Given the continuous increase in the worldwide burden, it is essential to explore alternate approaches to conventional treatment to mitigate the risk of age-related disorders. Lycopene, a carotenoid pigment, is abundantly found in several fruits and vegetables, including tomatoes, grapefruits, and watermelons. It possesses a distinctive molecular configuration that imparts robust antioxidant characteristics. This nutraceutical exhibits various anti-ageing attributes, including the mitigation of age biomarkers and the improvement of some chronic illnesses. A thorough review to assess the efficacy of lycopene in mitigating ageing progression and age-related chronic disorders has yet to be conducted. This review analyses prior pre-clinical, clinical, and epidemiological studies on lycopene to assess its efficacy in addressing age-related disorders and its function as a calorie restriction mimic. Research has shown that diets rich in lycopene can aid in the prevention or reduction of age-related illnesses. This review indicates that lycopene may be employed in therapeutic contexts to enhance human health and alleviate the onset of ageing and age-related disorders, as supported by current findings.

Keywords: Lycopene, Pharmacological, Aging, Neurodegenerative Disease, Therapeutics

Introduction

The global population is affected by the increasing number of elderly individuals and the associated challenges of ageing due to extended life expectancies. MacNee et al. (2014) project that the proportion of individuals aged 60 and beyond will increase from 11% to 22% between 2000 and 2050, potentially totalling 2 billion, an increase from 605 million. Age is the primary risk factor for non-communicable chronic problems associated with ageing, such as cancer, diabetes mellitus, neurological disorders, renal diseases, and cardiovascular diseases. This results in about 100,000 deaths globally each day. In 2016, there were 54.7 million fatalities, with 29.5 million (72% of the total) resulting from age-related diseases (Harris, 2019). Epidemiological studies indicate that a diet rich in fruits and vegetables is associated with a reduced rate of ageing and related illnesses (Arif et al., 2018; Zhou et al., 2018). Despite the availability of numerous treatments for these conditions (Li et al., 2021), many exhibit adverse side effects and may prove ineffective if the illness escalates.

Consequently, investigations into ageing and chronic diseases are increasingly prioritising the implementation of nutraceutical-based therapies. Tomatoes and many tomato-derived products are abundant in the carotenoid compound lycopene. It is also present in trace amounts in several other fruits, such as pink guava, watermelon, and apricot (Rao & Rao, 2018). Research in public health has

focused extensively on lycopene due to its nutritional advantages. This pigment is lipid-soluble and predominantly occurs in red and orange fruits and vegetables; however, certain green fruits and vegetables, such as parsley and asparagus, also possess a little amount of it (Hedayati et al., 2019; Yin et al., 2019). The molecule known as lycopene comprises eleven double bonds arranged linearly and eight isoprene hydrocarbons. It is additionally referred to as a non-provitamin A carotenoid (Yin et al., 2019; Pennathur et al., 2010).

A recent study indicates that lycopene is the carotenoid with the highest content in organ tissues, serum, and blood (Saini et al., 2020). Lycopene is a powerful antioxidant capable of effectively inhibiting the production of reactive oxygen species (ROS) and eliminating singlet oxygen at a rate tenfold greater than α -tocopherol and double that of β -carotene (Przybylska, 2020). In addition to its antioxidant properties, lycopene has been associated with many health advantages that have attracted considerable attention in public health studies (Joshi et al., 2020). A review indicates that the consumption of lycopene-rich foods may diminish the risk of age-related conditions such as cardiovascular disease and cancer (Story et al., 2010). It is recommended to enhance lycopene supplementation to elevate its concentration in the bloodstream and serum, hence augmenting its efficacy in addressing ageing and age-related conditions (Ellis et al., 2019; Petyaev, 2016). The prospective advantages of lycopene in mitigating age-related disorders may encompass enhanced longevity and the promotion of healthy ageing in individuals. Nonetheless, no comprehensive study has been conducted to determine if lycopene is effective in postponing the onset of age-related chronic diseases and the ageing process itself. Nevertheless, the majority of research efforts focused on examining the specific effects of lycopene on ageing biomarkers or chronic age-related illnesses. The review examines the function of lycopene in ageing biomarkers and age-related illnesses by evaluating the mechanisms via which it exhibits anti-ageing properties. This understanding is essential for the advancement of clinically effective lycopene-based treatments. Furthermore, the review articulates theoretical viewpoints concerning the constraints, potential remedies, and prospective avenues for research to substantiate the nutraceutical as a viable anti-ageing pharmaceutical.

Methodology

Before initiating their literature search, the researchers used the patient-intervention-comparison-outcome-study design (PICOS) framework as described by Schardt et al. (2007). This guaranteed that the review study was explicitly focused on certain research questions and objectives. This study thoroughly examined the current understanding of lycopene utilisation in both human and non-human subjects. The objective was to advocate for the possible application of lycopene by the pharmaceutical industry in the development of anti-ageing therapeutics. Table 1 delineates the precise criteria employed to ascertain the inclusion or exclusion of literature throughout the screening step. The PICOS framework served as the basis for the specific review questions. What is the present level of research about the efficacy of lycopene in postponing the onset of chronic age-related diseases and mitigating ageing?

Can lycopene successfully impede ageing and replicate the benefits of caloric restriction? What are the limitations of utilising lycopene to mitigate age-related concerns?

Table 1. An assemblage of criteria used to determine the inclusion or exclusion of items in the evaluation process.

Parameters are variables or qualities used to define or describe a system, process, or situation.	Synthesis refers to the process of integrating disparate components or pieces into a cohesive whole.	Exclusion refers to the deliberate action of omitting or neglecting someone or something, which leads to their non-inclusion.
Year of publication	From January 2001 until October 31, 2021	Before 2001
Research methodology	Published original research papers, which have undergone peer review, include a broad spectrum of topics, encompassing inquiries that involve humans, animals, and cells.	The inclusion criteria cover systematic reviews, meta-analyses, comments, and non-peer-reviewed studies. • Unpublished dissertations and articles are also considered.
Age	Individuals that are 18 years of age or older	Individuals that are under the age of 18
Sexual intercourse	• Masculine • Feminine	Excluded atypical gender identities, such as transgender, non-binary, agender, and gender dysphoria.
Classification of aging indicators	Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to remove them, leading to damage to cells. • Inflammation-induced DNA damage is the harmful effect of inflammation on DNA, causing genetic mutations and other forms of DNA damage. • DNA methylation involves adding methyl groups to DNA molecules, which affects gene expression and could potentially lead to various health outcomes. • Telomere length shortening refers to the gradual reduction in the size of protective caps found at the ends of chromosomes. This process is intricately connected to the process of aging and the onset of age-related disorders. Cellular senescence is a state in which cells experience irreversible cessation of growth, usually associated with the process of aging and the accumulation of cellular damage.	Epigenetic markers, such as the reduction of histones, the presence of histone variations, and changes in histone structure, Transcriptomic biomarkers are distinct gene expression patterns that can function as indications for various illnesses or disorders. Proteostasis failure, or proteostatic imbalance, refers to the disruption or impairment of the body's ability to regulate protein folding and breakdown. This disorder leads to many health issues. • Mitochondrial dysfunction refers to the malfunctioning of mitochondria, the cellular organelles responsible for energy production, which can result in various physiological problems.
Age-related disorders categorization	The enumerated factors are associated with the subsequent health conditions: obesity, diabetes, cancer, cardiovascular diseases, skin aging, kidney disorders, and neurological issues.	• Alopecia and dental attrition • Degeneration of the macula • Skeletal, muscular, and articular disorders • Pulmonary pathology • Impaired reproductive capacity

Classification of additional products	• Raw tomato • Purified lycopene • Therapeutic compound obtained from lycopene	• Tomato condiment refers to a sauce made from tomatoes. • Tomato sauce is a liquid made from tomatoes that is used as a condiment or ingredient in cooking. • Fast food products that contain tomatoes, such as pizza, are examples of foods that incorporate tomatoes.
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Table 2. The influence of lycopene on markers of the aging process.

Research methodology	Academic disciplines	Dose	Length of time	Primary functions	Molecular biomarkers	Citations
Studies conducted in the discipline of zoology	Rats of the Wistar breed that were subjected to HgCl ₂ exposure	A group consisting of 40 rats. The recommended dosage is 5 milliliters per kilogram of body weight, administered either orally or by injection.	A duration of 48 hours	Antioxidation refers to the process of inhibiting or preventing oxidation, a chemical reaction that can cause damage to cells and tissues.	The concentrations of MDA decrease, whereas the concentrations of ROS increase. The concentrations of GSH-Px, SOD, and GSH exhibit an increase.	The study conducted by Yang et al. in 2011.
	A group consisting of 24 fully-grown male albino rats.	The suggested dose is 10 milligrams per kilogram of body weight, to be administered orally.	A time period of 5 weeks.	Antioxidation refers to the process of inhibiting or preventing oxidation, which is a chemical reaction that produces free radicals and can lead to cellular harm.	The concentrations of MDA and LPO are reduced, while the levels of total nitrate/nitrite are lowered. In contrast, the levels of glutathione (GSH), superoxide dismutase (SOD), and total antioxidant capacity (TAC) are increased.	A study was conducted in 2012 by Mansour and Tawfik.
	A group of 28 male Wistar rats were subjected to cisplatin treatment.	The recommended dosage is 6 milligrams per kilogram of body weight administered once daily via a single injection.	A period of 10 days.	Properties that prevent oxidation and reduce inflammation.	The expression of NF- κ B p65 has decreased. The concentrations of Nrf2 and HO-1 are increased. The concentrations of glutathione (GSH), catalase (CAT), glutathione peroxidase	Sahin et al. (2010) did the study.

					(GPx), and superoxide dismutase (SOD) are increased.	
	Kunming mice of the female gender who were given colistin	The recommended dosage is either 5 or 20 milligrams per kilogram of body weight per day, administered orally.	A week	Antioxidation refers to the process of inhibiting or preventing oxidation, which is a chemical reaction that can cause damage to cells and tissues.	The levels of LPO have decreased. The levels of HO-1 have increased. The levels of Nrf2 and HO-1 mRNA have increased. There has been an observed rise in the levels of glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD). The expression of NF- κ B mRNA is decreased.	The study conducted by Dai et al. in 2015
	Male Kunming mice were given croton oil to elicit a reaction.	The recommended dose is 0.5 grams per kilogram, administered orally using a gavage technique.	A period lasting four days.	Effects that reduce inflammation	Diminished rate of inflammation	The research conducted by Yaping et al. in 2003
	Wistar rats that were experimentally developed with diabetes using streptozotocin	The recommended dosage is 1, 2, and 4 milligrams per kilogram.	A duration of 10 weeks.	Properties that prevent oxidation and reduce inflammation.	Reducing oxidative stress leads to a decrease in the generation of TNF- α .	A study was conducted in 2008 by Kuhad, Sethi, and Chopra.
	A cohort of 50 Sprague-Dawley rats exhibiting hyperhomocysteinemia.	10, 15, and 20 mg/kg	A duration of 12 weeks.	Suppression of inflammation	The levels of VCAM-1, MCP-1, and IL-8 have reduced.	The study was conducted by Liu et al. (2007).
	Altogether, 60 Fischer 344 rats were given alcohol as a component of their diet.	The optimal dosage is 1.1 to 3.3 milligrams per kilogram of body weight daily.	An interval of eleven weeks	Effects that reduce inflammation	The expression of TNF- α mRNA is heightened in the liver, indicating an augmentation in inflammatory regions inside the liver.	The study conducted in 2008 by Veeramachaneni et al.
	OVA-stimulated BALB/c mice	The suggested dose is either 8 or 16 milligrams per kilogram of body weight	Anti-inflammatory effects	A period lasting three days.	The expression levels of IFN- γ and T-bet mRNA are elevated, while the expression	The 2013 study done by Hu et al.

		each day, delivered by intraperitoneal injection in a 200-microliter volume.			levels of IL-4 mRNA are reduced.	
	The study involved a cohort of 48 juvenile rats, comprising both male and female specimens	The values correspond to 0, 267, 534, and 1068 milligrams per kilogram. BW	A period lasting one month.	Antioxidation is the act of impeding or averting oxidation, a chemical reaction that can harm cells and tissues.	The concentrations of CAT, SOD, and GSH-Px are elevated, whereas the synthesis of MDA and ROS is reduced.	The 2013 study done by Hu et al.
	The investigation involved the use of 28 male rats from the Wistar-Albino strain.	The suggested dose is 10 milligrams per kilogram of body weight each day.	Twenty-eight days	Antioxidation is the act of impeding or averting oxidation, a chemical reaction that can harm cells and tissues.	Reduced concentrations of blood glucose and HbA1c. Decreased levels of oxidative DNA damage. Reduced concentrations of 8-OHdG.	In 2018, Karahan et al. published a study.
Human volunteers undergo clinical trials to evaluate the safety and effectiveness of novel medicines or into	A total of 32 male patients were diagnosed with prostate cancer.	The suggested daily dosage is 30 milligrams.	A period of twenty-one days.	Antioxidation refers to the process of inhibiting or preventing oxidation, which is a chemical reaction that can cause damage to cells and tissues.	Reduction in oxidative DNA damage	The study conducted by Chen et al. in 2001
	There was a total of 57 persons who received a diagnosis of Type 2 diabetes	The daily usage is 500 milliliters.	A period of four weeks.	Antioxidation refers to the process of inhibiting or preventing oxidation, which is a chemical reaction that can cause damage to cells and tissues.	The lycopene plasma concentration increased thrice.LDL exhibits increased resistance to oxidation.	The study conducted by Upritchard et al. in 2000.
	A cohort of twelve female volunteers exhibiting optimal health and possessing regular lipid levels.	Administer a dosage of 8 milligrams each day.	A period of twenty-one days.	Antioxidation refers to the action of inhibiting or preventing oxidation, a chemical process that can produce harmful free radicals.	The concentration of lycopene in the blood plasma increased. The urine concentration of 8 iso-PGF2 α decreased. The LDL's vulnerability to oxidation decreased.	The study was conducted by Visioli et al. (2003).

	A group of senior individuals, consisting of 33 females and 20 males, who demonstrate strong physical health and receive sufficient nutrition.	The recommended daily intake of tomato is 330 mL, which provides 47.1 milligrams of lycopene.	An eight-week duration.	Immunomodulation results in elevated amounts of lycopene in the bloodstream.	The levels of TNF- α and IL-4 have increased, while the level of IL-2 has decreased.	The study conducted by Watzl et al. in 2000
	A group of 26 individuals who are in exceptional physical condition and are of young age freely took part in the study.	5.7 milligrams	26 days	Reducing inflammation	The level of TNF- α has decreased.	Riso et al. (2006) did the study.
	A group of 37 postmenopausal women who are non-smokers and in excellent health.	The recommended daily dosage is 4 mg when taken as a mix of supplements and 12 mg when taken alone.	The duration is 56 days in total.	Antioxidation refers to the process of inhibiting or preventing the oxidation of substances within the body.	Reduction in the level of oxidative damage to DNA	The study conducted by Zhao et al. in 2006.
Cellular-level investigation	Murine macrophages (RAW 264.7) were stimulated with lipopolysaccharide (LPS).	The values are 0.5 μ M, 1 μ M, and 2 μ M.	24 hours	Effects that reduce inflammation	The mRNA expression levels of IL-6 and IL-1 β are decreased, as well as the phosphorylation of JNK.	The research was carried out by Marcotorchino et al. (2012).
	Lipopolysaccharide (LPS) was used to activate the RAW 264.7 macrophages.	Concentration ranging from 1 to 10 micromolar	24 hours	Properties that prevent oxidation and reduce inflammation.	The expression of inducible nitric oxide synthase (iNOS) messenger RNA (mRNA) is decreased. The levels of nitric oxide (NO) and interleukin-6 (IL-6) are also decreased. The phosphorylation of p38, ERK1/2, and I κ B is decreased. Moreover, there is a decrease in the mobility of NF- κ B.	The study conducted by Feng et al. in 2010
	THP-1 is a cell line consisting of human monocytic cells.	0.5 to 2 micromolar	A time span of 6 hours.	Properties that prevent oxidation and reduce inflammation.	Inhibition of IL-8 gene expression. The concentrations of reactive oxygen species (ROS) and	Simone et al. (2011)

					NOX-4 are decreased. The binding of NF- κ B to DNA is reduced, as well as the translocation of NF- κ B/p65 into the nucleus. The phosphorylation of IKK α and I κ B α is diminished. The phosphorylation of ERK1/2, JNK, and p38 MAPK is decreased.	
	Human umbilical vein endothelial cells (HUVECs), obtained from the umbilical vein of humans, were stimulated by lipopolysaccharide (LPS).	0 to 20 micromolar	A time period of 6 hours.	Effects that reduce inflammation	Suppression of HMGB1, HMGB1-triggered TNF- α , and sPLA2-IIA. The concentrations of VCAM-1, ICAM-1, and E-selectin are decreased. The levels of TLR-2, TLR-4, and RAGE receptors are decreased.	The study conducted in 2012 by Lee et al.

This investigation adhered to the recognised systematic review protocols as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). The procedural parameters of PRISMA 2020 encompassed several critical operations, as depicted in Figure 1 (Haddaway et al., 2018). The duties in this procedure encompassed doing an extensive search in a large database to locate pertinent publications, evaluating the articles' relevancy, analysing their quality, and extracting important data. We performed a comprehensive examination of the scientific literature, including both primary research and review publications published from October 2001 to October 2021. We performed an extensive analysis of the effects of lycopene on several markers of ageing and age-related chronic diseases, employing the databases PubMed, Scopus, and Google Scholar. We performed a preliminary search with diverse terms like lycopene, ageing, oxidative stress, inflammation, DNA alterations, telomere length, and cellular senescence. A thorough examination of the scientific literature was performed to examine the effects of lycopene on various age-related chronic illnesses. Our search methodology included a comprehensive array of subjects, including obesity, diabetes, cancer, cardiovascular disease (CVD), skin ageing, renal complications, neurological disorders, preclinical and clinical investigations, and pharmacological development.

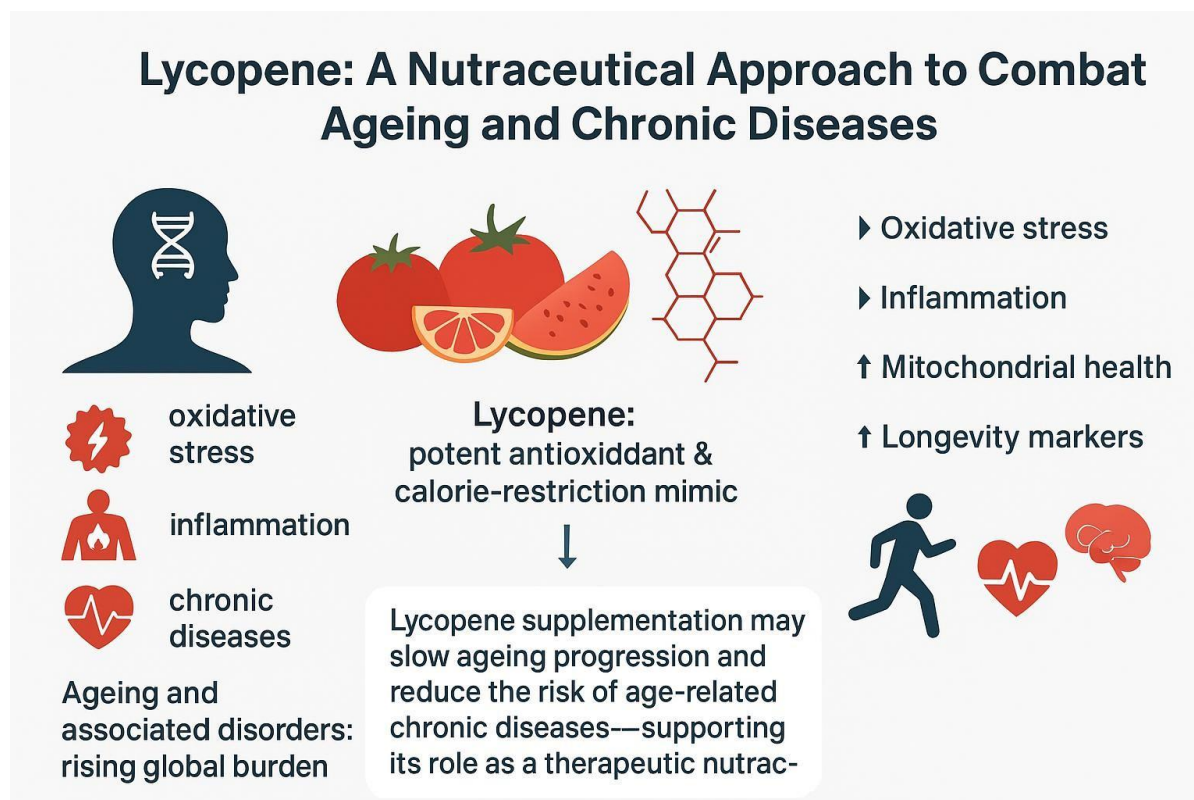


Figure 1 Lycopene supplementation delaying ageing process and chronic disease progressions

The examination of the chemical and biological properties of lycopene

Lycopene is a vital constituent of the carotenoid pigment category. Carotenoids in plants exhibit various colours mostly due to the presence of lutein and lycopene groups. Carotenoid pigments are vital for the metabolism of vitamin A and other metabolites. Hydrocarbon carotenoids consist only of hydrogen and carbon, while xanthophyll carotenoids contain oxygen, hydrogen, and carbon (Story et al., 2010). The molecular and biological characteristics of lycopene are significant due to its potential as a therapeutic agent and its ability to provide numerous health benefits when converted into an active state. The substance's structure, chemistry, and biochemistry illustrate the activity and mechanism of the reaction. Lycopene is classified as a non-cyclic carotenoid due to its structure, characterised by 11 linear double bonds. The compound's chemical formula is $C_{40}H_{56}$ (Bunghez et al., 2011). Due to the absence of ring structures, it does not engage in the metabolism of vitamin A. Lycopene is susceptible to detrimental abiotic factors, including elevated temperatures, pH levels, and moderately stressful environments (Srivastava & Srivastava, 2015). These factors result in substantial alterations to its structure. Consequently, lycopene transitions from a trans-state to a cis-state, altering its bioavailability and conferring significant health advantages. The cis-isomer of lycopene displays superior stability relative to the trans-isomer, along with a reduced melting point, increased oil solubility, and diminished tendency for crystallisation. The cis isomer of lycopene demonstrates properties that enhance its bioavailability in humans (Shi & Le Maguer, 2000; Srivastava & Srivastava, 2015). The primary form of lycopene found in the human body is the cis isomer. Nonetheless, it can undergo isomerisation into a trans-state in the stomach, liver, and intestines (Richelle et al., 2010; Teodoro et al., 2009). Walfisch et al. (2003) noted no alterations in the distribution of isomers in serum and tissues following the addition of a highly concentrated all-trans isomer to tomato lycopene oleoresin. It was determined that more over 90% of the lycopene existed in the all-trans configuration. The chemical is predominantly absorbed in the colon with the aid of two scavenger receptors, CD36 and B1 (Moussa et al., 2011, 2008). Furthermore, a degree of material breakdown transpires within the enterocytes (Imran et al., 2020). The capacity of lycopene to undergo

oxidation and isomerisation significantly influences its medicinal efficacy. These characteristics can modify the nutritional composition and color-enhancing properties of lycopene.

Moreover, numerous thermal and non-thermal mechanisms have been demonstrated to cause structural degradation of lycopene (Martínez-Hernández et al., 2016).

Four potential benefits of lycopene in combating the manifestations of ageing and age-associated diseases

Ageing is a natural process of deterioration resulting from the accumulation of harmful changes or damage in molecular pathways and cellular structures. The ageing process is marked by alterations in the biochemical makeup of tissues, progressive reductions in physiological capacity and responsiveness to environmental changes, heightened susceptibility to various non-communicable diseases, and elevated mortality rates (MacNee et al., 2014; Troen, 2003). Numerous biomarkers, including DNA damage, DNA methylation, telomere length reduction, cellular senescence, oxidative stress, and inflammation, have been linked to the ageing process (Xia et al., 2017). Ageing is a crucial factor in the progression of various chronic illnesses, such as cardiovascular diseases, kidney disorders, neurological disorders, cancer, diabetes, and obesity. Furthermore, it exacerbates the severity and mortality associated with these diseases (Prasad et al., 2012). Numerous studies have shown that lycopene significantly influences age indicators, slows the ageing process, and alleviates the severity of age-related chronic disorders. The results are delineated in the subsequent sections, encapsulated in Tables 2–4, and depicted in Figures 2–4.

Lycopene's anti-aging biomarker effects

Oxidative stress, a crucial indicator of ageing, arises when free radical concentrations exceed those of antioxidants, resulting in tissue damage, DNA impairment, and the activation of inflammatory pathways. Lycopene, a carotenoid, has demonstrated protective effects against oxidative damage via multiple antioxidative pathways. Research indicates that lycopene mitigates oxidative stress in human monocytic cell lines (THP-1) by downregulating reactive oxygen species (ROS) generation, 8-OHdG synthesis, NOX4, NADPH oxidase, Hsp70, and Hsp90 expressions, while also reducing inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated macrophages. Lycopene diminishes lipid oxidation and oxidative DNA damage in both healthy individuals and those with chronic illnesses. Inflammation is a significant characteristic of ageing, and lycopene can diminish pro-inflammatory cytokine synthesis and regulate inflammatory pathways and co-factors. In vitro studies on LPS-activated macrophages revealed that lycopene decreased inflammation by decreasing IL-6 and IL-1 β mRNA expressions, as well as inhibiting the NF- κ B pathway and the phosphorylation of p38, I κ B, ERK1/2, and JNK. The anti-inflammatory properties of lycopene were confirmed by in vitro and in vivo studies, indicating its potential to mitigate inflammation-related ageing (Figure 1). Lycopene also mitigates reactive oxygen species, especially singlet oxygen, and plays a crucial role in oxidative stress and cancer. It diminishes DNA oxidation in vivo and prevents DNA damage. Nonetheless, there is inadequate evidence regarding its processes for preventing DNA damage, especially in humans.

Additional investigation is required to elucidate the mechanisms, routes, and effects of lycopene in preventing DNA damage.

Lycopene has demonstrated anti-aging effects on several conditions, including obesity, sedentary lifestyle, and insufficient physical activity. Telomeres are 6-base pair sequences of TTAGG associated with chromosomes that govern cellular lifespan. Telomere length reduction serves as a biomarker for ageing and age-related conditions; nonetheless, oxidative stress significantly contributes to the shortening of telomeres. Research has linked reduced telomere length to ageing and age-associated diseases. Lycopene has demonstrated the ability to diminish p38 MAPK activity in endothelial progenitor cells (EPCs) exposed to elevated glucose levels, hence mitigating damage and facilitating senescence. Nevertheless, additional research is required to validate lycopene's significance in cellular senescence and ageing. Research on lycopene's influence on DNA methylation indicates that it does

not alter the DNA methylation of the GSTP1 promoter in prostate cancer LNCaP cell lines. Lycopene supplementation has been demonstrated to reduce GSTP1 methylation in androgen-independent PC3 prostate cancer cell lines, but not in androgen-dependent LNCaP cell lines. Lycopene exhibits potential anti-aging properties in relation to adiposity. Lycopene diminished blood cholesterol levels, hepatic fat accumulation, weight gain, and the size of hepatocytes and adipocytes in animal models, while enhancing PPAR γ mRNA expression. It decreased obesity-related adipose inflammation by obstructing adipocyte-macrophage interaction and regulating macrophage polarisation. In conclusion, lycopene has demonstrated beneficial effects on obesity biomarkers and may serve as a potential phytochemistry for the prevention of obesity and its associated diseases. Additional research is required to comprehensively elucidate its prospective advantages and therapeutic applications. Lycopene has demonstrated several effects on diabetes, such as lowering blood glucose levels, diminishing oxidative stress, and enhancing antioxidant enzyme activity. Research indicates that lycopene can prevent and treat diabetes in both animal models and people, and may also diminish the incidence of type 2 diabetes and diabetic neuropathy in albino rats. Ingesting 10 mg/day of lycopene for 2 months may mitigate long-term consequences of T2DM by enhancing total antioxidant capacity (TAC), diminishing malondialdehyde (MDA) and MDA-modified LDL production, and elevating serum levels of anti-oxidized LDL IgG and IgM1. Lycopene has been shown to reduce the risk of diabetic retinopathy and gestational diabetes. Lycopene possesses anticarcinogenic properties, suppressing the proliferation of lung, breast, prostate, and endometrial cancer cells. It has been demonstrated to elevate p53 and Bax mRNA expressions in A549 cells, inhibit pancreatic and prostate cancer by activating the Bax gene and downregulating Bcl-2 gene expression, and diminish cell proliferation by inducing apoptosis in MCF-7 cells. Lycopene supplementation has demonstrated the ability to inhibit HL-60 cell lines, decelerate cell cycle progression, and obstruct protein kinases in breast and endometrial cancer cell lines. It has been demonstrated to diminish prostaglandin E2 and nitric oxide levels in colorectal cancer cells while enhancing BCO2 gene expression in prostate cancer research. Lycopene has demonstrated cancer preventative effects in multiple animal models, including rats, hamsters, and mice. It has been demonstrated to synergistically inhibit carcinogenic substances, and clinical trials indicate it offers protection against the progression of prostate cancer. Lycopene also suppresses TTSPs and ERG gene fusion in prostate cancer patients, reducing PSA levels and blocking prostatic apoptosis. Lycopene is advantageous for ageing skin, the greatest organ exposed to environmental factors. It can enhance collagen integrity and avert wrinkles by neutralising reactive oxygen species (ROS), decelerating ageing, and sequestering peroxy radicals. Nonetheless, plasma lycopene concentrations decline markedly with age, resulting in significantly lower blood lycopene levels in the elderly compared to younger individuals.

The dermal preventive effects of lycopene in animal models are limited; nonetheless, research indicates that it safeguards the skin against photoaging by stimulating antioxidant enzymes, enhancing collagen content, and reducing TBARS levels. Clinical trials indicate that lycopene enhances skin parameters and mitigates UV radiation-induced skin conditions, including erythema, oxidative damage, and inflammation. Further investigation is required to ascertain the mechanisms by which lycopene mitigates aging-related dermatological issues, including pruritus, eczematous dermatitis, purpura, skin cancer, and others. Cardiovascular disorders are prevalent health concerns affected by biological, genetic, dietary, oxidative, antioxidant, and lifestyle variables. Meals abundant in lycopene may mitigate the risk of cardiovascular disease by 17% when contrasting the greatest and lowest dietary intakes. Lycopene supplements or foods can decrease LDL cholesterol, enhance endothelial function, lower both systolic and diastolic blood pressure, mitigate inflammatory processes, diminish cell adhesion molecules, reduce triacylglycerols, and elevate HDL cholesterol. Lycopene diminished LDL-C, elevated HDL-C, and decreased hyperactivity of cardiac enzymes in animal experiments. Clinical trials indicate that lycopene consumption may diminish cardiovascular disease risk by decreasing blood pressure, LDL oxidation, LDL peroxidation, plasma TBARS levels, 8 iso-PGF2 α excretion, and enhancing serum HDL-c levels. Nonetheless, some individuals remain suspicious, and the majority of research advocate for the consumption of tomato-based foods over lycopene

supplementation.

Neurological disorders such as Alzheimer's and Parkinson's contribute to neurodegeneration, while lycopene mitigates these conditions by traversing the blood-brain barrier and ameliorating motor deficits in mice. Lycopene also safeguards against cognitive and motor deficits induced by the irreversible succinate dehydrogenase inhibitor 3 nitro-propionic acid associated with Huntington's disease. The antioxidant, anti-inflammatory, and anti-apoptotic characteristics of lycopene confer protection against neurological disorders. It safeguards the brain by diminishing oxidative stress, restricting the production of inflammatory mediators and their functional actions, and suppressing enzymes that metabolise neurotransmitters. Nonetheless, additional pre-clinical and clinical studies are required to elucidate lycopene's neuroprotective processes, assess neurotoxicity, and establish clinical dosages.

Lycopene may also be advantageous for renal conditions. Normal ageing predominantly impacts kidney function across all organ systems, resulting in nephron loss, structural alterations in the tubulointerstitium, thickening of the glomerular basement membrane, reductions in GFR and salt reabsorption, buildup of extracellular matrix, and glomerulosclerosis. Focussing on the kidney's antioxidant system may mitigate renal ageing and associated disorders. Lycopene, owing to its antioxidant characteristics, has demonstrated the capacity to enhance renal functions and ameliorate kidney tissue disorders by mitigating oxidative stress and inflammation. Pre-clinical investigations indicate that lycopene treatment can reduce serum urea and creatinine levels, rectify chemically induced nephrotoxicity, and safeguard against renal tubular necrosis, degeneration, dilatation, and vacuolization. Lycopene also inhibits renal tubule necrosis, degeneration, dilatation, vacuolization, interstitial oedema, inter-tubular fibrosis, focal subendocardial fibrosis, perinuclear vacuolization, luminal cast formation, and basement membrane thickening. Nevertheless, additional clinical trials are required to evaluate the lycopene dosages for renal patients.

Calorie restriction and lycopene

Eating fewer calories than what is required to stay at a healthy weight but still getting all the nutrients you need is what calorie restriction (CR) is all about. Calorie restriction (CR) is defined by López-Lluch and Navas (2020) as cutting calories without causing starvation. Cancer, heart disease, and degenerative diseases can all be averted or postponed by CR, according to Guijas et al. (2020). The effects of CR on animals include alterations to their metabolic rate, insulin sensitivity, oxidative stress levels, and neuro-endocrine and autonomic nervous systems (Heilbronn & Ravussin, 2003). Reducing caloric intake (CR) slows the metabolism and uses less oxygen. Reducing oxygen utilisation may increase longevity via reducing ROS production. According to Heilbronn and Ravussin (2003), both diabetics and non-diabetics who are overweight can benefit from calorie restriction (CR) and weight loss via improving insulin effects and glucose metabolism. Inflammatory markers such TNF- α , IL 6, CRP, and NF- κ B are reduced and HDL2b is increased by calorie restriction (CR) (Lane et al., 1999; Trepanowski et al., 2011). Furthermore, metabolic reactions produced by caloric restriction involve the sirtuin SIRT3 (López-Lluch & Navas, 2020). Research by Palacios et al. (2009) indicated that skeletal muscle SIRT3 levels are elevated under caloric restriction (CR) and decreased on a high-fat diet. Thus, sirtuins control caloric intake and ought to be a part of physiological responses. Masoro (1988) and Lee et al. (2000) found that gene expression changes with age in skeletal muscles, brains, and hearts of mice studied using microarrays. Many of these variants are prevented by calorie restriction (CR). Tissue gene expression profiles associated with ageing were identified by Park et al. (2009) using DNA microarrays. The results of the study showed that lycopene, resveratrol, acetyl-l-carnitine, tempol, α -lipoic acid, and coenzyme Q10 are dietary antioxidants that effectively decrease transcriptional genes related to ageing. In the heart, lycopene reduced ageing by simulating calorie restriction (CR) and inhibiting gene activity associated with ageing.

To study the development of prostate cancer in rats, researchers gave them lycopene or tomato powders to eat while they cut back on calories and fat. The mortality rate from prostate cancer was compared to a 20% decrease in caloric intake. One hundred ninety-four male rats were tested. In rats,

prostate cancer was induced by N-methyl-N-nitrosourea and testosterone. In addition, rats were given 13 milligrams of lycopene per kilogramme in the form of whole tomato powder. Two studies (Boileau et al., 2003; Gann & Khachik, 2003) found that rats given tomato powders or lycopene had a 32% reduction in prostate cancer mortality when calorie restriction was implemented. Fatty liver disease, also known as hepatic steatosis, is a serious condition that can develop in children who are overweight. Research has demonstrated that a calorie-restricted diet (CRR) can alleviate this issue. The effects of lycopene-rich tomato sauce with oreganos and basil on hepatic steatosis in children who are obese were investigated in a recent CRR study. The sixty-one overweight children were a part of a randomised cross-over clinical study. Split into two groups, 27 kids had CRR and 34 got a combo of CRR and lycopene-rich tomato juice. Tomato supplementation was seen to lower body mass index (BMI), HOMA-IR, cholesterol, TG, liver measurement, and CRR steatosis, according to the study. Tomato juice supplements improved glucose and lipid metabolism, decreased inflammation and oxidation, and regulated T cell mitochondrial metabolism in CRR (cardiovascular risk reduction). The immune systems of the youngsters with CRR were able to remain balanced because of all of these factors. In contrast to CRR's effects on glycolysis and T lymphocyte development, tomato juice's lycopene promotes T lymphocyte-mediated glycolytic metabolism. Tomato juice's lycopene content may prevent CRR in overweight youngsters (Negri et al., 2020).

Conclusion

Deadly diseases associated with ageing are on the rise. As a result, public health calls for non-pharmaceutical approaches to disease management, taking into account the potential negative impacts of conventional medicine and the implications of catastrophic disease scenarios. This review looked at the subject's chemical and biological properties, evaluated its potential to treat age-related diseases and biomarkers, and identified its benefits and drawbacks. The genotoxic and teratogenic effects of the therapeutic drug, as well as its physiological dosages, require additional research. Furthermore, there are a number of inconsistencies that need to be resolved about the absorption, biological activity, and tissue lycopene metabolites at physiologically normal concentrations. The anti-aging properties of lycopene or its metabolites need more investigation.

Discussions

Lycopene, a naturally occurring acyclic carotenoid, possesses distinctive structural and biochemical features that underpin its extensive biological activities. Its linear configuration, composed of 11 conjugated double bonds, confers exceptional antioxidant potential by enabling efficient quenching of singlet oxygen and neutralization of reactive oxygen species (ROS). The transition from trans- to cis-isomeric forms enhances its bioavailability and stability, thereby facilitating superior absorption and biological activity. Unlike other carotenoids, lycopene is not a precursor of vitamin A, yet it plays a critical role in modulating oxidative and inflammatory pathways implicated in the ageing process. These structural and chemical characteristics collectively explain lycopene's capacity to counteract oxidative stress, a key driver of cellular senescence and chronic degenerative diseases.

Biologically, lycopene demonstrates extensive therapeutic potential across multiple physiological systems. It exhibits anti-inflammatory, antioxidant, anti-apoptotic, and anti-proliferative effects, contributing to the attenuation of several age-related conditions. Lycopene downregulates the expression of inflammatory mediators such as NF- κ B, IL-6, and IL-1 β , while enhancing antioxidant enzyme activity and reducing lipid peroxidation. Experimental and clinical studies have revealed its protective effects in cardiovascular, metabolic, renal, dermatological, and neurological disorders. Regular consumption of lycopene-rich foods has been associated with decreased low-density lipoprotein (LDL) oxidation, improved endothelial function, and enhanced insulin sensitivity. Moreover, lycopene's ability to inhibit tumor proliferation, induce apoptosis, and modulate oncogenic gene expression underscores its potential as a chemopreventive agent. These findings highlight lycopene's multifaceted role in mitigating molecular and physiological manifestations of ageing and related pathologies.

An additional dimension of lycopene's biological significance lies in its calorie restriction–mimetic activity. Calorie restriction (CR) is widely recognized for its capacity to delay ageing and extend lifespan through modulation of metabolic and genetic pathways, including activation of sirtuins such as SIRT3. Lycopene has been shown to emulate these effects by enhancing mitochondrial efficiency, reducing oxidative stress, and regulating gene expression patterns associated with longevity. Comparative studies suggest that the combination of lycopene supplementation with moderate calorie restriction may produce synergistic benefits in preventing metabolic and inflammatory deterioration. Nevertheless, further research is warranted to delineate its pharmacokinetics, optimal dosage, and long-term safety profiles in human populations. Overall, lycopene emerges as a promising nutraceutical agent capable of modulating ageing-related biomarkers and offering broad-spectrum protection against chronic degenerative diseases.

Author Contributions

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