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Advancing lycopene research: Health benefits, technological applications, and emerging strategies for optimization

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ABSTRACT

Lycopene ($C_{40}H_{56}$), a carotenoid abundant in tomatoes, exhibits potent antioxidant, anti-inflammatory, anti-cancer, and cardioprotective properties. Its 11 conjugated double bonds confer superior singlet oxygen quenching activity with reduced prostate cancer and cardiovascular risks via modulation of NF-κB, IGF-1, MMP activities, and epigenetic pathways. Despite its therapeutic potential, clinical application is hindered by poor availability. Recent advances in delivery systems including nanoemulsions, smart carriers, and 3D-printed nutraceuticals enhance stability and targeted absorption. Concurrently, production is shifting toward sustainable methods like supercritical CO_2 and microbial biosynthesis using engineered *E. coli* and *Yarrowia lipolytica*, further optimized by AI-assisted fermentation and omics-based tools. While lycopene holds GRAS-certified (FDA) and E160d (EU) status, regulatory inconsistencies and limited clinical substantiation of health claims remain. Future research should emphasize systems biology, genotype-specific trials, and harmonized regulations to unlock lycopene's potential in precision health and nutraceutical innovation.

1. Introduction

Lycopene, a naturally occurring carotenoid pigment, has garnered considerable scientific and commercial interest due to its robust antioxidant properties and extensive applicability in preventive nutrition, functional food development, therapeutic research, and various industrial sectors. Chemically classified as a linear tetraterpene, lycopene comprises 40 carbon atoms ($C_{40}H_{56}$) and possesses a series of 13 double bonds, including 11 conjugated double bonds. This unique structural configuration not only imparts its characteristic deep-red hue but also significantly enhances its efficiency in neutralizing reactive oxygen species, specifically singlet oxygen, thus ranking it among the most potent natural antioxidants known (Perveen et al., 2015; Stahl & Sies, 2012).

Predominantly sourced from tomatoes (*Solanum lycopersicum*) and processed tomato products like sauces, pastes, and juices, lycopene is also abundantly present in watermelon (*Citrullus lanatus*), pink grapefruit (*Citrus paradisi*), red guava (*Psidium guajava*), and papaya (*Carica papaya*) (Grabowska et al., 2019; Ilahy et al., 2019; Khan et al., 2021; Kulawik et al., 2024). The bioavailability of lycopene is influenced profoundly by factors such as its food matrix, thermal and mechanical processing techniques, isomeric transformations (cis/trans isomerization), and co-ingestion with dietary fats, distinguishing its absorption characteristics from other carotenoids (Boileau et al., 2002; Juric et al., 2021; Perveen et al., 2015; Shafe et al., 2024). These determinants also indicate that the biological relevance of lycopene depends not only on dietary intake, but also on its digestive release, intestinal absorption, transport, metabolic conversion, tissue distribution, and elimination. In addition, the relative proportion of all-trans and cis isomers is increasingly recognized as a key factor influencing both bioaccessibility and biological performance.

Extensive research over recent decades has established lycopene as a significant health-promoting bioactive compound. Epidemiological and clinical studies have demonstrated its protective roles in mitigating

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oxidative stress and inflammation, thereby reducing the risk of chronic diseases. Lycopene intake correlates inversely with incidences of cardiovascular diseases, cancers particularly prostate, colorectal, breast, lung, and pancreatic cancers as well as metabolic syndrome, neurodegenerative disorders, and premature skin aging. Rather than reflecting isolated effects, these activities are now understood to arise from shared molecular mechanisms involving redox regulation, inflammatory signaling, growth-factor-related pathways, and gene-regulatory events, which are expressed differently across tissues and disease contexts. Its mechanisms include antioxidation, modulation of cell signaling pathways, and gene regulation, with emerging attention also being given to epigenetic regulation and gut microbiota-related interactions (Gao et al., 2023; Grabowska et al., 2019; Khan et al., 2021; Singh & Goyal, 2008; Viuda-Martos et al., 2014).

Beyond its nutritional and therapeutic applications, lycopene has emerged prominently in industrial sectors due to its functional versatility and commercial value. It is utilized as a natural coloring agent and bioactive additive in functional foods, beverages, dietary supplements, and nutraceutical formulations. Lycopene has also gained traction in cosmetic industries for its protective effects against UV-induced skin damage and dermatological formulations aimed at skin health and anti-aging (Viuda-Martos et al., 2014). Advances in formulation and materials science have further extended lycopene applications into stabilization, preservation, and delivery systems designed to improve product shelf life, protect bioactivity, and enhance compatibility with food, cosmetic, and pharmaceutical matrices(Long et al., 2024; Shafe et al., 2024).

Despite these promising attributes, lycopene's clinical and industrial utility faces significant challenges, primarily stemming from its hydrophobic nature, poor aqueous solubility, limited bioavailability, and susceptibility to degradation upon exposure to environmental factors such as light, heat, and oxygen. Moreover, regulatory inconsistencies across global markets have posed additional hurdles. Recent technological innovations, including improved extraction, purification, encapsulation, and stabilization strategies, together with emerging scalable biosynthetic platforms, are being developed to overcome these limitations and improve lycopene's functional stability, bioaccessibility, and practical applicability (Khan et al., 2021; Kulawik et al., 2024).

This comprehensive review critically evaluates lycopene's molecular characteristics, biochemical functionality, health-promoting properties, technological applications, extraction methods, stability concerns, and regulatory frameworks. Particular emphasis is placed on issues that are often dispersed or insufficiently integrated in the literature, especially the relationship between cis-trans isomerism and functional behavior, the contribution of in vivo metabolism and pharmacokinetics to biological response, the distinction between core shared mechanisms and system-specific effects, and the translational gap between experimental evidence and clinically substantiated outcomes. Furthermore, it addresses existing limitations and highlights contemporary strategies to optimize lycopene's potential as both a bioactive health-promoting compound and a versatile industrial ingredient, providing a roadmap for future research and industrial innovations.

2. Methods

2.1. Literature search strategy

A structured narrative literature review was conducted to critically evaluate the current state of knowledge regarding lycopene, including its biochemical properties, biological activities, technological applications, extraction methods, stability, bioavailability, and industrial utilization. A comprehensive search of peer-reviewed literature was performed using major scientific databases including Web of Science, Scopus, PubMed, ScienceDirect, and Google Scholar.

The search encompassed publications available up to June 2025. Both controlled vocabulary and free-text keywords were applied to maximize retrieval of relevant studies. The search strategy incorporated combinations of the following terms: “lycopene,” “carotenoids,” “lycopene bioavailability,” “lycopene antioxidant activity,” “lycopene anti-inflammatory,” “lycopene health benefits,” “lycopene nano-encapsulation,” “lycopene extraction techniques,” “lycopene industrial applications,” “lycopene stability,” “lycopene metabolism,” and “lycopene functional foods.” Boolean operators (AND, OR) were used to refine database queries and improve search specificity.

2.2. Study selection and eligibility criteria

Publications were screened based on predefined inclusion and exclusion criteria to ensure scientific relevance and reliability. Eligible studies included peer-reviewed original research articles, systematic reviews, meta-analyses, and authoritative review papers written in English. Particular emphasis was placed on studies addressing the biological functions of lycopene, molecular mechanisms of action, extraction technologies, formulation strategies, industrial applications, and health-related outcomes.

Studies were excluded if they contained insufficient methodological information, duplicated datasets, non-peer-reviewed material, or findings considered outdated and no longer representative of current scientific understanding. When necessary, additional references were incorporated to provide contextual background on carotenoid biochemistry, oxidative stress mechanisms, and functional food development.

2.3. Data synthesis and thematic organization

The selected literature was critically analyzed and organized into thematic sections covering lycopene sources, chemical properties, bioavailability, health-promoting activities, technological applications, extraction technologies, formulation strategies, and stability considerations. Priority was given to recent and high-impact studies that significantly contributed to advances in lycopene research.

This approach allowed the integration of multidisciplinary evidence from food science, nutrition, biotechnology, pharmacology, and industrial processing, enabling a comprehensive synthesis of current knowledge and emerging strategies aimed at optimizing the functional and technological potential of lycopene in health-related and industrial applications.

3. Lycopene: An overview

3.1. Definition and sources

Lycopene is an acyclic, lipophilic hydrocarbon classified as a non-provitamin A carotenoid. Its structure lacks cyclic end groups, differentiating it from β-carotene, and includes a conjugated polyene chain responsible for its coloration and antioxidant efficacy (Grabowska et al., 2019; Perveen et al., 2015; Rao & Agarwal, 2000). In human tissues, lycopene predominantly accumulates in its cis-isomeric forms, associated with higher bioavailability.

Tomatoes (*Solanum lycopersicum*) and their derivatives are the principal dietary sources, contributing to over 85% of intake in Western diets (Singh & Goyal, 2008). Other sources include watermelon (*Citrullus lanatus*), pink grapefruit (Citrus *paradisi*), red guava (*Psidium guajava*), papaya (*Carica papaya*), rosehip, and apricot (Grabowska et al., 2019; Ilahy et al., 2019) (Table 1). Lycopene content varies with cultivar, ripeness, environmental conditions, and post-harvest treatments. Heat processing, e.g., cooking and homogenization induces isomerization to cis forms, enhancing intestinal absorption (Boileau et al., 2002; Juric et al., 2021). Overall, lycopene should be regarded primarily as a diet-derived carotenoid whose nutritional relevance is strongly influenced by its dietary source, food matrix, isomeric profile, and processing conditions (Mutmainah et al., 2026), whereas its metabolic fate and

Table 1
Lycopene Content in Various Food and Bioavailability Influences.

Source	Lycopene Content (mg/100 g FW)	References
Tomato (fresh)	3.0–7.2	(Ilahy et al., 2019; Khan et al., 2021; Stahl & Sies, 2012)
Tomato paste	15.0–30.0	(Shi & Maguer, 2000; Juric et al., 2021; Kulawik et al., 2024;)
Watermelon	4.1–5.2	(Duduit et al., 2022; Khan et al., 2021; Shafe et al., 2024)
Pink grapefruit	1.1–3.6	(Crowe-White et al., 2019, Rao & Agarwal, 2000, Shafe et al., 2024)
Pink-flesh guava	5.0–7.1	(Khan et al., 2021; Long et al., 2024)
Factor	**Effect on Bioavailability**	**References**
Thermal processing	↑ Isomerization, ↑ absorption	(Boileau et al., 2002; Juric et al., 2021; Khan et al., 2021)
Co-ingested dietary fats	↑ Micelle formation, ↑ uptake	(Crowe-White et al., 2019; Shafe et al., 2024; Unlu et al., 2007)
Raw vs. cooked matrix	Processed > raw	(Khan et al., 2021; Kulawik et al., 2024; Long et al., 2024)
Encapsulation technology	↑ Bioavailability	(Juric et al., 2021; Shafe et al., 2024; Ziani et al., 2021)

biotechnological production are discussed separately in the following sections.

3.2. Chemical structure and properties

Lycopene is a symmetrical, acyclic hydrocarbon with the molecular formula $C_{40}H_{56}$ and a molecular weight of 536.85 g/mol. It belongs to the carotenoid family and consists of eight isoprene units linked in a head-to-tail fashion, except for a central tail-to-tail connection, forming a linear tetraterpenoid chain. The molecule contains 13 carbon–carbon double bonds, of which 11 are conjugated, forming a highly electron-rich polyene system that imparts lycopene its intense red coloration and confers potent singlet oxygen quenching capacity (Amorim et al., 2022; Saini et al., 2019).

Due to its entirely hydrocarbon nature, lycopene is highly lipophilic and insoluble in water, but it dissolves in non-polar organic solvents such as hexane, benzene, and chloroform (Carvalho et al., 2021). It exhibits strong absorption in the visible spectrum, with maxima at 450, 470, and 505 nm, which is characteristic of its extensive conjugation (Mozos et al., 2018).

Naturally, lycopene predominantly occurs in the all-trans

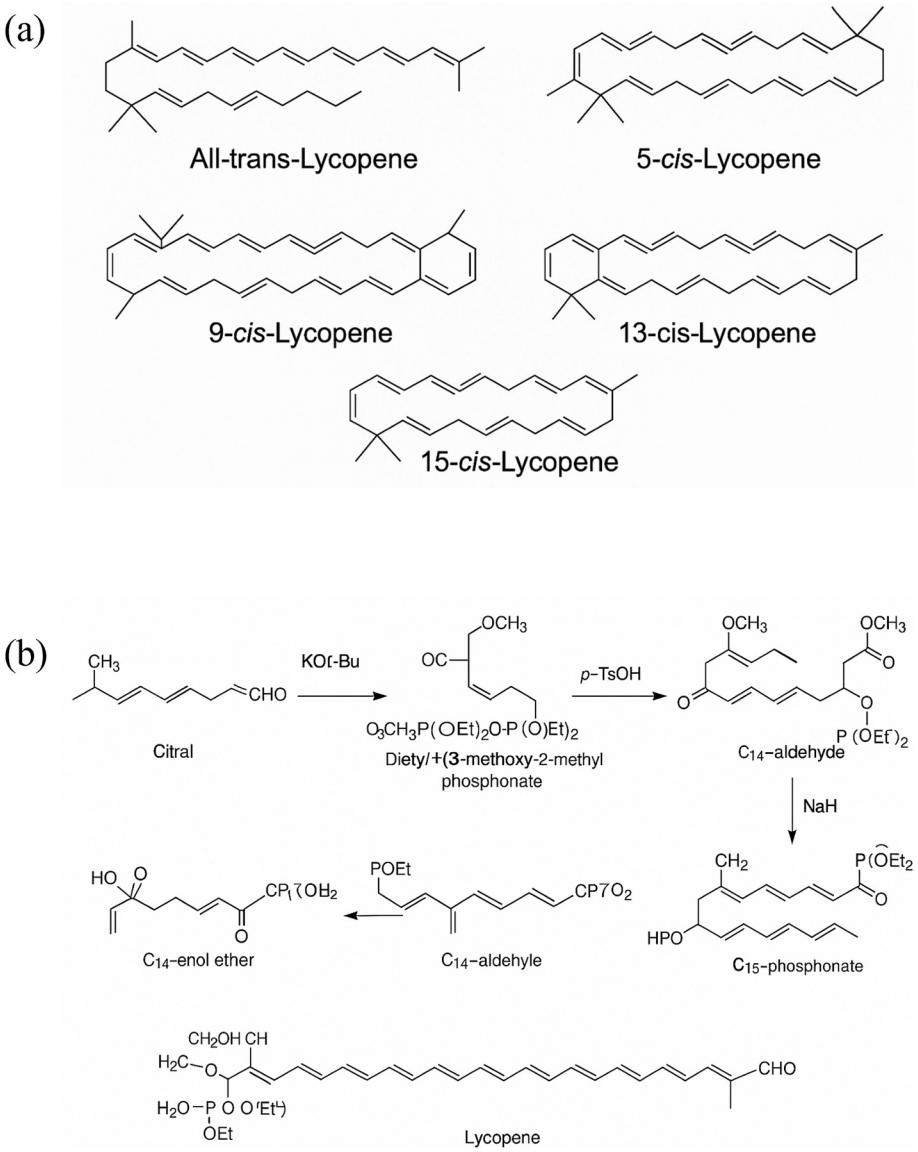

Fig. 1. **(a)** Structural isomers and **(b)** synthetic pathway for lycopene via citral-derived phosphonate intermediates.

configuration, which is more thermodynamically stable and has higher color intensity. However, this form is poorly bioavailable. Under thermal, photonic, or acidic stress, lycopene undergoes isomerization to various cis-isomers (Fig. 1) which exhibit higher solubility in bile salt micelles and greater bioaccessibility in the human gastrointestinal tract (Amorim et al., 2022; Srivastava & Srivastava, 2015).

Lycopene is highly sensitive to oxidative degradation, particularly in the presence of heat, oxygen, light, and metal ions (e.g., Fe^{3+}, Cu^{2+}), leading to loss of bioactivity (Saini et al., 2019). Recent advancements in encapsulation technologies, including nanoemulsions, liposomes, and nanostructured lipid carriers, have been developed to protect lycopene from degradation and improve its delivery in pharmaceutical and functional food applications (Amorim et al., 2022; Carvalho et al., 2021).

3.3. Isolation and synthesis of lycopene

Lycopene is primarily isolated from tomato (*Solanum lycopersicum*) using solvent extraction methods followed by purification. Myong-Kyun et al. (2013)developed a simplified method combining ethyl acetate extraction with anti-solvent precipitation (methanol), achieving a 77.4% recovery rate and 3.5 mg/g yield from freeze-dried tomato powder. This approach offers scalability for industrial isolation. Crystallization and column chromatography remain essential for refining lycopene from mixed carotenoid fractions.

Thermal isomerization of (all-E)-lycopene generates various *Z*-isomers, including (15Z)-lycopene. Takehara et al. (2015) isolated (15Z)-lycopene from thermally processed tomato-derived (all-E)-lycopene and structurally confirmed it using NMR and UV–Vis spectroscopy. The isomer was purified with >99% purity using a three-step chromatographic method.

Chemically, lycopene can be synthesized via the Wittig–Horner reaction. Song et al. (2016) described a four-step synthetic route starting from citral, yielding lycopene through modular C15–C10–C15 fragment assembly (Fig. 1), providing high efficiency and configurational control. Additionally, Reynaud et al. (2011) reported the first total synthesis of two apo-lycopenoic acids (C_{100} and C_{140}), which demonstrated bioactivity by upregulating BCO2 expression in mouse tissues.

3.4. Bioavailability of lycopene

The bioavailability of lycopene is modulated by a complex interplay of dietary, molecular, and physiological factors. The release of lycopene from the food matrix is a primary limiting step. In raw tomatoes, lycopene is predominantly in the all-trans configuration and tightly bound within chromoplast crystalline structures, leading to poor absorption (Arballo et al., 2021). Thermal processing disrupts plant cell walls and promotes trans-to-cis isomerization, improving solubility in bile acid micelles and enhancing absorption (Arballo et al., 2021; Honest et al., 2011) (Table 1). Overall, lycopene should be regarded primarily as a diet-derived carotenoid whose nutritional relevance is strongly influenced by its dietary source, food matrix, isomeric profile, and processing conditions (Yu et al., 2025), whereas its metabolic fate and biotechnological production are discussed separately in the following sections.

Dietary fat is essential for effective lycopene absorption. Fat co-ingestion stimulates bile secretion and enhances micelle formation. Human trials demonstrate a dose-dependent improvement in lycopene absorption when consumed with 10–20 g of fat, independent of fat source (Arballo et al., 2021). Absorption mechanisms include passive diffusion and transporter-mediated uptake via scavenger receptor class B type I (SR-BI) and CD36, which are highly expressed in intestinal enterocytes (Arballo et al., 2021; Ross et al., 2011).

Additionally, advanced formulations such as nanoemulsions, liposomes, and beadlets have been shown to improve both solubility and metabolic stability. These delivery systems help protect lycopene from oxidative degradation and enhance pharmacokinetic profiles (Arballo et al., 2021; Honest et al., 2011).

3.5. Lycopene in vivo metabolism and pharmacokinetics

The biological efficacy of lycopene is governed not only by intake, but also by the efficiency of its release from the food matrix, incorporation into mixed micelles, intestinal uptake, systemic transport, and retention in target tissues. In practical terms, lycopene pharmacokinetics begins with matrix disassembly during digestion. Recent work shows that processing strategies favoring *Z*-isomer formation can markedly improve this early phase. In a simulated tomato-based food system, sulfur-containing compounds promoted lycopene isomerization toward Z-rich forms, and garlic-juice-assisted processing increased total-Z lycopene while significantly enhancing the bioaccessibility of 5-Z- and 9-Z-enriched fractions (Yu et al., 2025). Likewise, lycopene-loaded self-emulsifying delivery systems improved proximal-intestinal solubilization and lipolysis-associated bioaccessibility, confirming that efficient digestive transfer depends on both isomeric profile and lipid organization during digestion (Lin et al., 2025). Together, these findings indicate that the first major pharmacokinetic bottleneck is not absorption per se, but the successful transfer of lycopene from plant tissue or formulated carriers into an absorbable micellar phase. Following intestinal uptake, lycopene undergoes rapid post-absorptive transformation and redistribution in vivo. A pivotal human tracer study using accelerator mass spectrometry showed that 92% of orally administered all-trans-lycopene was rapidly isomerized in vivo to a mixture of cis-isomers, particularly 5-cis (38%) and 13−/15-cis forms within 24 h, supporting extensive post-ingestion isomerization (Ross et al., 2011).

Once bioaccessibility has been achieved, epithelial transport becomes a second critical determinant. Recent intestinal cell-model studies show that lycopene handling is highly formulation-sensitive. Lycopene-loaded nanomicelles increased cellular uptake into Caco-2 cells by 2.20-fold and involved endoplasmic reticulum-, Golgi apparatus-, and lysosome-associated intracellular trafficking, demonstrating that nano-enabled delivery can substantially improve intestinal handling of lycopene (Su et al., 2025). Consistent with this, (Gao et al., 2026) reported that nanocarrier-based systems enhanced lycopene uptake, reduced efflux, and promoted transport across Caco-2 monolayers, further showing that intestinal absorption is shaped by carrier design and stereoselective behavior rather than by passive diffusion alone. These findings are particularly important because they shift the discussion of lycopene bioavailability from a purely compositional issue to a mechanistic question involving digestive release, carrier architecture, and epithelial transport processes.

Beyond the intestine, recent human evidence highlights that lycopene disposition is highly individualized and strongly influenced by postabsorptive transport and storage. (Zumaraga et al., 2026) reported marked interindividual variability in subcutaneous adipose lycopene concentration, with only a moderate correlation between adipose and fasting plasma lycopene, indicating that plasma status alone does not fully predict tissue accumulation. The same study identified a multigene model involving lipid- and carotenoid-related genes such as ABCA1, APOB, CD36, PPARG, IRS1, and TCF7L2, emphasizing that tissue distribution reflects a combination of lipoprotein trafficking, cellular uptake, and storage efficiency rather than intake alone. Recent human work also continues to support the relevance of enzymatic cleavage products such as apo-lycopenoids, although these metabolites occur at much lower concentrations than parent lycopene isomers and remain less comprehensively characterized than absorption and tissue deposition. Overall, lycopene should therefore be understood through a pharmacokinetic continuum encompassing digestive release, micellization, epithelial transport, systemic trafficking, selective tissue retention, and metabolite formation, with the terminal stages of clearance still requiring deeper clarification in contemporary human studies (Zumaraga et al., 2026).

3.6. cis-trans isomerism and structure-activity relationship

Geometric isomerism is one of the most important determinants of lycopene functionality at the interface of chemistry, digestion, and biological response. In foods, lycopene occurs predominantly as the all-E form, whereas in human circulation and tissues *Z*-isomers are proportionally enriched, indicating that structural conversion accompanies digestion, absorption, and tissue distribution. Recent processing studies confirm that this shift can be intentionally modulated. (Yu et al., 2025) showed that plant-derived sulfur-containing compounds such as allicin, alliin, and sulforaphane markedly promoted lycopene Z-isomerization, while garlic-juice-assisted processing generated tomato pulp with substantially higher total-Z lycopene and significantly improved bioaccessibility. Thus, E/Z configuration should not be treated as a minor analytical detail, but as a central structural variable affecting dispersibility, micellar incorporation, and tissue delivery.

The functional significance of this structural conversion is increasingly supported by recent experimental evidence. Heat treatment of tomato increased cis-lycopene conversion and enhanced antioxidant activity in HepG2 cells, linking thermally induced isomerization with improved cellular redox protection (Kim & Imm, 2025). In addition, (Honda, 2023) demonstrated that Z-isomer-rich lycopene exhibited stronger UV-A/UV-B shielding and superior skin-related biological activities than the corresponding all-E form. When considered together with the higher bioaccessibility of Z-rich lycopene systems reported by (Yu et al., 2025), these findings indicate that two preparations containing the same nominal amount of total lycopene may differ substantially in biological performance if their isomeric distributions are not equivalent. This point is especially relevant for supplementation studies, because dose alone is not an adequate surrogate for functional exposure when stereochemical composition varies.

A rigorous structure-activity interpretation, however, should remain mechanistically precise rather than simplistic. Recent density functional theory analysis showed that major lycopene isomers differ in predicted antioxidant behavior, with 5-cis displaying the most favorable radical-scavenging profile among the principal forms examined (Karunarathna et al., 2025). At the same time, recent biological evidence suggests that the apparent superiority of a given isomer depends on the endpoint considered, since bioaccessibility, photoprotection, singlet-oxygen quenching, and cellular activity do not necessarily rank the isomers identically. This means that Z-isomers should not be described as universally “better” in every context; rather, they often show specific advantages in absorption-related, physicochemical, and selected biofunctional outcomes. For that reason, future lycopene studies should systematically report isomer composition and interpret efficacy in relation to the dominant molecular species instead of treating “total lycopene” as a chemically uniform dose (Honda, 2023; Karunarathna et al., 2025).

4. Health benefits of lycopene

Lycopene has garnered significant attention for its multifaceted role in human health, largely due to its potent antioxidant activity and regulatory effects on several critical cellular pathways. As a highly unsaturated acyclic carotenoid, lycopene acts as an effective quencher of singlet oxygen and scavenger of reactive oxygen and nitrogen species, surpassing β-carotene and α-tocopherol in efficacy (Khan et al., 2021; Krinsky & Johnson, 2005; Przybylska, 2020).

Its health-promoting effects span a wide spectrum, including cardioprotective, anticancer, anti-inflammatory, neuroprotective, hepatoprotective, and photoprotective actions. These are mediated through modulation of cellular signaling pathways such as NF-κB, Nrf2/ARE, IGF-1/IGF-1R, and MAPK, as well as through the suppression of oxidative stress, lipid peroxidation, and pro-inflammatory gene expression (Anlar & Bacanli, 2020; Przybylska & Tokarczyk, 2022). However, the interpretation of these benefits is often weakened by repeated description of the same molecular pathways across multiple physiological sections. Rather than viewing antioxidant, anti-inflammatory, cardiometabolic, and anticancer effects as mechanistically independent, recent evidence supports a more integrated framework in which lycopene acts through a limited set of interconnected redox-, inflammation-, and growth-related pathways that are subsequently expressed in tissue-specific and disease-specific contexts (Maaz et al., 2025).

In cardiovascular health, lycopene has been shown to reduce LDL oxidation, inhibit HMG-CoA reductase, and lower systolic blood pressure. Daily supplementation (e.g., 60 mg/day for 3 months) significantly decreased LDL cholesterol by 14%, with effects comparable to statins in certain clinical trials (Przybylska, 2020). It also improves endothelial function and decreases the size of atheromatous plaques (Khan et al., 2021).

In oncology, epidemiological and in vitro studies support lycopene's role in reducing the risk of prostate, lung, colorectal, breast, and uterine cancers. Mechanistically, lycopene inhibits cancer cell proliferation, induces apoptosis, suppresses angiogenesis, and prevents metastasis by modulating ROS-sensitive pathways (Palozza et al., 2012; Przybylska, 2020). Lycopene derivatives such as apo-10′-lycopenoic acid also contribute to its anticancer effects by inducing phase II detoxification enzymes via Nrf2 activation (Linnewiel et al., 2009).

Furthermore, lycopene offers neuroprotective benefits. It mitigates neuronal apoptosis, modulates oxidative stress, and enhances synaptic signaling, with observed benefits in models of Alzheimer's and Parkinson's diseases (Khan et al., 2021). Its ability to cross the blood-brain barrier and regulate inflammation-associated kinases such as MAPK and ERK underlies its therapeutic potential in neurodegenerative conditions. Lycopene also supports skeletal health by modulating bone remodeling processes and inhibiting osteoclastogenesis, thereby reducing the risk of osteoporosis (Przybylska, 2020; Sołtysiak & Folwarczna, 2015).

4.1. Antioxidant properties

Lycopene exhibits one of the highest antioxidant capacities among dietary carotenoids, primarily due to its extensive system of 11 conjugated double bonds that efficiently quench singlet oxygen and neutralize a wide spectrum of reactive oxygen species (ROS) and free radicals (Di Mascio et al., 1989; Khan et al., 2021). Its singlet oxygen quenching rate constant exceeds that of β-carotene and α-tocopherol, making it particularly effective in preventing lipid peroxidation and oxidative DNA damage (Caseiro et al., 2020; Kulawik et al., 2024) (Table 2). Beyond direct radical scavenging, recent literature indicates that lycopene-associated antioxidant protection is also linked to broader redox-regulatory signaling, particularly the modulation of Nrf2/ARE-related cytoprotective responses, which helps explain its relevance across several chronic disease models (Lei et al., 2026).

In vitro and in vivo studies have demonstrated lycopene's ability to enhance the endogenous antioxidant defense system by upregulating enzymatic activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Li et al., 2020; Ranjbar Nedamani et al., 2019; Shafe et al., 2024). These enzymatic pathways are crucial in maintaining redox homeostasis and protecting cellular macromolecules from oxidative stress.

The antioxidant potency of lycopene is not solely dependent on its concentration but also on its isomeric form. Müller et al. (2011) demonstrated that cis-isomers, particularly 5Z-lycopene, possess superior scavenging activity against lipid peroxyl radicals compared to the all-trans form. These isomers are more bioavailable, less prone to aggregation, and more easily integrated into micellar systems that facilitate cellular uptake.

Additionally, lycopene-rich extracts obtained through optimized supercritical CO_2 extraction preserve antioxidant activity under controlled thermal and pressure conditions, with antioxidant potential remaining high below 70 °C (Yi et al., 2009). However, higher

Table 2
Health Benefits of Lycopene in Different Models.

Antioxidant properties			
Model/System	Intervention	Outcome Measures	References
HepG2 cells + H_2O_2	5–10 μM lycopene	↓ ROS, ↑ SOD, ↑ CAT, ↓ MDA	(Caseiro et al., 2020; Imran et al., 2020; Khan et al., 2021; Shafe et al., 2024)
Rats (CCl_4-induced damage)	10 mg/kg lycopene orally	↓ MDA, ↑ GSH, ↑ SOD activity	(Anlar & Bacanli, 2020; Imran et al., 2020; L. Li et al., 2020; Ranjbar Nedamani et al., 2019)
Human (MetS patients)	15–20 mg/day (6–12 wk)	↑ TAC, ↓ lipid peroxidation biomarkers	(Caseiro et al., 2020; L. Li et al., 2020; Ranjbar Nedamani et al., 2019; Shafe et al., 2024)
Cardiovascular benefits			
Study Population	**Lycopene Dose & Duration**	**Outcomes**	**References**
Overweight adults	15 mg/day for 8 weeks	↓ oxLDL, ↑ flow-mediated dilation (FMD)	(Caseiro et al., 2020; Imran et al., 2020; Khan et al., 2021; Ranjbar Nedamani et al., 2019)
Patients with hypertension	12 mg/day for 6 weeks	↓ SBP by ~5 mmHg, ↓ CRP	(Anlar & Bacanli, 2020; Imran et al., 2020; L. Li et al., 2020; Shafe et al., 2024)
Meta-analysis (12 RCTs)	10–30 mg/day (4–12 weeks)	↓ LDL-C (−9.3%), ↓ triglycerides, ↑ HDL	(Caseiro et al., 2020; Khan et al., 2021; L. Li et al., 2020; Ranjbar Nedamani et al., 2019)
Anticancer properties			
Model	**Target Cancer**	**Key Molecular Findings**	**References**
LNCaP prostate cells	Prostate cancer	↓ PSA, ↓ IGF-1, ↑ caspase-3	(Anlar & Bacanli, 2020; Caseiro et al., 2020; Imran et al., 2020; Khan et al., 2021)
MCF-7 breast cancer cells	Breast cancer	↓ cyclin D1, ↑ Bax/Bcl-2, ↑ G1 arrest	(Caseiro et al., 2020; Imran et al., 2020; Ranjbar Nedamani et al., 2019; Shafe et al., 2024)
HT-29 colon cancer cells	Colorectal cancer	↓ MMP-9, ↑ p53, ↓ cell proliferation	(Anlar & Bacanli, 2020; Caseiro et al., 2020; Khan et al., 2021; L. Li et al., 2020)
Retinal protective properties			
Model	**Lycopene Dose & Duration**	**Protective Mechanisms**	**References**
ARPE-19 cells + H_2O_2	5 μM (24 h)	↓ ROS, ↓ MDA, ↑ mitochondrial function	(Caseiro et al., 2020; Jing et al., 2021; Yeung et al., 2022)
Mice exposed to blue light	10 mg/kg/day for 14 days	↓ apoptosis, ↓ lipid peroxidation	(Anlar & Bacanli, 2020; Liang et al., 2021; Shafe et al., 2024; Zia-Ul-Haq et al., 2021)
Laser-induced CNV model	20 mg/kg orally for 2 weeks	↓ VEGF, ↓ neovascular area	(Khan et al., 2021; Tufail et al., 2024; Yeung et al., 2022)

temperatures promote isomerization and partial degradation, which may reduce efficacy depending on the extraction conditions.

Topically applied lycopene has also been shown to significantly enhance cutaneous antioxidant status and photoprotection. Andreassi et al. (2004) found that lycopene-based formulations offered superior protection against UV-induced oxidative damage compared to vitamin E and C combinations, likely due to lycopene's superior reductive potential and synergistic interaction with another lipid-phase antioxidants.

Ilahy et al. (2019) further confirmed that in high-lycopene tomato cultivars, lipophilic antioxidant activity (LAA) was strongly correlated with lycopene and total carotenoid content during ripening. These findings reinforce lycopene's dominant role among plant-derived antioxidants in tomatoes and its derivatives. Taken together, these findings indicate that the antioxidant role of lycopene should be interpreted not only as a direct chemical scavenging effect, but also as a central mechanistic basis that underpins many of its anti-inflammatory, cardiometabolic, and anticancer actions discussed in the following sections (Maaz et al., 2025).

4.2. *Anti-inflammatory and immunomodulatory effects*

Lycopene exhibits potent anti-inflammatory properties by modulating key signaling pathways involved in the inflammatory cascade. One of the primary mechanisms involves the downregulation of nuclear factor kappa B (NF-κB), a central transcription factor that regulates the expression of several pro-inflammatory cytokines and enzymes. Lycopene has been shown to significantly suppress the production of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), while inhibiting the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), both of which are markers of chronic inflammation (Caseiro et al., 2020; Shafe et al., 2024). Recent reviews further indicate that anti-inflammatory activity is one of the most consistently reported biological effects of lycopene, although the current evidence base remains substantially stronger in cellular and animal models than in human intervention studies, making a clear distinction between mechanistic plausibility and clinical substantiation essential (de Carvalho & Martinez, 2025).

In human colorectal cancer cells (SW480), lycopene treatment led to a dose-dependent reduction in mRNA and protein expression of TNF-α, IL-6, IL-1β, COX-2, and iNOS. It also reduced nitric oxide (NO) and prostaglandin E2 (PGE2) levels, confirming its suppression of NF-κB and JNK pathway activation (Cha et al., 2017). Similar results were observed in prostate cancer cells, where lycopene attenuated inflammation-related gene expression and significantly reduced tumor burden in vivo by downregulating inflammatory mediators (Jiang et al., 2019).

Animal models have also validated these findings. In a rat model of endotoxin-induced uveitis, lycopene pretreatment significantly lowered intraocular levels of IL-6, TNF-α, and NO, while histopathological analysis revealed reduced inflammatory cell infiltration comparable to dexamethasone, a standard corticosteroid therapy (Göncü et al., 2016). More recent preclinical studies have extended this anti-inflammatory profile to intestinal and barrier-associated models. Dietary lycopene pretreatment improved jejunal inflammation, intestinal barrier function, and microorganisms potentially associated with anti-inflammatory effects while reducing LPS-driven TLR4/NF-κB signaling in mice (Mou et al., 2025). In parallel, lycopene alleviated deoxynivalenol-induced enterotoxicity by suppressing MAPK/NF-κB activation and NLRP3 inflammasome signaling, supporting a broader role in inflammation control beyond classical cytokine inhibition alone (Cai et al., 2025).

Moreover, lycopene exerts immunomodulatory actions by enhancing anti-inflammatory cytokine production. Hazewindus et al. (2012) reported that lycopene upregulates interleukin-10 (IL-10), an immunosuppressive cytokine, contributing to the resolution of inflammation. When combined with ascorbic acid and α-tocopherol, lycopene exhibited synergistic effects in modulating inflammatory cytokines while complementing antioxidant activity.

A broader perspective provided by Maheshwari et al. (2022) underlines the immunostimulatory role of lycopene among other fruit-derived phytochemicals. It promotes lymphocyte proliferation, enhances T cell function, and modulates macrophage-mediated cytokine production, supporting both innate and adaptive immune responses. Taken together, these observations suggest that the anti-inflammatory role of lycopene should be interpreted not only in terms of cytokine suppression, but also through preservation of epithelial integrity and possible microbiota-linked modulation of inflammatory tone. Nevertheless, direct human evidence remains limited. A recent pilot intervention reported that daily intake of a lycopene-rich juice reduced

several circulating inflammatory markers, including IL-1β, TNF-α, IL-6, IL-17 A, IL-12p70, IL-23, and IL-33, in participants with obesity, supporting translational relevance while also underscoring the need for larger controlled trials and better population stratification (de Carvalho & Martinez, 2025; Jilcott Pitts et al., 2026).

4.3. Cardiovascular health

Lycopene exerts cardioprotective effects through multiple interrelated mechanisms, supported by epidemiological, clinical, and molecular evidence. Its strong antioxidant capacity plays a central role in reducing oxidative stress and lipid peroxidation, both of which are critical contributors to atherosclerosis and endothelial dysfunction. Lycopene inhibits low-density lipoprotein (LDL) oxidation, prevents foam cell formation, and downregulates adhesion molecules and inflammatory cytokines, thereby mitigating vascular inflammation and plaque development (Cheng et al., 2017; Müller et al., 2016; Przybylska & Tokarczyk, 2022). Recent evidence indicates that the cardioprotective role of lycopene should be interpreted primarily through vascular-specific outcomes, including endothelial function, blood pressure regulation, vascular inflammatory status, and thrombosis-related responses, rather than through repeated general references to antioxidant or anti-inflammatory activity alone (Nam et al., 2026).

Mechanistically, lycopene enhances endothelial function by upregulating endothelial nitric oxide synthase (eNOS), leading to improved nitric oxide (NO) bioavailability and vasodilation (Przybylska & Tokarczyk, 2022). It also suppresses pro-atherogenic markers such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and high-sensitivity C-reactive protein (hs-CRP), which are strongly associated with early atherogenesis (Böhm, 2018; Müller et al., 2016). From a mechanistic perspective, these cardiovascular effects appear most relevant at the level of LDL oxidation, endothelial nitric oxide bioavailability, adhesion-molecule expression, and vascular inflammatory tone, which together provide a more precise framework for discussing lycopene in cardiovascular prevention than broad pathway repetition across multiple sections (Nam, Hwang and Jang, 2026).

A systematic review and meta-analysis by Cheng et al. (2017) involving 25 studies found that higher serum lycopene levels were significantly associated with reduced risks of stroke (HR = 0.74), cardiovascular disease (HR = 0.86), and all-cause mortality (HR = 0.63). Another review by Costa-Rodrigues et al. (2018) confirmed that lycopene reduces systolic blood pressure and improves lipid profiles by lowering total and LDL cholesterol without significantly affecting HDL levels (Table 2).

Clinical intervention studies support these observations. In hypertensive individuals, lycopene supplementation (15–30 mg/day) over 8–12 weeks significantly reduced systolic blood pressure and improved flow-mediated dilation, a marker of vascular endothelial health (Thies et al., 2017). In addition, lycopene reduces HDL-associated inflammation and modulates HDL functionality toward an antiatherogenic phenotype, a novel mechanism contributing to vascular protection. Importantly, the current human evidence is more convincing for improvement in vascular endothelial function and blood pressure than for consistent lipid-profile modification. In a recent randomized, placebo-controlled, double-blind trial, lycopene-rich tomato juice significantly improved flow-mediated dilation after 12 weeks, while an umbrella review of systematic reviews and meta-analyses concluded that daily lycopene intakes of approximately 5–30 mg are associated most consistently with blood-pressure improvement, whereas lipid outcomes remain heterogeneous (Nam et al., 2026; Yoshida et al., 2025).

Moreover, lycopene influences thrombosis by reducing platelet aggregation and inhibiting pro-coagulant factors, potentially lowering the risk of acute thrombotic events. In vitro studies and small-scale trials demonstrate that lycopene-rich tomato extract decreases fibrinogen levels and reduces markers of platelet activation (Böhm, 2018).

4.4. Anti-cancer activity

Lycopene demonstrates significant anti-cancer properties by targeting multiple stages of tumorigenesis, including initiation, promotion, and progression. Its anticancer potential is mediated through both antioxidant-dependent and independent mechanisms that affect key molecular targets, signaling pathways, and cellular events involved in carcinogenesis (Anlar & Bacanli, 2020; Caseiro et al., 2020; Khan et al., 2021; Ranjbar Nedamani et al., 2019; Shafe et al., 2024). Recent evidence indicates that the anticancer role of lycopene should be interpreted primarily through cancer-relevant outcomes such as proliferation control, apoptosis induction, cell-cycle arrest, angiogenesis suppression, and inhibition of invasion and metastasis, rather than through repeated general references to oxidative stress modulation alone. At the same time, the strength of evidence remains uneven, with mechanistic support being strongest in cellular and animal models, whereas human evidence is still more convincing for risk association than for therapeutic efficacy in established cancer (Balali et al., 2025;Maaz et al., 2025 ; Yin et al., 2025).

One of the pivotal mechanisms is the induction of apoptosis, wherein lycopene modulates pro- and anti-apoptotic proteins. Studies show that lycopene upregulates Bax and caspase-3 while downregulating Bcl-2, leading to mitochondrial-mediated apoptosis across various cancer cell lines including prostate, breast, and hepatocellular carcinomas (Puah et al., 2021; Wang et al., 2021) (Table 2).

Additionally, lycopene interferes with growth factor signaling, particularly by suppressing the insulin-like growth factor-1 (IGF-1) axis and its downstream PI3K/Akt/mTOR pathway. This inhibition reduces cell proliferation, survival, and migration in cancer models (Ozkan et al., 2023; Wang et al., 2021).

Anti-metastatic effects are mediated through the downregulation of matrix metalloproteinases (MMP-2 and MMP-9), which are critical for extracellular matrix degradation, tumor invasion, and metastasis. Lycopene also reduces vascular endothelial growth factor (VEGF) expression, thereby suppressing angiogenesis (Kim & Kim, 2015; Ono et al., 2015; Puah et al., 2021). Recent molecular syntheses further support the recurrent involvement of apoptosis-related regulators, the IGF-1/PI3K/Akt/mTOR axis, VEGF, and MMP-mediated remodeling in lycopene-responsive cancer models, reinforcing the view that its anticancer effects are multi-targeted but still predominantly preclinical in nature (Maaz et al., 2025; Yin et al., 2025).

Preclinical studies confirm that lycopene arrests the cell cycle at G_0/G_1 or G_2/M phases depending on the cancer type, impairing the replication of transformed cells. This is often associated with inhibition of cyclins and cyclin-dependent kinases (CDKs) and activation of CDK inhibitors such as p21 and p27 (Ozkan et al., 2023; Puah et al., 2021).

Encapsulation strategies, such as whey protein isolate nanoparticles and niosomes, have been shown to improve the anticancer efficacy of lycopene by enhancing its stability, solubility, and tumor site delivery. These advanced delivery systems demonstrated superior cytotoxicity and tumor growth inhibition in breast cancer models compared to free lycopene (Jain et al., 2018; Sharma et al., 2016). This formulation dimension remains important because poor aqueous solubility and low bioavailability continue to limit translational performance, and newer reviews increasingly emphasize combination strategies and delivery-system optimization as prerequisites for improving clinical applicability (Yin et al., 2025).

Furthermore, a systematic review by Kapała et al. (2022) revealed that lycopene supplementation reduced tumor incidence, inhibited progression, and improved outcomes across 72 in vivo studies. The mechanisms varied depending on tumor type but consistently involved modulation of oxidative stress, apoptosis, angiogenesis, and immune responses. Recent prospective evidence has also strengthened the epidemiological relevance of lycopene. A 2025 systematic review and

dose-response meta-analysis of prospective cohort studies reported that higher dietary intake and higher blood lycopene levels were associated with lower overall cancer risk and lower cancer mortality, while a 2025 prospective cohort analysis in men at high cardiovascular risk suggested a protective association between higher lycopene intake and lower prostate cancer incidence. These findings support a preventive rather than therapeutic interpretation of the current human evidence and indicate that prostate cancer remains one of the most consistently implicated targets, although further controlled trials are still required (Balali et al., 2025; López-Solís et al., 2025).

4.5. Neuroprotective and cognitive effects

Lycopene demonstrates strong neuroprotective potential by mitigating oxidative stress, suppressing neuroinflammation, and modulating apoptosis-related pathways in the central nervous system. These effects are particularly relevant in the context of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and toxin-induced cognitive impairments (Anlar & Bacanli, 2020; Caseiro et al., 2020; Khan et al., 2021; Shafe et al., 2024). Recent findings indicates that the neuroprotective role of lycopene should be interpreted primarily through neuro-specific outcomes, including preservation of neuronal viability, mitochondrial integrity, synaptic plasticity, microglial homeostasis, and cognitive or motor performance, rather than through repeated general references to oxidative stress suppression alone (Tufail et al., 2024).

In PD models induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), lycopene significantly attenuated striatal dopamine depletion, improved motor performance, and reduced apoptosis through modulation of Bax/Bcl-2 and caspase pathways. Western blot analyses revealed lycopene's ability to restore mitochondrial integrity and decrease pro-apoptotic markers, suggesting its antiapoptotic and antioxidative efficacy (Prema et al., 2015). In Alzheimer's disease models, lycopene mitigates β-amyloid (Aβ)-induced cytotoxicity by inhibiting mitochondrial dysfunction, oxidative damage, and inflammatory cytokine release. Lycopene was shown to decrease lipid peroxidation, restore glutathione levels, and reduce hippocampal expression of pro-apoptotic proteins such as Bax and caspase-3, while increasing Bcl-2 levels, thus preventing neuronal apoptosis (El Morsy & Ahmed, 2020). More recent preclinical studies have expanded this neuroprotective profile beyond classical AD and PD models. In mice, functional-food lycopene ameliorated obesity-related cognitive decline, improved cognitive performance, and restored neuronal density through regulation of lipid metabolism and taurine- and glutathione-related neuroprotective pathways, while in chronic social defeat stress-induced mice it alleviated depression-like behavior by promoting hippocampal synaptic plasticity via the BDNF–TrkB pathway (Wu & Liu, 2025; Xu et al., 2025). More recently, lycopene also mitigated atrazine-induced hippocampal neuroinflammation and microglial efferocytosis dysfunction through MERTK-related regulation, indicating that microglial homeostasis may represent an additional neuro-specific target of action (Zhang et al., 2025).

Mechanistically, lycopene modulates key neuroprotective signaling cascades, including the MAPK/ERK/CREB/BDNF pathway. In models of bisphenol A-induced cognitive impairment, lycopene activated TrkB and downstream neurotrophic factors, restoring cognitive function as measured by Morris water maze and novel object recognition tests. These effects were correlated with reduced oxidative markers and enhanced acetylcholine esterase (AChE) activity, highlighting both antioxidant and cholinergic modulatory roles.

In addition, a comprehensive review by Chen et al. (2019) showed that lycopene crosses the blood–brain barrier and attenuates neurodegeneration in AD, PD, and Huntington's disease models by reducing ROS, restoring mitochondrial membrane potential, and activating the Nrf2 pathway. The compound also inhibits the nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) pathways, which are central to neuroinflammatory responses. Furthermore, Adeyeye et al. (2024) demonstrated that lycopene reduced cerebellar damage and improved motor coordination in lipopolysaccharide (LPS)-induced neurotoxicity, suggesting its potential in preserving cerebellar and cognitive function in AD-related conditions. Taken together, these findings support lycopene as a promising neuroprotective nutraceutical, but the evidence remains predominantly preclinical. Importantly, a 2025 systematic review of randomized controlled trials did not confirm a significant influence of lycopene intake on mental health outcomes, underscoring the need for longer, phenotype-specific human studies using validated cognitive and neuropsychiatric endpoints before strong clinical conclusions can be drawn (Głąbska et al., 2025).

4.6. Effects on metabolic syndrome and type 2 diabetes

Lycopene exerts significant regulatory effects on glycolipid metabolism, insulin sensitivity, and inflammation, which are key components of metabolic syndrome and type 2 diabetes mellitus (T2DM). Its protective role has been consistently demonstrated in both clinical and experimental models, acting through antioxidant, anti-inflammatory, and insulin-sensitizing mechanisms (Caseiro et al., 2020; Imran et al., 2020; Ranjbar Nedamani et al., 2019; Shafe et al., 2024). Recent evidence indicates that the metabolic role of lycopene should be interpreted primarily through outcomes related to insulin resistance, glycemic regulation, lipid handling, hepatic steatosis, and obesity-associated inflammatory burden, rather than through repeated general references to oxidative stress attenuation alone. At the same time, the current evidence base remains substantially stronger in experimental models than in human intervention studies, and recent syntheses emphasize that clinical translation is still limited by heterogeneity in formulation, dose, duration, and baseline metabolic status (Viña et al., 2025).

In animal models of T2DM induced by high-fat diet (HFD) and streptozotocin (STZ), lycopene supplementation (10–20 mg/kg/day) significantly improved fasting blood glucose, glycosylated hemoglobin (HbA1c), HOMA-IR index, and lipid profiles. It reduced serum triglycerides, total cholesterol, LDL-C, and restored HDL-C levels, reflecting improved insulin sensitivity and lipid handling (Yin et al., 2019). Lycopene also upregulated key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while lowering malondialdehyde (MDA) and oxidized LDL (ox-LDL) levels in pancreatic and hepatic tissues (Zheng et al., 2019).

At the molecular level, lycopene modulates the Nrf2 signaling pathway (Fig. 2), enhancing the cellular antioxidant response, and suppresses NF-κB and TNF-α signaling, reducing systemic and adipose tissue inflammation (Albrahim & Robert, 2022). This dual action not only protects pancreatic β-cells from oxidative stress-induced apoptosis but also improves insulin receptor sensitivity in peripheral tissues (Leh & Lee, 2022).

In addition, lycopene restores hepatic PPAR-γ expression, which plays a central role in adipocyte differentiation, lipid metabolism, and insulin action. Through this modulation, lycopene attenuates hepatic steatosis, fibrosis, and inflammation, as evidenced by decreased expression of TGF-β1, α-SMA, and inflammatory cytokines in obese rats (Albrahim & Alonazi, 2021). More recent translational work also suggests that obesity-associated inflammation may be one of the most responsive metabolic domains. In a 2025 pilot intervention, daily consumption of lycopene-rich juice reduced several circulating inflammatory markers in participants with obesity, but the study did not establish long-term glycemic efficacy or dose-response relationships. Accordingly, lycopene should presently be viewed as a promising adjunctive metabolic bioactive rather than a clinically validated stand-alone strategy for metabolic syndrome or T2DM management (Jilcott Pitts et al., 2026; Kulawik et al., 2024).

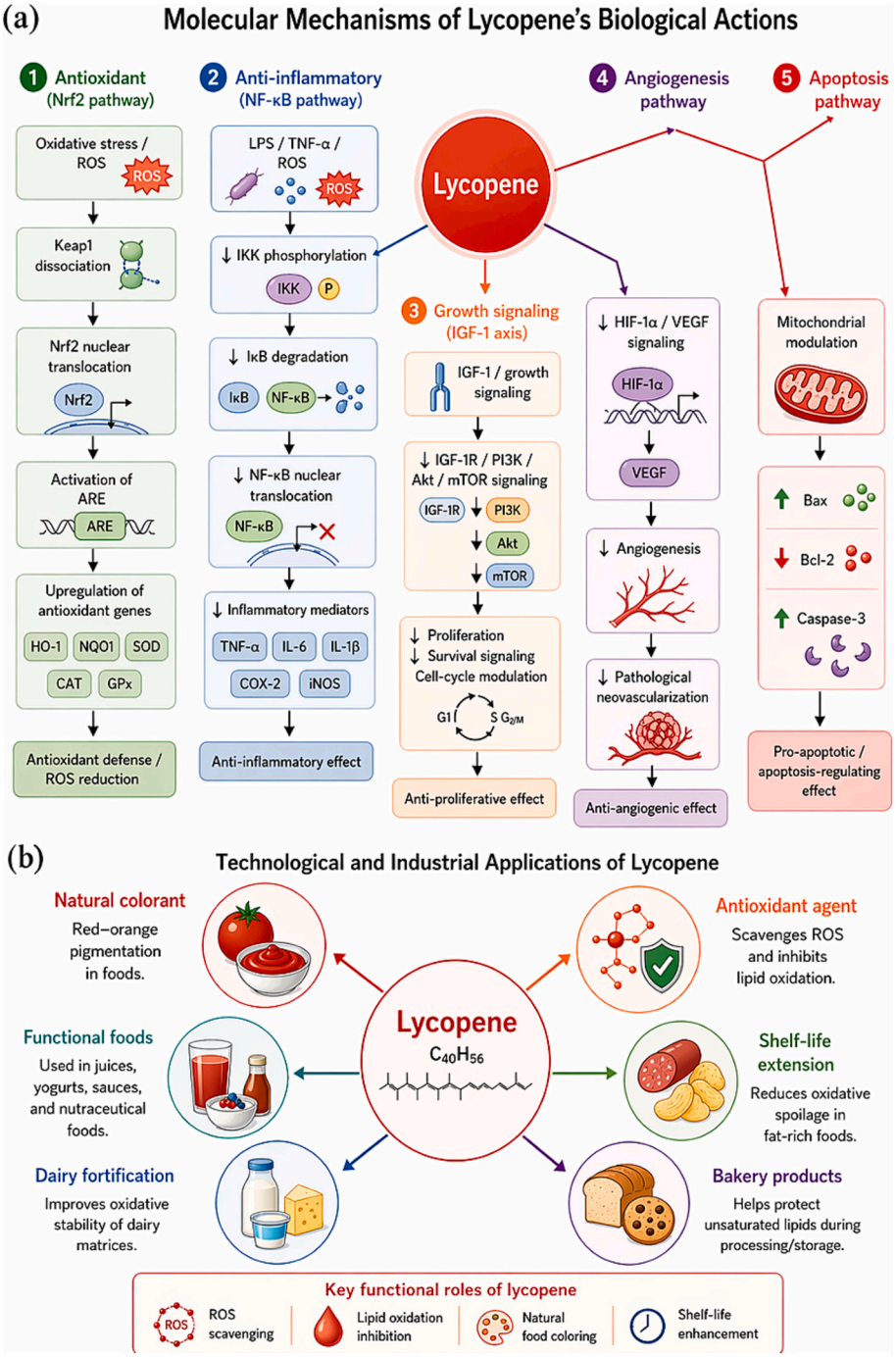

Fig. 2. Molecular mechanisms underlying the biological actions of lycopene and its technological and industrial applications.

5. Lycopene and eye health

Lycopene has emerged as a promising bioactive in ocular health because several major eye disorders are strongly linked to oxidative injury, chronic inflammation, mitochondrial dysfunction, and apoptosis. The retina, retinal pigment epithelium (RPE), and lens are especially vulnerable to oxidative stress owing to their high metabolic activity, continuous exposure to light, and abundance of oxidation-prone lipids. In this context, lycopene is of particular interest because its lipophilic nature favors localization within ocular tissues, where it may contribute to the control of reactive oxygen species, preservation of membrane integrity, attenuation of inflammatory signaling, and protection of cellular viability (Bungau et al., 2019; Johra et al., 2020; X. Li et al., 2023; Zia-Ul-Haq et al., 2021). Compared to other carotenoids, lycopene is a non-provitamin A compound but exhibits superior singlet oxygen quenching efficiency. These protective actions extend to modulating inflammatory responses, stabilizing mitochondrial membranes, and preventing photoreceptor apoptosis, thereby delaying or preventing retinal degeneration (Table 2).

5.1. Protection against age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is a leading cause of irreversible central vision loss in the elderly, characterized by progressive degeneration of the macula and retinal pigment epithelium (RPE). The pathophysiology of AMD involves a complex interplay of oxidative

stress, mitochondrial dysfunction, lipid peroxidation, complement activation, and chronic inflammation. Lycopene, a potent lipophilic antioxidant, has demonstrated significant protective effects against these pathological processes. It effectively scavenges reactive oxygen species (ROS), thereby reducing intracellular oxidative burden in RPE cells subjected to photic or chemical stress. Furthermore, lycopene exerts anti-inflammatory effects by inhibiting NF-κB activation and downregulating the expression of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), which are implicated in chronic retinal inflammation (Bungau et al., 2019; Zia-Ul-Haq et al., 2021). Additionally, lycopene exhibits anti-angiogenic properties by suppressing vascular endothelial growth factor (VEGF) expression, a key driver of neovascularization in wet AMD (Johra et al., 2020; Yeung et al., 2022). Its mitochondrial protective activity is also well-documented; lycopene maintains mitochondrial membrane potential, attenuates lipid peroxidation, and modulates apoptotic pathways by balancing Bax/Bcl-2 ratios and downregulating caspase-3 activity, thereby preserving photoreceptor and RPE cell viability (Jing et al., 2021; Liang et al., 2021). These effects should be interpreted mainly through AMD-specific outcomes, particularly preservation of RPE integrity, attenuation of retinal inflammation, control of neovascular signaling, and protection against mitochondrial-dependent apoptosis, rather than through repeated general references to antioxidant activity alone (Starvaggi et al., 2025). Preclinical studies support these mechanisms: dietary lycopene supplementation has been shown to improve retinal morphology and reduce oxidative damage markers in animal models of light-induced retinal injury. In vitro findings using ARPE-19 cell lines further corroborate lycopene's efficacy in mitigating mitochondrial dysfunction and oxidative lipid damage, underscoring its therapeutic potential in the prevention and management of AMD (Jing et al., 2021; X. Li et al., 2023). However, the current evidence remains predominantly experimental, and stronger human studies are still required before lycopene can be positioned as a clinically substantiated strategy for AMD prevention or management (Che et al., 2025; Starvaggi et al., 2025).

5.2. Cataract prevention

Cataracts, the predominant cause of blindness globally, develop primarily due to oxidative damage affecting lens proteins, epithelial cells, and fiber cell membranes. The lens, lacking vasculature and continuously exposed to light-induced oxidative stress, relies heavily on endogenous antioxidant systems to preserve its transparency and functional integrity. Oxidative insult leads to protein misfolding, aggregation, and opacification, hallmarks of cataractogenesis. Lycopene, a highly conjugated lipophilic carotenoid, has shown protective effects against these degenerative processes. It suppresses lipid peroxidation and protein carbonylation by scavenging free radicals, thereby preventing oxidative modification of lens membrane lipids and crystallins, key structural proteins essential for maintaining lens clarity. Furthermore, lycopene enhances the activity of critical antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which are responsible for detoxifying reactive oxygen species and preserving redox homeostasis within the lens epithelium (Kwatra, 2020; Tufail et al., 2024). It also maintains membrane integrity and inhibits calcium influx, thereby preventing the activation of calpain, a calcium-dependent protease involved in the degradation of lens proteins. In vivo studies, particularly in selenite-induced cataract models, have demonstrated that lycopene supplementation significantly delays the onset of nuclear lens opacity and preserves histological architecture, indicating its potential to mitigate cataract formation under oxidative stress conditions (Anlar & Bacanli, 2020; Caseiro et al., 2020). From an evidence-based perspective, the significance of lycopene in cataract prevention should be interpreted mainly through lens-specific outcomes, particularly preservation of crystallin stability, maintenance of membrane integrity, attenuation of oxidative protein damage, and delay of opacity development, rather than through repeated general references to antioxidant activity alone (Starvaggi et al., 2025; Tufail et al., 2024). These mechanistic insights support lycopene's role as a promising non-pharmacological intervention for cataract prevention, particularly among vulnerable populations such as diabetic individuals, aging adults, and those exposed to elevated oxidative burdens. Nevertheless, the current evidence remains largely experimental, and stronger human studies are required before lycopene can be considered a clinically substantiated strategy for cataract prevention (Starvaggi et al., 2025).

5.3. Synergistic role with other nutrients

The biological efficacy of lycopene in ocular tissues is significantly enhanced when administered in combination with other micronutrients involved in complementary antioxidant pathways, resulting in synergistic effects that surpass the impact of individual compounds. For instance, the combined intake of lycopene with lutein and zeaxanthin (xanthophyll carotenoids that selectively accumulate in the macula) provides comprehensive, spatially distributed antioxidant protection across multiple retinal layers. While lutein and zeaxanthin defend the inner retina and macula against phototoxic damage, lycopene penetrates deeper into the choroidal and peripheral retinal regions, offering broad-spectrum oxidative defense (Zia-Ul-Haq et al., 2021). Furthermore, co-supplementation with vitamins C and E enhances lycopene's redox capacity. Vitamin E, a lipid-soluble antioxidant, stabilizes lycopene in membrane structures, while vitamin C regenerates both oxidized lycopene and tocopherol radicals, thereby sustaining antioxidant cycling and reinforcing free radical neutralization (Brilyanda & Prajnaparamita, 2024). This mechanism exemplifies the nutrient network hypothesis, which posits that specific combinations of antioxidants exert superior protective effects through mutual regeneration and tissue-specific complementarity. Experimental evidence supports this model: Li and Yu (2023) demonstrated that co-administration of lycopene and lutein markedly reduced oxidative biomarkers and photoreceptor apoptosis in retinal tissues compared to single-agent treatments. These findings echo the principles underlying large-scale clinical trials, such as AREDS2, which highlighted the efficacy of multinutrient combinations in delaying the progression of age-related macular degeneration. Although lycopene was not part of the original AREDS formulations, its emerging profile, safety, and compatibility with other carotenoids underscore its potential for future inclusion in evidence-based ocular health strategies. Collectively, this synergistic role should be discussed mainly as a complementary ocular-support mechanism based on nutrient interaction, spatial antioxidant coverage, and cooperative redox cycling, rather than as isolated proof of a lycopene-specific clinical effect (Starvaggi et al., 2025; Tufail et al., 2024). Accordingly, lycopene currently appears most convincing as part of a broader multimicronutrient strategy for ocular protection, while its independent contribution still requires clearer clinical validation (Che et al., 2025; Starvaggi et al., 2025).

6. Industrial applications of lycopene

Lycopene has transitioned from a dietary antioxidant to a multifunctional compound with growing relevance across diverse industrial sectors, including food technology, nutraceuticals, pharmaceuticals, and cosmetics. Its physicochemical characteristics (namely, intense red coloration, high lipophilicity, and reactivity toward reactive oxygen species) make lycopene an attractive bioactive for functional formulation and processing innovation.

In the food industry, lycopene is widely used as a natural colorant and preservative due to its GRAS (Generally Recognized As Safe) status. Natural lycopene extracted from tomatoes or microbial sources is preferred over synthetic alternatives for clean-label products. Its application in dairy products, beverages, and meat analogs not only improves aesthetic appeal but also enhances antioxidant capacity and shelf life

(Ciriminna et al., 2016; Papaioannou et al., 2015).

In the cosmetic sector, lycopene is integrated into anti-aging creams, sunscreens, and skin-repair formulations owing to its capacity to scavenge singlet oxygen and protect skin from UV-induced damage. Its incorporation into lipid-based nanocarriers improves dermal penetration and stabilizes the active compound against oxidation (Ciriminna et al., 2016; Jing et al., 2021).

In pharmaceuticals and nutraceuticals, lycopene is marketed in tablets, capsules, syrups, and soft gels, either alone or in combination with vitamins and other carotenoids. It has shown therapeutic potential in managing oxidative stress-related disorders such as cardiovascular diseases, prostate cancer, and metabolic syndrome. Moreover, lycopene's anti-inflammatory and cytoprotective actions have opened avenues for its use in neurodegenerative and immune-related disorders (Ashraf et al., 2022; Ciriminna et al., 2016).

Technological advances have enabled more efficient lycopene recovery, including enzyme-assisted extraction, ultrasound, supercritical fluid extraction, and microemulsion techniques. Notably, microemulsion systems using natural surfactants like saponins have been optimized to extract lycopene from tomato pomace with minimal solvent use, offering an environmentally sustainable and cost-effective platform for industrial-scale recovery (Amiri-Rigi et al., 2016).

Furthermore, biotechnological production using engineered yeasts and bacteria such as *Saccharomyces cerevisiae*, *Yarrowia lipolytica*, and *Escherichia coli* has emerged as a robust alternative to traditional extraction methods. These microbial chassis enable scalable, sustainable production through the mevalonate or MEP pathways, allowing greater control over yield, purity, and cost (Jing et al., 2021).

Encapsulation technologies, particularly nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs), are being widely employed to improve lycopene's stability, solubility, and bioavailability during processing and storage. These delivery systems are also being explored in functional foods, nutraceutical beverages, and targeted drug delivery (Ashraf et al., 2022; Ciriminna et al., 2016).

6.1. Food and beverage industry

Lycopene is extensively utilized in the food and beverage industry both as a natural colorant (E160d) and a biofunctional ingredient (Fig. 2). Its vibrant red hue, derived from its conjugated polyene structure, makes it particularly appealing for product enhancement in juices, soups, sauces, dairy products, snacks, and ready-to-drink formulations (Pasupuleti & Kulkarni, 2014; Tufail et al., 2024; Zia-Ul-Haq et al., 2021) (Table 3).

In tomato-based and lycopene-fortified products, lycopene contributes not only to visual appeal but also to health value, offering antioxidative and cholesterol-lowering properties that align with the rising demand for functional foods (Bruno et al., 2007). For instance, pink guava beverages enriched with tomato-derived lycopene showed improved sensory quality and nutritional value, with lycopene content reaching up to 2010 μg/100 g and maintaining stability over six months at room temperature (Pasupuleti & Kulkarni, 2014).

Given lycopene's lipophilic and oxidation-prone nature, its incorporation into aqueous food systems requires innovative delivery methods to preserve its bioactivity. Emulsification technologies have emerged as efficient strategies to stabilize lycopene during processing and enhance its gastrointestinal bioavailability (Kim et al., 2014; Meroni & Raikos, 2018). For example, nanoemulsions with droplets under 100 nm offer high transparency, which is ideal for beverage applications without compromising visual clarity (Kim et al., 2014).

Thermal processing in the presence of dietary fats (e.g., olive or sesame oil) promotes the isomerization of all-trans lycopene into bioavailable cis-isomers. Products such as tomato soup and puree containing added vegetable oils show significantly increased proportions of (5Z)-lycopene, ranging from 27% to 50%, following controlled heat treatments at 120 °C (Honda et al., 2017). These findings support the design of lycopene-enriched products with optimized absorption profiles.

Table 3
Applications of Lycopene.

Food products			
Food Matrix	Functionality	Formulation Strategy	References
Yogurt, milk beverages	Antioxidant, pigment	Nanoemulsion, microencapsulation	(Tufail et al., 2024; Zia-Ul-Haq et al., 2021)
Sauces and purees	Nutritional enrichment	Thermal processing	(Brilyanda & Prajnaparamita, 2024; Liang et al., 2021)
Clear fruit beverages	Colorant, bioactive delivery	Liposomal carriers	(Kwatra, 2020; Zia-Ul-Haq et al., 2021)
Cosmetic products			
Product Type	**Skin Benefits**	**Formulation Technology**	**References**
Anti-aging serums	Reduces wrinkles, improves tone	Liposomes, emulsion gels	(Kwatra, 2020; ZH & BEKNAZAR, 2024)
Sunscreen creams	UV-block, anti-inflammatory	Solid lipid nanoparticles	(Tufail et al., 2024; Zia-Ul-Haq et al., 2021)
Whitening lotions	Brightening, antioxidant effects	Liposomal encapsulation	(Zia-Ul-Haq et al., 2021)

Furthermore, food preservation studies demonstrate that lycopene can extend shelf-life by inhibiting lipid peroxidation in meat and dairy systems, offering a natural alternative to synthetic antioxidants like TBHQ and BHA, which are restricted in several regions due to health concerns (Li & Yu, 2023; Xianquan et al., 2005).

6.2. Nutraceutical and dietary supplements

Lycopene is extensively formulated into nutraceutical products such as capsules, soft gels, functional beverages, powders, and chewable tablets, primarily targeting cardiovascular protection, oxidative stress mitigation, prostate cancer prevention, and male fertility enhancement (Henson et al., 2008; Khan et al., 2021). Daily supplementation doses range from 5 to 30 mg, with a favorable safety profile and documented efficacy across several randomized clinical trials and meta-analyses (Zia-Ul-Haq et al., 2021).

To overcome lycopene's poor aqueous solubility and vulnerability to oxidative degradation, several advanced delivery systems have been developed to enhance its stability, absorption, and bioavailability. Among these, chitosan-based nanoparticles have gained attention due to their mucoadhesive properties and capacity to promote intestinal uptake. Cyclodextrin inclusion complexes are also widely used, as they improve lycopene's dispersibility in aqueous environments and provide a protective matrix that shields the compound from enzymatic and acidic degradation in the gastrointestinal tract. Furthermore, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) offer additional benefits by enabling controlled release profiles, promoting tissue-specific delivery and extending lycopene's plasma half-life (Grabowska et al., 2019; Tufail et al., 2024).

In preclinical and clinical studies, these systems demonstrated significant increases in lycopene bioavailability compared to free lycopene (Antonuccio et al., 2020; Grabowska et al., 2019). For example, a chitosan-coated lycopene delivery platform enhanced antioxidant enzyme expression (CAT, GPx, SOD) and significantly reduced serum malondialdehyde levels in oxidative stress models (Imran et al., 2020).

Recent studies also highlight the synergistic effects of lycopene when combined with trace elements such as selenium, showing improved outcomes in testosterone levels, Bcl-2/Bax ratio, and apoptotic suppression in models of varicocele and testicular oxidative stress

(Antonuccio et al., 2020; Freni et al., 2023).

Consumer acceptance of lycopene-containing nutraceuticals is increasing globally. According to Henson et al. (2008), risk perception (e.g., of prostate cancer) and belief in lycopene's efficacy significantly influence purchase behavior, especially among men. Products combining lycopene with known health claims have successfully penetrated markets through education-driven marketing and clinical backing.

6.3. Cosmetics and dermatological products

Lycopene has emerged as a valuable active ingredient in modern dermatocosmetic formulations due to its potent antioxidant, anti-inflammatory, photoprotective, and anti-aging properties (Table 3). Its lipophilic nature allows it to localize in epidermal and dermal layers, where it neutralizes reactive oxygen species (ROS), prevents lipid peroxidation, and stabilizes cellular membranes, thus protecting skin from environmental stressors such as UV radiation, pollution, and oxidative insults (Stahl & Sies, 2012; Zia-Ul-Haq et al., 2021).

Topically applied lycopene protects against UV-induced erythema, reduces the expression of pro-inflammatory cytokines and matrix metalloproteinases (MMPs), and inhibits the activity of enzymes like collagenase and elastase (Cefali et al., 2015). Furthermore, studies have demonstrated lycopene's ability to stimulate collagen synthesis, improve

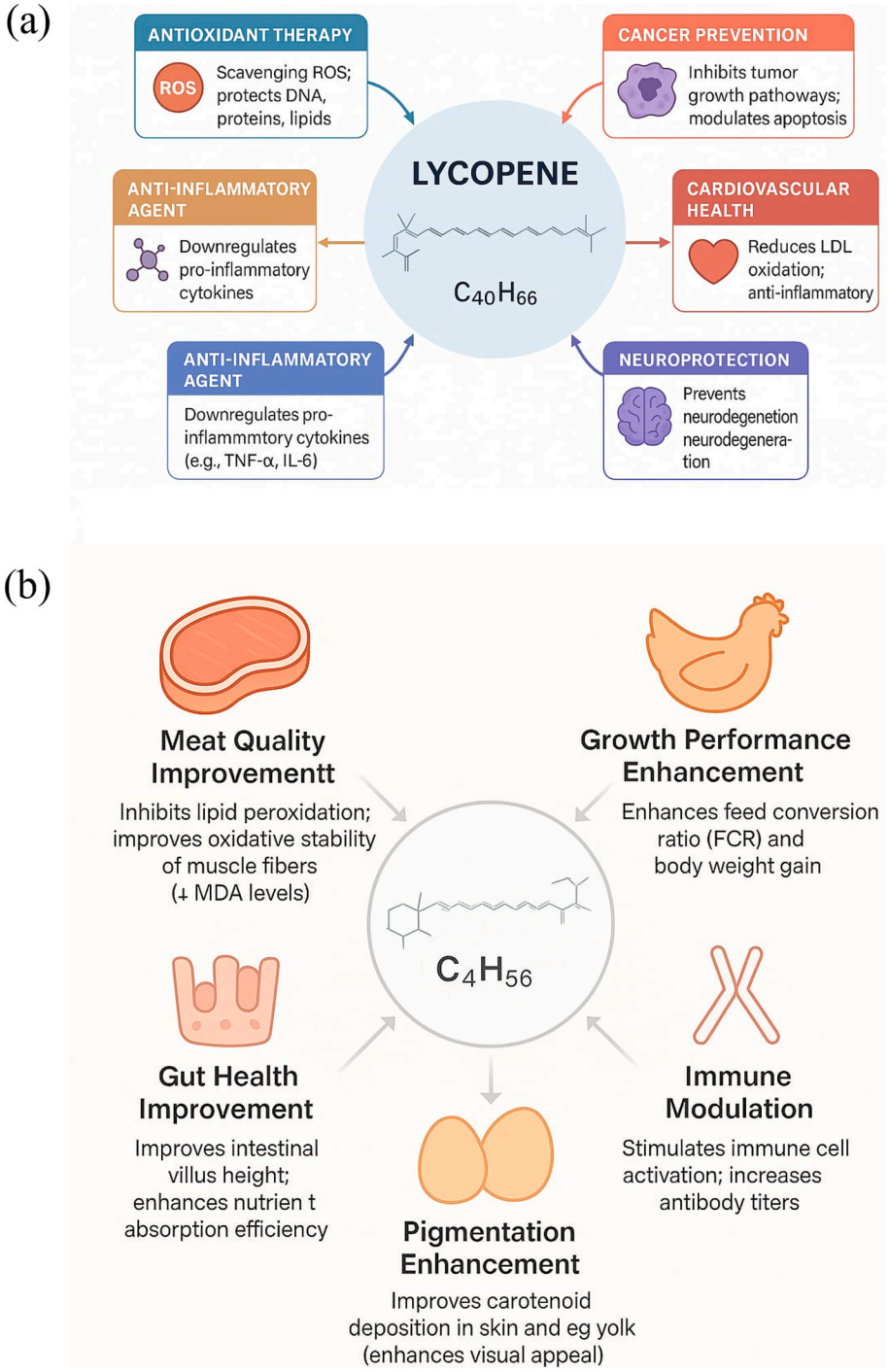

Fig. 3. Lycopene benefits in **(a)** human health and **(b)** livestock.

skin elasticity, reduce pigmentation, and support wound healing (Tarshish & Hermoni, 2023).

In formulation technology, lycopene is typically encapsulated in lipid nanoparticles, liposomes, polymeric hydrogels, and nanoemulsions, which enhance its photostability, improve dermal penetration, and prolong bioactivity (Cefali et al., 2015; Turcov et al., 2021). These advanced carriers maintain the integrity of lycopene under formulation stress and facilitate its controlled release within the skin, which is crucial for continuous protection and rejuvenation.

Recent clinical studies confirm the effectiveness of oral lycopene-based supplements, such as Lycomato™, in improving transepidermal water loss (TEWL), skin firmness, smoothness, and overall appearance in women over 12 weeks of daily use (Tarshish & Hermoni, 2023). Additionally, golden tomato extract, which contains high levels of phytoene and phytofluene alongside lycopene, was shown to modulate gene expression in dermal fibroblasts, enhancing skin immunity, DNA repair, and detoxification pathways, while significantly reducing TEWL (Tarshish et al., 2022).

6.4. Pharmaceutical and biomedical applications

Lycopene has garnered significant attention in pharmaceutical and biomedical research for its broad-spectrum bioactivity (Fig. 3), particularly its roles in mitigating oxidative stress, chronic inflammation, metabolic dysregulation, and cellular degeneration. Its capacity to modulate molecular pathways such as NF-κB, PI3K/Akt, and Nrf2, combined with low toxicity and favorable safety profile, has positioned lycopene as a promising adjunct or active therapeutic compound in a range of chronic and degenerative disorders (Jing et al., 2021; Tufail et al., 2024).

To enhance its clinical viability, lycopene has been incorporated into advanced drug delivery systems, including polymeric micelles, dendrimers, nanostructured lipid carriers (NLCs), and lipid-core nanocapsules. These systems improve bioavailability, tissue specificity, and pharmacokinetics, enabling sustained and targeted release of lycopene, particularly in pathologies where oxidative stress and inflammation are central (Brilyanda & Prajnaparamita, 2024; Jing et al., 2021).

In oncology, lycopene-loaded liposomes and SLNs have shown promise in potentiating the cytotoxic effects of conventional chemotherapeutics such as doxorubicin and cisplatin, while protecting non-cancerous tissues from oxidative injury. Lycopene modulates apoptosis-related genes (e.g., Bax/Bcl-2, caspase-3) and suppresses pro-survival signaling pathways, thereby enhancing chemosensitivity and minimizing systemic toxicity. Several in vivo studies confirm tumor volume reduction, decreased angiogenesis, and improved histopathological profiles when lycopene is co-delivered with anticancer agents (Jing et al., 2021).

In neurology, lycopene exhibits the rare ability among dietary antioxidants to cross the blood–brain barrier. In experimental models of Alzheimer's and Parkinson's diseases, lycopene reduces reactive oxygen species (ROS) accumulation, attenuates neuroinflammation, and prevents mitochondrial dysfunction in neuronal cells. These effects are associated with improved cognitive performance, restoration of acetylcholine activity, and inhibition of pro-apoptotic signaling cascades (Brilyanda & Prajnaparamita, 2024).

Additionally, in metabolic syndrome, lycopene-loaded nanocarriers targeting the liver, adipose tissue, and pancreas have demonstrated efficacy in improving insulin sensitivity, reducing lipid accumulation, and downregulating inflammatory markers such as TNF-α, IL-6, and CRP. These therapeutic effects are particularly relevant for the development of non-pharmacologic interventions for type 2 diabetes and obesity-related complications.

6.5. Textile and functional materials

The use of lycopene as a natural pigment in textile finishing is gaining interest, particularly for applications requiring UV-blocking and antimicrobial functions. Lycopene can be embedded into polymeric fibers or applied as a finishing extract to impart natural red tones and enhance fabric stability against sunlight-induced degradation. In recent trials, lycopene-treated cotton and viscose fabrics exhibited reduced microbial colonization and retained colorfastness after multiple washing cycles (Bhavana Garapati & Malaiappan, 2023). These properties support lycopene's role in the development of bio-based textiles with added functional value.

6.6. Animal feed and veterinary applications

Lycopene supplementation in animal diets (Fig. 3), particularly in poultry and swine, has been associated with improved antioxidant status, growth performance, and immune modulation. In broilers, dietary lycopene (15–30 mg/kg feed) has been shown to reduce malondialdehyde levels, improve feed conversion ratio, and enhance meat oxidative stability (Sahin et al., 2018). Moreover, in swine, lycopene improves semen quality and reduces testicular oxidative stress, suggesting applications in reproductive management (Aitken et al., 2022). These benefits position lycopene as a valuable natural feed additive in livestock systems seeking alternatives to synthetic antioxidants and growth promoters.

6.7. Environmental and biosensing technologies

Recent explorations have proposed lycopene as a component in environmental remediation systems, including biosensors and photocatalytic composites. Its strong ROS-scavenging capability and redox potential enable its integration into nanocomposite films for the detection and removal of oxidative pollutants in water and air. For example, lycopene-modified ZnO nanoparticles have demonstrated enhanced photocatalytic degradation of organic dyes under sunlight (Das & Choudhuri, 2023).Though still in the early stages, these innovations highlight lycopene's versatility in the field of sustainable environmental technologies.

7. Extraction techniques of lycopene

Efficient extraction of lycopene is fundamental to its commercial application in food, pharmaceutical, and cosmetic industries (Fig. 4). Lycopene's lipophilic character, sensitivity to heat and oxidation, and structural isomerization demand carefully controlled techniques. Conventional methods remain prevalent, but emerging technologies now offer greener, more efficient, and higher-yielding alternatives (Table 4). Recent studies further indicate that lycopene extraction technologies should be evaluated not only by recovery yield, but also by solvent safety, energy demand, selectivity, thermal and isomeric stability, food-grade suitability, scalability, and environmental burden, because these criteria ultimately determine whether a method remains a laboratory optimization tool or becomes industrially deployable (Joshi et al., 2025; Mutmainah et al., 2026). (See Table 5.)

7.1. Conventional solvent extraction (CSE)

Conventional solvent extraction (CSE) is widely employed due to its simplicity and cost-effectiveness. It typically involves solvents such as hexane, acetone, ethanol, and ethyl acetate, often in binary or ternary mixtures. The most cited combination has shown effective recovery of all-trans lycopene from tomato pulp and processing residues (Jiang et al., 2019; Myong-Kyun et al., 2013). However, CSE presents key drawbacks including solvent toxicity, low selectivity, high energy consumption, and environmental burden. These limitations hinder its suitability for large-scale, food-grade applications.

Recent studies advocate replacing petroleum-derived solvents with green alternatives such as ethyl lactate, limonene, and vegetable oils,

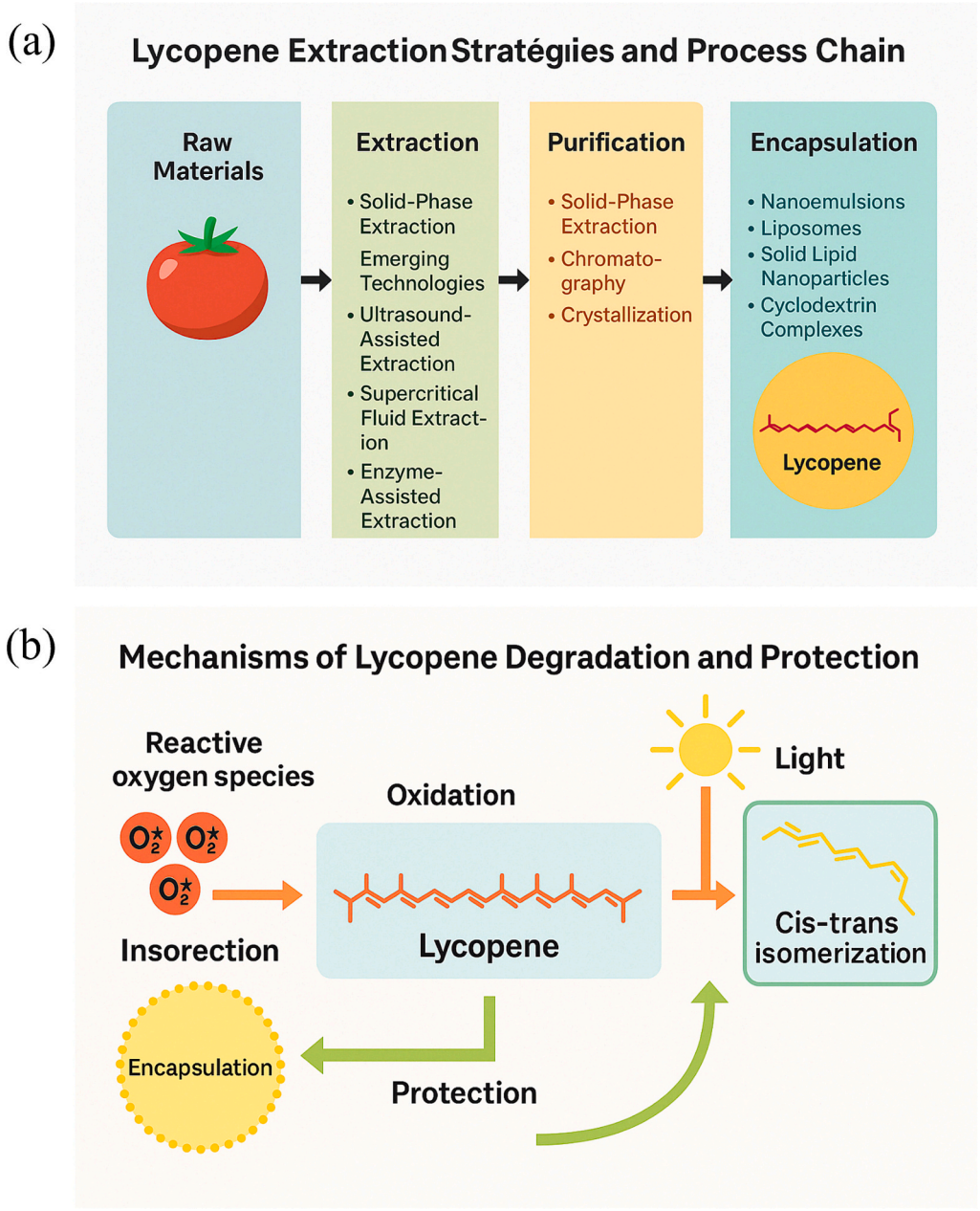

Fig. 4. **(a)** Lycopene extraction strategies and processing chain **(b)** Mechanisms of lycopene degradation and protective strategies.

which are biodegradable, non-toxic, and consumer-acceptable (Jazaeri et al., 2018; Kehili et al., 2018). For instance, coconut oil exhibits superior solubility for lycopene compared to olive or soybean oil due to its saturated fatty acid profile, improving both yield and oxidative stability (Deng et al., 2021; Kunthakudee et al., 2020).

7.2. *Ultrasound-assisted extraction (UAE)*

Ultrasound-assisted extraction (UAE) is a powerful non-thermal method that enhances mass transfer and solvent penetration through acoustic cavitation. The rapid collapse of microbubbles causes mechanical disruption of cell walls, releasing intracellular lycopene into the solvent phase. UAE improves extraction yields by 2–3 fold and significantly reduces processing time and temperature. It is particularly compatible with green solvents and edible oils, making it attractive for functional food formulations (Deng et al., 2021; Jiang et al., 2019).

7.3. *Microwave-assisted extraction (MAE)*

Microwave-assisted extraction (MAE) leverages dielectric heating to accelerate solvent-matrix interactions. It creates localized superheating, increasing cell permeability and facilitating rapid release of lycopene. A key benefit of MAE is its ability to induce isomerization of all-trans lycopene into cis-isomers, which are more soluble in bile micelles and better absorbed in the intestine (Lu et al., 2020; Zhou et al., 2023). MAE shortens extraction time to less than 10 min and enhances the antioxidant capacity of the extract.

7.4. *Supercritical fluid extraction (SFE)*

Supercritical fluid extraction (SFE) using CO_2, with or without ethanol as a co-solvent, is recognized as a clean and efficient lycopene extraction method. SFE operates at moderate temperatures (40–60 °C) and high pressures (250–400 bar), preventing oxidative degradation and

Table 4
Comparative Performance of Lycopene Extraction Methods and Delivery Stability.

Extraction methods					
Technique	Yield (mg/100 g)	Extraction Time	Energy Use	Solvent Toxicity	References
CSE (hexane mix)	5–20	3–6 h	High	Moderate–High	(Deng et al., 2021; Jiang et al., 2019)
UAE	25–40	30–60 min	Moderate	Low	(Deng et al., 2021; Tufail et al., 2024)
MAE	30–45	15–30 min	Low	Low	(Jiang et al., 2019; Lu et al., 2020)
SFE	20–50	1–2 h	Low	None	(Deng et al., 2021; Zia-Ul-Haq et al., 2021)
EAE	25–35	2–4 h	Low	Low	(Jiang et al., 2019; Tufail et al., 2024)
Stability in Delivery Systems					
Carriers	**Encapsulation Method**	**Retention After 30 Days (%)**	**Storage Temperature**	**Light Condition**	**References**
Corn oil	Unencapsulated	<20	25 °C	Light	(D. Wang et al., 2024)
Ovalbumin	HIPE	~65	25 °C	Light	(D. Wang et al., 2024)
Ovalbumin-chitosan complexes	HIPE (5% complex)	98.2	25 °C	Not mentioned	(D. Wang et al., 2024)
Solid particles stabilizer	Pickering Emulsion	~90	Refrigerated (4°C)	Not mentioned	(Gao et al., 2023; Murakami et al., 2022)
Lipid-based carrier	SLNs	~70	Room temperature	Dark	(Nazemiyeh et al., 2016)

Table 5
Engineered Microbial Systems and Spectroscopic Techniques for Lycopene Production and Detection.

Strain / System Used	Engineering Strategy	Metabolic Targets / Pathways	Yield Achieved	Key Highlights	Study
Engineered *E. coli* BL21 (DE3) with lycopene biosynthetic genes	Chromosomal integration of crtE, crtB, crtI; endotoxin removal using supercritical CO_2 (SC-CO_2)	Heterologous carotenoid pathway; endotoxin-free recovery	Highly pure lycopene (quantitative yield not specified)	Innovative endotoxin-free extraction avoiding downstream purification; pharmaceutical suitability enhanced	(Puniredd et al., 2025)
E. coli with plasmid pTB-EI4B expressing crtE, crtB, crtI from *Pantoea ananatis*	Optimized operon with arabinose-inducible promoter; low-copy plasmid; controlled temperature induction	MEP pathway; crtE, crtB, crtI; enhanced precursor flux via idi	260 mg/L after 60 h in shake flask culture	Balanced gene expression and optimized cultivation parameters (inducer concentration, temperature) emphasized	(S.-W. Kim et al., 2009)
E. coli CAR001 and derived LYC010 strain	MEP pathway refinement; crtX and crtY knockouts; overexpression of dxs, idi; ribosome binding site (RBS) library tuning	Carotenoid synthesis and upstream central metabolic pathways; enhanced ATP/NADPH availability	3.52 g/L in fed-batch fermentation; 50.6 mg/g dry cell weight (DCW)	Achieved record-high titer through combinatorial engineering, regulatory optimization, and precursor flux balance	(Sun et al., 2014)
E. coli with synthetic lycopene biosynthetic pathway	Iterative promoter strength optimization; modular separation of biosynthetic pathways; dual-phase induction strategy	Upstream (dxs, idi, ispDF) and downstream (crtE, crtB, crtI) pathway modularization	1.23 g/L lycopene	Optimized timing and balance of precursor and product pathway expression through modular engineering	(Zhu et al., 2015)
Recombinant *E. coli* BL21	CRISPR interference (CRISPRi) targeting competing pathways; crtEBI, fni, idi pathway overexpression	Enhanced Farnesyl pyrophosphate (FPP) and MEP pathway flux	4.2 g/L lycopene	Effective combination of CRISPRi and metabolic pathway overexpression yielding high productivity	(Zhao et al., 2022)
E. coli with evolved truncated HMGR (tHMGR) and MVA pathway	Directed evolution of tHMGR enzyme; optimized fermentation strategy; membrane engineering	Mevalonate pathway; enhanced flux via tHMGR, ispA, idi; improved membrane permeability	5.1 g/L (fed-batch fermentation)	Membrane stress reduction and flux enhancement through directed evolution, synthetic biology, and bioprocess optimization	(Xie et al., 2023)
Portable Vis-SWNIR spectrophotometer (410–940 nm) with AS7265x multispectral sensor on Arduino Uno platform	Logistic Regression (LR), Linear Discriminant Analysis (LDA), Random Forest (RF), Artificial Neural Networks (ANN), Support Vector Machine (SVM)	ANOVA-identified key wavelengths (14 significant bands); noise reduction via 3D-printed sensor housing	ANN: highest accuracy (95%); LDA/SVM (90%); LR/RF (80%); validated using confusion matrix	Integration of open-source hardware/software with machine learning enabling cost-effective, real-time lycopene quantification in tomatoes	(A. Sharma et al., 2024)
Near-infrared hyperspectral imaging (480.80–1002.20 nm) for lycopene visualization and quantification	Support Vector Classification (SVC), Support Vector Regression (SVR), Partial Least Squares Regression (PLSR)	Spectral preprocessing via SNV transformation; wavelength selection by CARS algorithm	SVR achieved high predictive accuracy (R^2 = 0.9652, RMSEP = 0.0166 mg/kg); effective spatial visualization with pseudo-color maps	Accurate quantification and spatial distribution visualization of lycopene, enabling maturity assessment and content determination	(Dai et al., 2023)
Handheld NIR device (740–1070 nm) for in-situ prediction of lycopene changes due to processing	Partial Least Squares (PLS), Random Forest (RF), Support Vector Regression (SVR)	Savitzky-Golay smoothing and MSC preprocessing	SVR model with R^2 = 0.94 validated externally	Portable NIR spectroscopy combined with ML for rapid, reliable field-level lycopene assessment during processing	(Emsley et al., 2021)
Short-wave infrared (SWIR) hyperspectral imaging (980–1600 nm)	Regression models (PLSR, SVR), Linear Discriminant Analysis (LDA)	SNV preprocessing, CARS wavelength selection (1200–1400 nm)	SVR best model (R^2 = 0.973); LDA 98.3% accuracy	Non-destructive quantification of lycopene during storage; intelligent packaging potential	(Y. Wang et al., 2023)

preserving the thermodynamically stable all-trans isomer. The selectivity of CO_2 for non-polar compounds makes it ideal for lycopene

extraction, yielding high-purity, solvent-free products (Jiang et al., 2019; Montesano et al., 2008). Innovations in flow modulation and static-dynamic extraction cycles have improved SFE reproducibility and scalability.

7.5. Enzyme-assisted extraction (EAE)

Enzyme-assisted extraction (EAE) utilizes cell wall-degrading enzymes (e.g., pectinase, cellulase, protease) to break down polysaccharide matrices and enhance lycopene release. Operating at mild conditions (pH 4–5, 40–50 °C), EAE avoids thermal degradation and supports integration with other techniques such as UAE. Studies have shown up to 25–30% higher yields when EAE is used in combination with ethanol or sunflower oil (Deng et al., 2021; Hussain et al., 2017).

7.6. Pressurized liquid extraction (PLE)

Also known as Accelerated Solvent Extraction (ASE), PLE applies high pressure and subcritical temperatures (100–200 °C) to maintain solvents in liquid state above their boiling points. This enhances diffusion, solvent penetration, and lycopene solubilization. When optimized, PLE achieves rapid extraction within 10–20 min and high yields without significant degradation, especially when using ethanol as a solvent (Ashraf et al., 2022; Deng et al., 2021).

7.7. Anti-solvent precipitation and crystallization

Anti-solvent techniques involve dissolving lycopene in a compatible organic solvent, followed by precipitation with a non-solvent such as ethanol or water, enabling recovery in crystalline form. This method allows controlled purification, avoids thermal damage, and is increasingly used in conjunction with UAE or SFE for lycopene enrichment (Myong-Kyun et al., 2013). From a comparative perspective, conventional solvent extraction remains attractive because of its simplicity and low equipment demand; however, its solvent burden, lower selectivity, and weaker environmental profile limit its suitability for modern food-grade scale-up. In contrast, (Drosou et al., 2025) showed that a hybrid UAE–MAE approach using ethyl lactate achieved high lycopene recovery from tomato peels, illustrating the value of intensified green extraction for tomato by-product valorization. (Mutmainah et al., 2026) further indicate that supercritical CO_2 is among the most industrially promising approaches because it combines high purity with safe, recyclable solvents, whereas greener solvent systems may be especially useful for environmentally oriented process development at smaller scale. Likewise, (Joshi et al., 2025) stress that emerging extraction systems should be selected according to the intended product format, required purity, oxidative stability, and cost-performance balance rather than recovery yield alone. Overall, no single extraction route is universally optimal; instead, method selection should be guided by the final application, solvent constraints, desired carotenoid integrity, and industrial scalability.

8. Purification and formulation processes

Following the extraction of lycopene from natural matrices, downstream processing involves its purification and formulation to enhance stability, bioavailability, and product compatibility. Crude lycopene extracts often contain unwanted pigments, waxes, and lipid-soluble impurities, necessitating further refinement to meet quality standards for food, pharmaceutical, and cosmetic applications.

8.1. Purification methods

Solid-phase extraction (SPE) is frequently employed as a rapid, selective method for lycopene purification, particularly when using C18 silica-based cartridges. SPE is suitable for separating lycopene from co-extracted carotenoids and degradation products in low-viscosity solvents (Berman et al., 2017).

Column chromatography, particularly open-column silica gel chromatography, remains a widely used technique for lycopene fractionation and isolation. Elution with gradient mixtures of hexane, ethyl acetate, or acetone allows effective separation based on polarity. While highly effective, this method is labor-intensive and less scalable (Niu et al., 2024).

Crystallization and anti-solvent precipitation are increasingly adopted due to their scalability and eco-compatibility. By dissolving crude lycopene in a non-polar solvent (e.g., dichloromethane or ethyl acetate) and gradually adding an anti-solvent (e.g., ethanol or methanol), purified lycopene precipitates under controlled temperature and agitation conditions (Deng et al., 2021; Myong-Kyun et al., 2013). Recent advancements also include membrane-based separations, such as nanofiltration or supercritical CO_2 anti-solvent fractionation, which offer solvent-free recovery with reduced thermal degradation (Castro-Muñoz, 2024).

8.2. Formulation and stabilization strategies

Due to its high susceptibility to light, oxygen, and heat, lycopene is often formulated into protective delivery systems to improve its shelf-life, solubility, and bioefficacy. Among the most effective encapsulation technologies are nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cyclodextrin inclusion complexes. Nanoemulsions, with droplet sizes typically between 20 and 200 nm, significantly increase surface area and dispersion of lycopene in aqueous media. Stabilizers such as whey protein isolate, lecithin, and modified starch have been shown to protect lycopene in functional beverages (Khan et al., 2021). Liposomes, composed of phospholipid bilayers, effectively entrap lycopene in their hydrophobic cores, shielding it from oxidation and improving its transport across biological membranes, making them suitable for both oral and topical delivery (Tufail et al., 2024). SLNs and NLCs, made from biocompatible lipids like mono-, di-, and triglycerides, allow for controlled release and targeted delivery, and are frequently used in dermocosmetic formulations due to their stability and compatibility with skin barriers (Amorim et al., 2022). Cyclodextrin inclusion complexes, particularly those based on β-cyclodextrin, enhance the water solubility and photostability of lycopene through non-covalent interactions and are widely adopted in dietary supplements and powders (Imran et al., 2020).

Collectively, these advanced formulation strategies not only protect lycopene from environmental degradation but also enhance its physicochemical stability, cellular uptake, and biological activity. Current innovations are exploring hybrid delivery systems, responsive release carriers, and co-encapsulation with synergistic bioactives to further improve performance and broaden the scope of lycopene applications in functional foods, nutraceuticals, and cosmeceuticals (Li & Yu, 2023; Zhou et al., 2023). Beyond oral and topical delivery, formulation-oriented stabilization can also be extended to preservation systems in which lycopene is incorporated into packaging matrices to protect food quality during storage.

8.2.1. Active packaging and food preservation

Lycopene's antioxidant and antimicrobial activities make it an ideal bioactive for active food packaging systems. Incorporating lycopene into biodegradable films enhances the shelf life of perishable foods by inhibiting lipid oxidation and microbial proliferation. For instance, lycopene-enriched starch films have been shown to reduce peroxide values and microbial load in stored chicken breast over 10 days at refrigeration temperatures (Nikmanesh et al., 2023). Additionally, nanostructured lycopene coatings are under development to create oxygen-scavenging and UV-protective layers in eco-packaging for dairy and oily foods (Bhatia et al., 2023).

From a comparative standpoint, the principal formulation and

stabilization systems for lycopene differ more by application fit than by any universal superiority. Nanoemulsion or self-emulsifying systems are particularly attractive when rapid dispersion and improved intestinal solubilization are required, as recent work showed enhanced proximal-intestinal bioaccessibility for MCT-based lycopene self-emulsifying systems (Lin et al., 2025). Liposomes remain especially useful when membrane compatibility and food or topical delivery are priorities, and recent lycopene-specific work has shown that surface-modified liposomes can improve physicochemical stability and biocompatibility in functional-food-oriented systems (Lin et al., 2025). By contrast, SLNs and especially NLCs are generally more relevant when controlled release and storage stability are prioritized, because NLCs typically offer higher loading capacity and lower expulsion risk than SLNs (Jacob et al., 2025). Cyclodextrin-based systems are most valuable when the objective is to improve water dispersibility, powder incorporation, or protection of lipophilic antioxidants through inclusion complexation (Jug et al., 2025). Following the relocation of active packaging to this section, packaging-oriented stabilization should be viewed separately from oral or topical delivery, since its main objective is not systemic bioavailability but oxidative protection, UV shielding, and shelf-life extension; for example, lycopene-microcapsule starch/alginate films recently improved film stability and extended blueberry shelf life in a biodegradable packaging format (Li et al., 2025). Overall, the most appropriate carrier should therefore be selected according to the intended end use rather than on encapsulation efficiency alone.

9. Industrial-scale production and biotechnology advances

While the majority of commercial lycopene is still sourced from tomato fruits and processing by-products, biotechnological innovations have dramatically enhanced the feasibility of large-scale, non-agricultural lycopene production. Current production strategies are centered mainly on microbial fermentation and plant-based bioreactors, both of which are being explored as scalable and more controllable alternatives to conventional crop-dependent sourcing (Rebelo et al., 2025; Saubenova et al., 2024; Wang et al., 2023).

9.1. Microbial fermentation

To meet growing industrial demand, microbial production of lycopene through synthetic biology and metabolic engineering has emerged as one of the most promising alternatives to plant-based extraction. Engineered strains of *Escherichia coli*, *Saccharomyces cerevisiae*, and *Yarrowia lipolytica* have been widely investigated for lycopene biosynthesis through optimization of precursor supply, carbon-flux redistribution, cofactor balancing, and pathway engineering of the mevalonate or MEP routes. These microbial platforms are especially attractive because they can be cultivated under controlled conditions and can use relatively inexpensive substrates, including agro-industrial by-products (Lee et al., 2025; Saubenova et al., 2024; Wang et al., 2023).

Microbial productivity has been further improved through overexpression of key biosynthetic enzymes, elimination of competing pathways, adaptive evolution, and CRISPR-enabled genome engineering. In *S. cerevisiae*, for example, adaptive evolution and metabolic engineering have been used to enhance precursor supply and lycopene accumulation, while broader biotechnology reviews consistently identify strain robustness and pathway fine-tuning as central determinants of industrial performance (Lee et al., 2025; Wang et al., 2023).

In filamentous fungi such as *Blakeslea trispora*, lycopene production is induced by co-cultivation of complementary mating types and nutrient optimization. This organism remains one of the best-established natural microbial routes for carotenoid production and is still relevant from an industrial perspective because it offers a non-synthetic microbial source of lycopene (Saubenova et al., 2024).

From a comparative perspective, engineered bacteria and yeasts offer stronger metabolic controllability, faster process optimization, and better compatibility with standardized fermentation systems, whereas *B. trispora* remains attractive as a more conventional natural-production platform. Overall, microbial fermentation is particularly promising for ensuring non-seasonal supply, high process control, and scalable production, although downstream purification, regulatory acceptance, and cost-performance balance remain critical determinants of industrial feasibility (Lee et al., 2025; Saubenova et al., 2024; Wang et al., 2023).

9.2. Plant-based bioreactors

Transgenic plants, hairy root cultures, and dedifferentiated callus systems represent alternative platforms for lycopene biosynthesis. Recent work on metabolically engineered plant cell cultures has reinforced the broader concept that plant-based systems can serve as biofactories for high-value carotenoids, while reviews of carotenoid biotechnology continue to support the relevance of gene overexpression, pathway redesign, and culture-condition optimization for improving carotenoid accumulation in plant tissues (Rebelo et al., 2025; Wang et al., 2023).

Compared to microbial systems, plant-based approaches offer the advantages of low-cost biomass production, scalability in open-field or greenhouse settings, and the ability to co-produce other valuable phytochemicals. However, they remain limited by slower growth rates, gene silencing phenomena, and regulatory hurdles associated with genetically modified crops. Accordingly, plant-based bioreactors may be especially attractive when biomass generation and phytochemical co-production are prioritized, whereas microbial systems remain more suitable when rapid production cycles, tighter process control, and industrial standardization are required (Rebelo et al., 2025).

10. Stability and storage of lycopene

Lycopene, owing to its highly unsaturated hydrocarbon structure with 11 conjugated and 2 non-conjugated double bonds, is exceptionally susceptible to oxidative, thermal, photolytic, and pH-induced degradation (Fig. 4). This instability poses major challenges during processing, storage, and delivery, particularly for industrial applications involving food, nutraceutical, or cosmetic matrices (Saini et al., 2019; Wang et al., 2024; Xianquan et al., 2005).

10.1. Factors affecting stability

Several extrinsic factors significantly influence lycopene stability during storage (Table 4). Elevated temperatures accelerate the rate of lycopene autooxidation and promote isomerization from the all-trans form to thermodynamically less stable *Z*-isomers. Studies have reported that storage at temperatures above 30 °C can result in up to 60–80% degradation in unprotected formulations within a month (Anguelova & Warthesen, 2000; Gupta et al., 2010). Lycopene is also highly sensitive to light, particularly visible and UV wavelengths, which induce cis-trans isomerization and the generation of reactive oxygen species, accelerating photooxidation. Continuous fluorescent exposure, as encountered in food storage environments, exacerbates degradation in tomato-based matrices such as powders and emulsions (Lavelli & Torresani, 2011; Martínez-Hernández et al., 2016).

Oxidative degradation is further intensified by the presence of oxygen and catalytic metal ions, including Fe^{3+} and Cu^{2+}. These species facilitate lipid peroxidation and the fragmentation of lycopene molecules into volatile aldehydes and ketones, which diminish both nutritional and sensory quality (Hackett et al., 2004; Saini et al., 2019; Xianquan et al., 2005). Additionally, lycopene is destabilized under extreme pH conditions, where acidic or alkaline environments compromise micellar solubilization and emulsion integrity, ultimately increasing degradation rates (Gupta et al., 2010; Martínez-Hernández et al., 2016).The role of relative humidity is also critical; Lavelli and Torresani (2011) demonstrated that water activity (aw) levels between

0.22 and 0.56 optimize lycopene retention, while higher humidity promotes microbial growth and oxidative deterioration.

10.2. Encapsulation strategies to improve stability

To counteract these degradation pathways, a range of encapsulation strategies has been developed to enhance lycopene's physicochemical stability and prolong its shelf life. High Internal Phase Emulsions (HIPEs), especially those stabilized with ovalbumin-chitosan complexes, have proven particularly effective in retaining *Z*-isomers of lycopene. Wang et al. (2024) showed that such systems retained approximately 98.2% Z-lycopene after 30 days at 25 °C and 41.8% even at elevated temperatures of 80 °C. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) represent another class of lipid-based carriers that provide thermal protection and controlled release, though SLNs may be limited by lower lycopene loading capacity (Amorim et al., 2022; Saini et al., 2019).

Pickering emulsions, stabilized by solid particles rather than surfactants, form gel-like barriers that afford enhanced protection against oxidative and photolytic degradation while facilitating sustained release. These systems are increasingly preferred for their improved structural stability and bioaccessibility (Falsafi et al., 2022). Furthermore, nanoemulsions and liposomes offer dual benefits: improving lycopene solubility in aqueous media and preserving its antioxidant capacity during gastrointestinal transit. They also enhance cellular uptake, making them suitable for functional food and nutraceutical applications (Gao et al., 2023; Sharma et al., 2021). Collectively, these encapsulation approaches represent effective tools to preserve lycopene's bioactivity and expand its applicability in health-promoting formulations.

10.3. Packaging and storage considerations

The packaging and storage of lycopene-containing products are pivotal in minimizing degradation and ensuring commercial shelf-life. Lycopene's vulnerability to photodegradation necessitates the use of opaque, UV-shielding containers such as amber glass bottles or polymeric films with integrated UV-blocking agents. These materials significantly reduce the photoisomerization of all-trans to cis-lycopene and mitigate free radical formation triggered by light exposure. Advanced multilayer flexible films, which include ethylene vinyl alcohol (EVOH) and polyethylene terephthalate (PET), have been adopted in the food and cosmetic sectors for their excellent oxygen and light barrier properties (Lavelli & Torresani, 2011; Xianquan et al., 2005).

In addition to light protection, oxygen management is essential. Modified Atmosphere Packaging (MAP) techniques that displace atmospheric oxygen with inert gases like nitrogen or argon help curb oxidative stress. This method, when combined with active packaging systems such as oxygen scavengers and antioxidant-impregnated films further enhances lycopene stability in emulsified or powdered formats (Gupta et al., 2010; Saini et al., 2019).The inclusion of natural antioxidants like α-tocopherol, ascorbic acid, or rosemary extract directly into the packaging matrix or formulation can also delay oxidative deterioration and preserve lycopene's color and bioactivity (Wang et al., 2024).

Temperature regulation is equally important (Fig. 4). Cold chain storage, typically below 4 °C, has proven effective in maintaining the isomeric integrity and antioxidant potential of lycopene. Low temperatures slow down the rate of autooxidation and isomerization, especially in lipid-based delivery systems such as SLNs or liposomes. Furthermore, short-term exposure to elevated temperatures should be avoided, as even brief thermal abuse can irreversibly degrade the compound (Anguelova & Warthesen, 2000).

Recent advancements have emphasized the importance of polymer-lipid interactions in packaging design. Incorporating biopolymers such as ovalbumin-chitosan (OVA-CS), gelatin, and whey protein isolate into nanocarrier emulsions contributes to interfacial stabilization, moisture barrier functionality, and pH buffering. These properties help mitigate the effects of environmental stressors during extended storage (Chen et al., 2024; Zhang et al., 2023).Research also indicates that such biopolymers can interact synergistically with encapsulation matrices to form more cohesive films and emulsions, enhancing both colloidal and chemical stability (Gao et al., 2023).

From a comparative standpoint, no single stabilization strategy is universally optimal for lycopene because the dominant degradation route depends on the product matrix and storage environment. Encapsulation systems are particularly useful when internal physicochemical protection is required against heat-, light-, and oxygen-driven degradation; for example, (Wang et al., 2024) showed improved lycopene stability in high-internal-phase emulsions, while (Wei et al., 2025) reported that Pickering emulsions stabilized by tannic acid–starch complexes enhanced environmental stability and bioaccessibility. By contrast, when external storage conditions are the major threat, packaging and storage management become more decisive. (Pereira et al., 2024) emphasized the importance of packaging and storage innovations for preserving tomato derivatives, and (Güler & Alkan, 2025) confirmed that storage temperature can markedly influence lycopene retention in tomato products. Overall, the most effective stability strategy should therefore be selected according to the matrix, storage duration, packaging format, and processing severity, with encapsulation favored for internal stabilization and packaging- or storage-based interventions favored when external conditions dominate lycopene loss.

11. Regulatory and safety considerations

Lycopene is broadly recognized for its health-promoting properties and is permitted in food, nutraceutical, and cosmetic formulations across major international markets. However, given its varying origins ranging from natural tomato extracts to synthetic forms and microbial fermentations the safety evaluation and regulatory approval of lycopene are subject to strict regional criteria to ensure consumer protection and consistency.

11.1. Regulatory approvals and status by region

United states (FDA): Lycopene derived from tomatoes, synthetic processes, and *Blakeslea trispora* fermentation is designated as "Generally Recognized As Safe" (GRAS). It is permitted as a food color additive under Title 21 of the Code of Federal Regulations (CFR) Section 73.295, where it is used in beverages, dairy, and processed foods (Kun et al., 2006).

European union (EFSA): Lycopene is listed as an authorized color additive (E160d) under Regulation (EC) No 1333/2008 and has undergone multiple safety evaluations. The European Food Safety Authority (EFSA) has set the acceptable daily intake (ADI) at 0–0.5 mg/kg body weight/day, applicable to lycopene from all sources including synthetic, microbial (*B. trispora*), and tomato-derived variants (EFSA Panel on Nutrition, N. F., Allergens, F, et al., 2023). Novel lycopene sources are assessed under the novel food regulation (EU) 2015/2283, and EFSA concluded that lycopene does not present genotoxic, carcinogenic, or reproductive toxicity risks within authorized limits (EFSA Panel on Nutrition, N. F., Allergens, F, et al., 2023).

Codex alimentarius: Lycopene is recognized under food additive provisions for use as a natural colorant. However, labeling and dosage depend on its source and processing method. Codex allows lycopene in specific food categories, often harmonized with local regulatory thresholds (World Health Organization (WHO), 2013).

China, India, and Japan: National regulations in these countries permit lycopene as a colorant and functional food component. In Japan, it is referred to as "tomato color" and permitted under the Food Sanitation Law. Typical allowable daily intake ranges from 10 to 75 mg/day depending on the food matrix (Tufail et al., 2024).

11.2. Acceptable daily intake (ADI) and toxicological assessment

The current ADI set by EFSA and JECFA for lycopene is 0.5 mg/kg body weight/day, based on conservative safety margins derived from subchronic and chronic studies. The NOAEL (No Observed Adverse Effect Level) for lycopene, depending on the source, ranges from 50 to 600 mg/kg bw/day in various animal models, including rats and rabbits (EFSA Panel on Nutrition, N. F., Allergens, F, et al., 2023).

Lycopene has not shown mutagenic or carcinogenic effects in in vitro or in vivo systems. A two-generation reproductive toxicity study in rats and developmental studies in rabbits confirmed the absence of teratogenic effects even at doses exceeding 500 mg/kg bw/day (EFSA Panel on Nutrition, N. F., Allergens, F, et al., 2023). JECFA and EFSA panels conclude that these results support a high safety margin, and thus endorse lycopene use in foods, beverages, and supplements (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2017; Kun et al., 2006).

Furthermore, human intervention trials have shown that oral intake of lycopene up to 75 mg/day for up to six months is well tolerated, with no serious adverse events reported (Khan et al., 2021; Tufail et al., 2024).

12. Future research directions

Although the therapeutic potential of lycopene has been widely recognized, many aspects remain insufficiently explored, particularly regarding molecular targets, advanced delivery systems, sustainable production, and clinical translation. Integrating omics technologies and biotechnological advances with traditional food science approaches will be key to unlocking lycopene's full potential.

12.1. Identifying the biologically active lycopene species

Future lycopene research should move beyond treating total lycopene as a chemically uniform exposure. A major unresolved question is whether the principal bioactive entities are the parent compound, specific *Z*-isomers, oxidative cleavage products such as apo-lycopenoids, or combinations of these forms that vary across tissues and physiological states. This distinction is essential because recent evidence indicates that human responses to lycopene are shaped not only by intake, but also by interindividual variability in tissue accumulation and metabolic handling. In particular, recent human work on adipose-tissue lycopene showed substantial between-subject variability and identified genetic determinants linked to lipid and carotenoid metabolism, supporting the need for future studies that combine isomer-resolved exposure assessment with nutrigenetic and tissue-distribution analysis (Zumaraga et al., 2026).

12.2. Validating emerging mechanisms beyond classical antioxidant activity

A second priority is the rigorous validation of mechanisms that extend beyond the classical redox- and inflammation-centered framework. Epigenetic regulation is one such area. Recent reviews of phytochemicals as epigenetic modulators include lycopene among compounds with potential relevance to DNA methylation, inflammatory signaling, and redox-sensitive transcriptional control, but the lycopene-specific evidence remains insufficiently resolved for definitive mechanistic interpretation (Cord et al., 2025). At the same time, growing preclinical evidence suggests that lycopene may influence host physiology through the gut microbiota, intestinal barrier function, and microbiota-derived metabolites. Recent mouse studies reported that lycopene improved gut barrier integrity, reshaped microbial composition, and altered short-chain fatty acid-related signaling in ways linked to cognitive and inflammatory outcomes, indicating that the microbiota–gut–organ axis may represent a meaningful but still developing dimension of lycopene biology (Wang et al., 2024). Future work should therefore integrate transcriptomics, metabolomics, and microbiome profiling to determine which of these pathways are causal, reproducible, and relevant in humans.

12.3. Priorities for future clinical trials

A third priority is to redesign human studies so that they explain variability in response rather than simply report average outcomes. Future trials should be structured around dose-ranging, formulation type, isomer profile, baseline nutritional or metabolic status, intervention duration, and relevant genetic background. This is particularly important because recent syntheses indicate that the human evidence is not equally strong across endpoints. Prospective evidence supports inverse associations between dietary or circulating lycopene and cancer risk and mortality, and umbrella-level evidence suggests more consistent benefits for blood pressure than for lipid outcomes, while randomized-trial evidence remains limited or inconclusive for some domains such as mental-health-related outcomes (Balali et al., 2025; Głąbska et al., 2025; Nam et al., 2026). In addition, recent pilot intervention work in participants with obesity showed reductions in multiple inflammatory markers after daily intake of a lycopene-rich juice, but such findings do not yet establish long-term efficacy, dose-response relationships, or durability of benefit across broader populations (Jilcott Pitts et al., 2026). Accordingly, the next generation of clinical studies should emphasize pharmacokinetically characterized interventions, predefined responder subgroups, and stronger endpoint standardization.

12.4. Industrial translation, standardization, and regulatory substantiation

A fourth research direction concerns translation from promising bioactive to robust industrial and regulatory application. Future work should link extraction method, formulation architecture, stability profile, and bioaccessibility to real product performance rather than evaluating these dimensions in isolation. This is especially relevant for nutraceutical deployment, where classification, safety assessment, quality control, and health-claim substantiation remain inconsistent across jurisdictions. Recent comparative regulatory analyses of nutraceuticals in the USA, India, and Europe show that differences in regulatory frameworks directly affect market entry, safety oversight, and evidence expectations, underscoring the need for stronger standardization and more harmonized substantiation strategies for lycopene-containing products (Bose & Sharma, 2025). In practical terms, future studies should combine quality-by-design manufacturing, stability-preserving processing, and clinically relevant outcome validation so that technological optimization can be translated into evidence-based functional foods and nutraceuticals rather than remaining a laboratory exercise.

13. Conclusion

Lycopene, a bioactive tetraterpenoid belonging to the carotenoid family, occupies a strategic position at the intersection of nutritional biochemistry, functional food development, and preventive medicine. Its potent antioxidant and anti-inflammatory properties have been widely documented through preclinical and clinical studies, with growing evidence supporting its modulatory effects on oxidative stress, lipid metabolism, inflammation, apoptosis, and cellular signaling. These attributes underpin lycopene's protective role in the prevention and adjunctive management of chronic conditions such as cardiovascular diseases, metabolic syndrome, certain cancers, neurodegenerative disorders, and age-related ocular degeneration.

Nevertheless, lycopene's clinical and industrial potential remains constrained by its inherent physicochemical limitations has considerably enhanced its gastrointestinal stability, absorption, and targeted

tissue delivery. These formulation strategies, coupled with enzyme-sensitive and responsive nanocarriers, pave the way for personalized lycopene supplementation with higher therapeutic efficacy.

On the production front, biotechnology-driven advances are mitigating economic and environmental barriers. Engineered microbial strains (e.g., *E. coli*, *Yarrowia lipolytica*) and transgenic plant systems offer scalable, sustainable alternatives to traditional agricultural sources. Concurrently, the valorization of agro-industrial waste streams through green extraction processes contributes to a circular bioeconomy, aligning with clean-label and eco-conscious market demands.

From an industrial perspective, lycopene is transitioning beyond its role as a natural colorant. It is now a critical active ingredient in the formulation of functional foods, dietary supplements, cosmeceuticals, and next-generation pharmaceuticals. However, its full potential cannot be realized without harmonized regulatory standards, validated biomarkers of efficacy, and comprehensive risk–benefit analyses. International bodies such as EFSA, FDA, and Codex Alimentarius must converge on specifications for source origin, isomer profiling, maximum allowable limits, and substantiated health claims to foster safe and equitable market expansion.

Looking ahead, research should prioritize integrative multi-omics (genomics, metabolomics, transcriptomics) to delineate lycopene's molecular interactions in human systems. Moreover, robust, multicenter randomized controlled trials are essential for validating clinical outcomes and establishing evidence-based guidelines for therapeutic use.

CRediT authorship contribution statement

Djilali Benabdelmoumene: Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **Ahmed Mediani:** Writing – review & editing, Data curation. **Wasim S.M. Qadi:** Writing – review & editing, Writing – original draft, Validation. **Pei Lou Wong:** Writing – review & editing, Writing – original draft, Investigation. **Said Dahmouni:** Writing – review & editing, Validation. **Zineb Bengharbi:** Writing – review & editing, Data curation. **Syarul Nataqain Baharum:** Writing – review & editing, Validation, Supervision, Conceptualization. **Faridah Abas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Ethics statement

This review article involves no experiments on humans or animals. Therefore, formal ethical approval from an institutional review board or ethics committee was not required. The review is based solely on publicly available data from peer-reviewed scientific literature. All information has been carefully and objectively synthesized, with proper citation of original sources to avoid any form of plagiarism. This article has been prepared in full compliance with academic ethical standards, ensuring accuracy, impartiality, and integrity throughout. The authors declare that there are no conflicts of interest.

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Data availability

Data will be made available on request.

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