Universidade de Lisboa

Faculdade de Farmácia

Lycopene in Human Health

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Mestrado Integrado em Ciências Farmacêuticas

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

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RESUMO

Embora o licopeno ainda não seja considerado um nutriente essencial, a sua ingestão alimentar é geralmente recomendada, pois é importante em todas as fases da vida humana devido às suas propriedades promotoras de saúde.

O licopeno é um pigmento carotenóide cuja ingestão varia de acordo com a população considerada. Embora a maior parte do licopeno presente no corpo humano derive do tomate e de alimentos processados a partir do tomate, este composto de cor vermelha também pode ser encontrado em outras frutas e vegetais.

Tendo em conta a baixa biodisponibilidade do licopeno, os seus níveis plasmáticos são mais adequados como dados prognósticos para resultados de saúde do que os seus valores de consumo alimentar.

Da mesma forma que outros carotenóides, o licopeno ocorre em várias configurações geométricas. Alguma parte do licopeno ingerido é oxidada e sofre degradação enzimática irreversível e / ou oxidação através de enzimas intestinais.

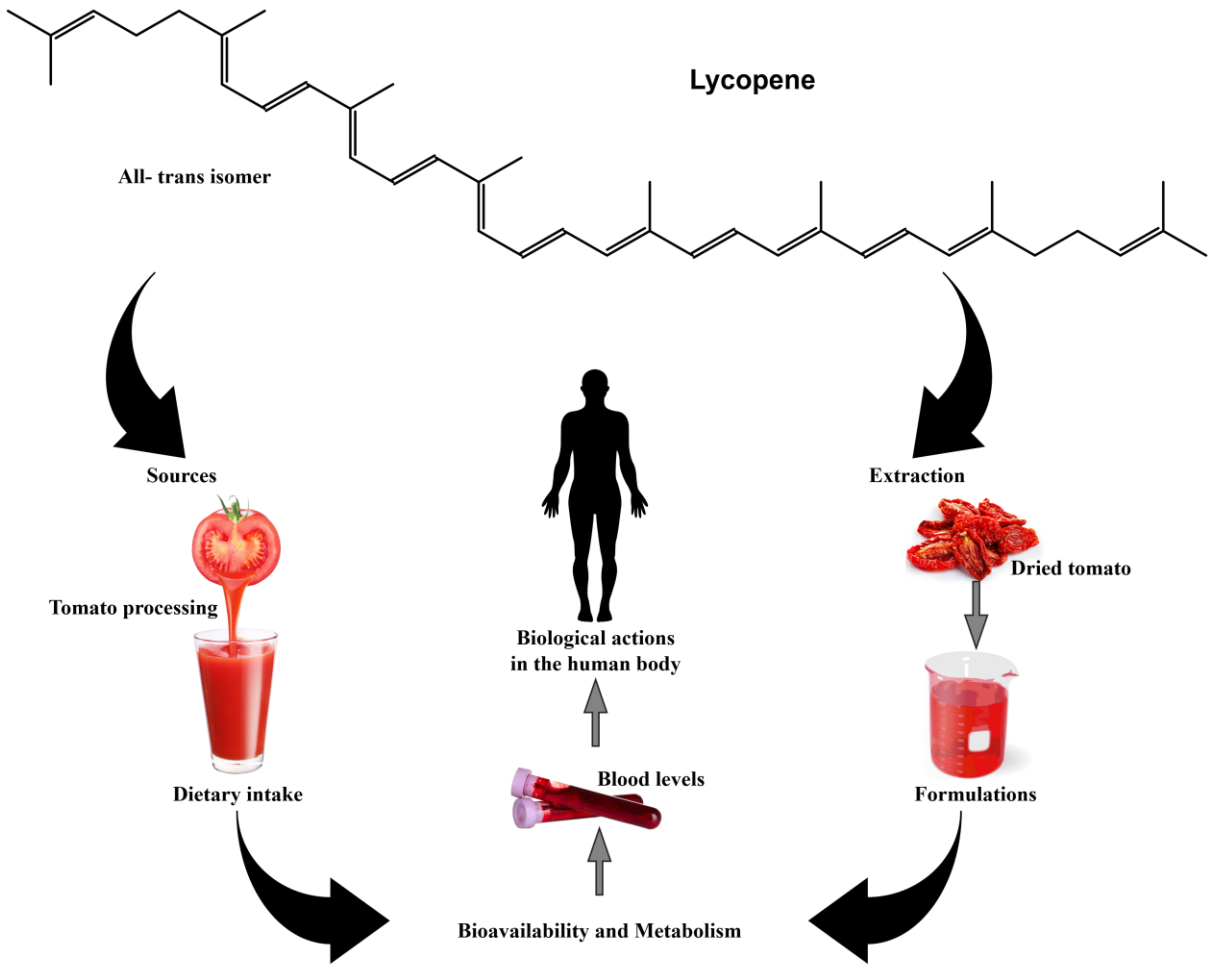
Considerando que o licopeno é muito sensível às condições ambientais (por exemplo, calor, luz, pH, oxigénio), ele deve ser protegido para preservar os seus potenciais benefícios. De facto, a estrutura insaturada do licopeno torna-o altamente susceptível à isomerização e oxidação durante o processamento e armazenamento.

O licopeno parece ser responsável pela saúde humana de diferentes maneiras. Pode proteger os lípidos, as proteínas e o ADN do dano oxidativo, estimular a modulação do crescimento celular e a expressão dos níveis sanguíneos da proteína de ligação da conexina 43, IGF-1 e / ou IGF, bem como ser intermediário em processos imunitários e inflamatórios.

Uma resposta celular benéfica ou prejudicial pelo licopeno dependerá das suas propriedades antioxidantes ou pró-oxidantes, respetivamente, dependendo do ambiente celular e extracelular. De uma forma geral, embora carotenóides e metabólitos em doses baixas possam apresentar efeitos benéficos, o mesmo não é observado em doses altas correspondentes a efeitos nocivos do prooxidante.

Palavras-chave: Licopeno; Anti-oxidante; Atividade Biológica, Saúde Humana; Formulações

GRAPHICAL ABSTRACT



ABSTRACT

Even though lycopene is still not considered an essential nutrient, its dietary intake is generally recommended, as it is quite important along all phases of human life due to its health-promoting properties.

Lycopene is a carotenoid pigment whose intake varies according to the population considered. Although most of the lycopene present in the human body derived from tomato and the processed foods from tomato, this red-coloured compound can be also found in other fruits and vegetables.

Taking into account the low bioavailability of lycopene, its circulating levels are more suitable as prognostic data for health outcomes than its dietary intake values.

Similarly to other carotenoids, lycopene occurs in various geometrical configurations. Some of the ingested lycopene is oxidized and suffers irreversible enzymatic degradation and/or oxidation through intestinal enzymes.

Whereas lycopene is very sensitive to environmental conditions (for instance, heat, light, pH, oxygen), it must be protected to preserve its potential benefits. In fact, the unsaturated structure of lycopene makes it highly susceptible to isomerisation and oxidation over processing and storage.

Lycopene seems to be responsible for human health in different ways. It can protect lipids, proteins and DNA from oxidative damage; stimulate the modulation of cell growth and the expression of connexin 43, IGF-1 and/or IGF binding protein blood levels as well as intermediate in immune and inflammatory processes.

A beneficial or prejudicial cellular response by lycopene will depend on its antioxidant or prooxidant properties respectively, depending on the cellular and extracellular environment.

In general, although carotenoids and metabolites at low doses may present the beneficial effects described above, the same is not observed at high doses corresponding to harmful prooxidant effects.

Keywords: Lycopene; Antioxidant; Biological Activity; Human Health; Formulations

LIST OF ABBREVIATIONS

7-KC : 7-ketocholesterol
Aβ$_{1–42}$: β-Amyloid$_{1–42}$
AD : atopic dermatitis
AP-1 : activator protein-1
ARE : antioxidant response element
CMO I: carotene-15,15'-oxygenase
CMO II: carotene-9',10'-oxygenase
CVD: cardiovascular disease
Cx 43 : connexin 43
EpRE : electrophile response element
GDM : gestational diabetes mellitus
GJC : gap junctional communication
HaCaT : Human Immortalized Keratinocyte
HHPE : High hydrostatic pressure
HMG-CoA : 3-hydroxy-3-methylglutaryl-coenzyme A
IFN-γ : interferon γ
IGF : insulin-like growth factors
IGF-1 : insulin-like growth factor-1
IGF-1R : insulin-like growth factor 1 receptor
IL-1β: interleukin 1β
IL-10 : interleukin 10
IL-12 : interleukin 12
Keap1 : inhibitor Kelch-like ECH-associated protein 1
LDL: low density lipoprotein
MAE : microwave-assisted extraction
MAPK : mitogen activated protein kinase
mAb: monoclonal antibody against lycopene
MCF-7 : human mammary cancer cell line
mRNA: messenger RNA
NF-kB : factor nuclear kB
Nrf2 : nuclear factor erythroid 2-related factor 2
O/W: emulsion oil-in-water
p53 : tumor supressor
PDGF-BB : platelet-derived growth factor BB
PIAS3 : protein inhibitor of activated STAT
RARs : retinoic acid receptors
Ras : protein family
ROS : reactive oxygen species
RSM : response surface methodology
RXRs : retinoid-X receptors
SFE : supercritical fluid extraction
STAT3 : signal transducer and activator of transcription 3
TGF-β : transforming growth factor β
TNC : tomato nutrient complex
TNF-α : tumor necrosis factor α
USA : United States of America
UV : ultraviolet

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1. INTRODUCTION

Phytonutrients are a hot topic nowadays specially regarding food, health and cosmetic issues (1). In fact, wide research and development on active ingredients extracted from food by-product is being performed under the paradigm of circular economy in line with sustainable environment (2). There are several groups of phytonutrients such as carotenoids, anthocyanidins, isoflavones and other flavonoids (1). Carotenoids have an important role in human health, being associated with cardiovascular diseases (CVD) and cancer (1). For instance, lutein and zeaxanthin are considered benefic for bone health, and lycopene for prostate cancer, among others (1).

Carotenoids are divided into two major groups based on their structural elements: carotenes, constituted by carbon and hydrogen (for example, α-carotene, β-carotene and lycopene), and xanthophylls, constituted by carbon, hydrogen and oxygen (for example, lutein, β-cryptoxanthin, zeaxanthin, astaxanthin and fucoxanthin) (3). Consumption of these phytonutrients varies between countries (1). For example, Taiwan, United States of America (USA) and Korea follow distinct patterns as lycopene and quercetin are more consumed in USA, anthrocyanidin in Korea and lutein and zeaxanthin in Taiwan (1).

Among carotenoids, lycopene will be here extensively revised considering its growing added-value as an important bioactive ingredient with several biological properties. **Lycopene** was first discovered in tomato by Millardet in 1876, and later was named by Schunck (4). Nowadays, it is ubiquitous in the diet of humans around the world (5), mainly in tomatoes and other vegetables and fruits (6). In plants, algae, and other photosynthetic organisms, lycopene is responsible for the yellow, orange and red pigmentations, photosynthesis, and photoprotection (6,7). Due to its strong colour and non-toxicity, lycopene is a useful food colouring (6). It not only has important applications in the functional food sector but also in the production of cosmetic and/or cosmeceutical products (8).

Considering the growing interest on the potential health benefits of lycopene, herein we review the relevant literature related to lycopene sources, intake, chemistry, bioavailability, safety and extraction. Additionally, we summarize the various biological effects of lycopene on cellular function and its involvement on some

diseases. Furthermore, we mentioned recent formulations of lycopene, and discuss the most promising directions of its use in future health perspectives.

1.1. Sources

Commercially available lycopene can be produced by **chemical synthesis**, **fermentation** or **isolation** from a small number of abundant natural sources (3). Therefore, it can be biosynthesized from bacteria, algae, fungi, plants and, at a smaller scale, by microorganisms (3). As animals may not produce it, they depend entirely on dietary sources for an adequate supply of this nutrient (3).

Although the main source of lycopene in the human diet is **tomato**, the lycopene content may vary significantly (7) due to environmental factors, agricultural techniques as well as tomato types and ripening (6,7,9). Lycopene also appears in seeds and peel residues of other **natural sources** like watermelon (9), Kalahari melon (10), gac fruit (11), apricot, papaya, guava, red grapes, pink grapefruit, pumpkins, rosehip fruit (12), orange, mango, pomegranate and carrot (4). Likewise, the lycopene content of the watermelon may change due to differences in genetic make-up, illumination and water supply (7). On the other hand, some authors support that watermelon and gac fruit have higher levels of lycopene than tomato (7,13,14).

When tomatoes suffer maturation, the chlorophyll degrades and gives rise to yellow pigments such as carotenes and xanthophylls (15). The accumulation of carotenes gives rise to the red colour of the tomato (15), being lycopene fivefold more concentrated in the skin than the pulp (9). The red colour of lycopene is due to the long chromophore in the polyene chain (16), that absorbs most of the visible light radiation, except the lowest frequencies (17). Although the red colour of certain fruits and vegetables is owed to the presence of lycopene, not all red-coloured foods contain it (18). The colour of lycopene depends on its isomeric form (19). Indeed, in all-trans isomer and most other isomers, its hue is red, while tetra-cis isomer corresponds to an orange tone (19).

1.2. Physicochemical Properties

Lycopene is a vibrant red carotenoid (13) whose **molecular weight** is 536.89 g/mol correspondent to 89.45% carbon and 10.51% hydrogen ($C_{40}H_{56}$) (4,20). It is an **unsaturated acyclic carotenoid** with 11 linear conjugated and 2 non-conjugated double bonds (4,20), and a tetraterpene assembled from 8 isoprene units (6). The optimal **pH** range for lycopene stability is 3.5 to 4.5 (21).

The **log P** value of lycopene is 17.64, being insoluble in water, ethanol and methanol (4,22), and usually solubilized in organic solvents such as tetrahydrofuran, chloroform, hexane, benzene, carbon disulphide, acetone, petroleum ether and oil (4,23). As a consequence of its extreme hydrophobicity among other factors, the absorption of lycopene from fruits and vegetables by the human body could be low (24). Moreover, it is also a limiting factor for its formulation and application (24). To

increase the solubility and bioavailability of lycopene, many efforts have been made using advanced technology systems, as presented in **section 4** (24).

The differential scanning calorimetry can be used to study the **thermal behaviour** of lycopene and to establish its relative purity between batches (22,25,26). As reported, lycopene assumes an endothermic peak at 172-173 ºC correspondent to the melting point of crystalline form (22,26,27). Despite assuming a melting point between 171 and 176ºC (22), the presence of impurities extends this range (26). A shift in the melting point of lycopene to a lower value plus the disappearance of some of the characteristic all-trans lycopene peaks may be related with the presence of a different crystalline structure such as cis isomers (25,28).

At **crystal form**, lycopene has long red needles separated from a mixture of carbon disulphide and ethanol (4). At **powder form**, it is dark reddish-brown (4).

The lycopene structure is quite vulnerable to thermal treatment and oxidative processes (29). Thus, it is important to protect lycopene from light, oxygen, high temperature, acids, catalyst and metal ions (4).

The estimated lycopene half-life can provide important information about the frequency at which lycopene should be consumed in order to maintain an intended plasma concentration (30). However, there are different half-live values among lycopene geometrical isomers probably due to several factors, such as endogenous isomerisation, higher bioavailability and thermodynamic stability of cis isomers at elevated temperatures (30).

1.3. Isomers and Tomato Processing

Lycopene is found in nature (including fresh tomatoes) in the **all-trans** form (31,32), which is the most thermodynamically stable form (32). Despite being less stable, **cis isomers** present a lower tendency to aggregate and crystallize and higher solubility in lipid media (11,13,16,33). Therefore, cis isomers are more bioactive and better absorbed (11,13,16,19,33).

Even though lycopene may assume 2048 geometrical configurations due to the 11 conjugated carbon-carbon double bonds in its molecular backbone, only certain double bond groups really undergo geometrical isomerisation related with steric hindrance (16). Therefore, lycopene may suffer isomerisation to produce an array of mono- or poly-cis isomers, such as 5cis-, 9cis-, 13cis- and 15cis- (16).

While the full-ripe tomatoes maximize the fruit antioxidant properties, the less-ripened tomatoes present higher firmness and storability properties (34). Thus, with the intention of obtaining an equilibrium between the nutraceutical and organoleptic properties of tomatoes, it must be taken into account which the ripening stage to harvest them should be chosen (34).

The disruption of the tomato matrix by **thermal food processing** or by **non-thermal treatment** (acid treatment, light irradiation, food mechanical processing operations such as chopping and pureeing) may facilitate lycopene cis isomerisation as well as influence sensory attributes like colour, flavour and consistency (16,35).

Thus, the bioavailability of lycopene is lesser in fresh tomatoes than in processed tomato products (such as pasteurized tomato juice, soup, sauce and ketchup) containing stable proportions and distribution of all-trans and cis-forms that do not experience retro-isomerisation (3,6,16,23,24,35,36).

The non-thermal processing is an alternative to thermal treatment because it offers minimally processed, microbiologically safe, additive free stable food products (32). On the other hand, the conventional thermal treatment provides more stable and viable lycopene isomers for industrial scaling, because it may be responsible for the convertion of all-trans lycopene into cis isomers (16). Consequently, the choice of tomato processing conditions may have a major impact on the content, quality and bio-accessibility of lycopene in tomato products (14,35).

1.4. Bioavailability and Metabolism

Lycopene **bioavailability** can be affected by food processing and cooking, dietary composition (19), mastication, isomeric configurations of lycopene (30) as well as probiotics (19). In fact, lycopene bioavailability is lowest in raw sources, lightly increased in mildly processed foods and highest in thermal processed food sources and purified oily preparations (16).

As a fat-soluble carotenoid, lycopene has a similar **absorption** as a dietary fat (4). In the stomach, it is released from the food matrix and dissolved in the lipid phase (4). Before absorption, bile salts react with pancreatic lipases, forming micelles in the lipid phase (4). In the small intestine, the lipid micelles are passively transported to the mucosa cells, and posteriorly, incorporated in triacylglycerol-rich chylomicrons that are then transferred to the liver via lymphatic system (4,18). After absorption, lycopene is transported in plasma in the core of low density lipoproteins (LDL) (4,18). Lycopene cis isomers are more easily incorporated in lipoproteins than all-trans isomers due to higher solubility (16,23) and shorter chain length that fits into micelles (4,16). In contrast, other authors suggest that there is no preferential absorption of lycopene isomers and that isomerisation to cis isomers can take place in the digestive tract and/or in plasma (16).

The lycopene absorption is influenced by age, gender, hormonal status, smoking, alcohol and other diet components (18). For instance, its bioavailability is impaired in elderly people (4), probably due to changes in the gastrointestinal tract age-related, which decreases its absorption (18). Moreover, the dietary fibbers reduce lycopene adsorption by decreasing its cellular uptake as well as reducing the plasma content more than 40% (4). On the contrary, lycopene absorption is improved when it is consumed with other lipids in the diet or cooked in an oily medium (4,6,16,18).

Even though the lycopene chemical structure influences the **distribution** process (4), it is distributed via the circulatory system, accumulating in various tissues, preferentially in the testes, adrenal glands, liver and prostate (4,6,18). This huge accumulation may be caused by the presence of a large number of lipoprotein receptors, a relatively higher uptake of lipoproteins and/or a higher

metabolic/oxidation rates in these tissues (18). Thus, the unequal distribution of lycopene suggests its exclusive biological role in certain tissues (18).

Regarding **metabolism**, the lycopene metabolites are formed by enzymatic or oxidative cleavage (4,18). Although carotene-15,15'-oxygenase (CMO I) is the major carotenoid cleavage enzyme in mammals, lycopene is a poor substrate for this enzyme, not being cleaved by it (5). Furthermore, it seems that the cleavage products resulting from the CMO I activity (such as acycloretinal and acycloretinoic acid) are much less bioactive than lycopene (5). Thereby, carotene-9',10'-oxygenase (CMO II) mediates lycopene cleavage specially the cis isomers (5). Thus, some of the possible products of lycopene with bioactive properties include apo-lycopenals, apo-carotenedials, apo-lycopenones, carboxylic acids and epoxides (37).

1.5. Safety

As evidenced, pure crystalline lycopene and formulated lycopene in stable conditions are not genotoxic (23). Accordingly, some authors reveal that lycopene consumed or formulated up to 3g/kg per day does not have adverse effects (4).

It is still important to mention that lycopene can modulate the toxicity and genotoxicity of different genotoxines (such as hydrogen peroxide, n-nitrosodiethylamine and aflatoxin B1) (38).

1.6. Extraction

The tomato industry produces sizable quantities of solid wastes, like **peels** and **seeds** (2,9). Consequently, most of the lycopene from these sources is wasted (2,9). This opened a new opportunity for several researchers start processing food waste to obtain new sources of active agents which in turn led to the selective extraction of main phytochemicals from natural material (2,9).

The value of lycopene recovered depends on the extraction method used and/or the previous processing of the peels and the type of raw material like tomato variety (39,40). The dielectric constant, chemical structure of organic solvent, solvent proportions and chemical properties of the compound also affect the extractability of lycopene (41).

Response surface methodology (RSM) determines the effect of various extraction parameters (for instance, solvent ratio, solid-liquid ratio, microwave power and energy equivalents) on lycopene yield (39). However, the extraction procedure using RSM is usually time consuming and presents the risk of lycopene degradation as samples are exposed to heat for extended periods of time (39).

Although the lycopene extraction is independent of the solvent flow rate, it is influenced by some factors, being increased with pressure and temperature (at 60ºC) and decreased with higher particle size at the beginning of extraction (9).

The lycopene extraction can be performed by different techniques using enzymes, ultrasounds, maceration, among others (9). The extraction with **enzymes**

presents several advantages such as high specificity and catalytic efficiency, aqueous solubility, absence of toxicity and biodegradability (9). Besides, it can be performed under mild operational conditions of pH, temperature and pressure (9). However, enzymes are relatively unstable and their recovery is expensive (9). On the other hand, **ultrasound-assisted extraction** is very easy and cheaper, but it induces the formation of a strong fibre network in the tomato pulp, entrapping lycopene in the tomato matrix thereby making it less accessible for digestion (9,42,43). In the **conventional extraction by maceration**, the lycopene recovery is usually low (9,43).

Some authors support that **organic solvents**, such as hexane and ethyl acetate, are the most efficient for carotenoid extraction from tomato seeds and peels (39). In fact, cis isomers extraction yields are higher as the solid-liquid ratio decreases and the ethyl acetate proportion increases (39). However, the lycopene extraction by conventional methods usually consumes large amounts of organic solvents that are expensive, toxic and dangerous (44).

Supercritical fluid extraction (SFE) is adequate for the lycopene extraction from tomato industrial wastes, since it reduces the use of toxic solvents obtaining a solvent free extract at moderate temperatures with higher selectivity and yield (9). Although, SFE is a nontoxic and non inflammable technique, it requires the presence of a stabilizer and a cosolvent due to its nonpolar character (44). Moreover, the degradation and/or isomerisation of lycopene can occur during any extraction step (44). Alternatively to supercritical carbon dioxide, ethane can be also used due to higher polarizability and low critical temperature and pressure (305.4 K and 48.2 atm, respectively), leading to a less expensive process and faster extraction with a higher recovery of lycopene (9).

Microwave-assisted extraction (MAE) is probably an improvement over conventional extraction and supercritical fluid extraction (39). While conventional extraction provides higher proportions of cis isomers, MAE is a rapid technique to recovery all-trans and total lycopene (17,39). MAE induces rapid heating of polar cellular components, improving lycopene migration into the extraction solvent whilst the short treatment time limits heat exposure of the nonpolar components (39).

High hydrostatic pressure extraction (HHPE) is used to extract phytochemicals from fruits and vegetables (41). Furthermore, HHPE can change the bio-accessibility of bioactive compounds (41). This method is faster and more effective than conventional extractions (41).

2. LYCOPENE EFFECT ON CELLULAR FUNCTION

The lycopene **reactivity** in biological systems depends of many factors, such as its molecular and physical structure, concentration, source type, location or site of action within the cells, competence to interact with other antioxidants and the contribution of partial pressure of oxygen (4,23).

Lycopene has human health benefic properties quite diversified (5). Thus, the several mechanisms of biological effects of lycopene (**Annex 1**) will be further discussed in detail.

2.1. Antioxidation

Lycopene is a **powerful antioxidant** (3,8), against the oxidation of proteins, lipids and DNA (18,23). Additionally, lycopene can act on other free radicals such as **hydrogen peroxide**, **nitrogen dioxide** and **hydroxyl radicals** (18). Furthermore, the lycopene activity against free radicals is synergistically increased by the presence of other tomato phytochemicals such as β-carotene, phytoene and phytofluene (3,8,18).

When lycopene is exposed to free radicals or oxidation agents, its double bonds can be cleaved or added, interrupting the polyene chain (4). With these reactions, lycopene can be degraded and lose the colour (4).

Among all carotenoids, lycopene has the highest **scavenging ability** for singlet species of oxygen free radicals because of high number of double bonds in its structure that provides many electrons that can be donated to free radicals, resulting in high reactivity (4,23). When the oxygen tension is low, lycopene can scavenge peroxyl radicals, suppressing the propagation step of lipid peroxidation, and thus, reverting tumor initiation (15,23). Thereby, lycopene can act as singlet oxygen and peroxyl radical scavenger (4).

The lycopene action regarding reactive oxygen species (ROS) comprises three major ways: firstly radical addition (**adduct formation**), followed by **electron transfer** to the radical, and then, **allylic hydrogen abstraction** (4,5,23). The adduct formation and allylic hydrogen abstraction are mechanisms that contribute to the antioxidative function of lycopene (45). These possible reactions are affected by many factors such as the nature of the reacting free radical, the lycopene structural

characteristics as well as the location and orientation of lycopene within the membrane, in case of biological systems (46). In fact, while polar environments benefit the electron transfer, the nonpolarity of cell membranes or micelles contributes for the adduct formation and the allylic hydrogen abstraction (45). Furthermore, the reactions between lycopene and free radicals can occur through more than one pathway simultaneously (46).

Lycopene can improve the cellular antioxidant defence system through the **regeneration of the non-enzymatic antioxidants**, vitamins E and C, from their radicals (5). In fact, it is believed that lycopene can protect vitamin E (4,47).

Apparently, while lycopene has an antioxidant action in systems that generate a singlet oxygen, it has a pro-oxidant activity in peroxide-generating systems (48,49). The antioxidant activity of lycopene can become pro-oxidant activity due to the redox potential of lycopene as well as the biological environment in which it acts (50,51). In fact, lycopene performs as a pro-oxidant at high concentrations and as an antioxidant at low concentrations (48,49).

The pro-oxidant potency is determined by many factors like oxygen tension of tissues, lycopene concentration, and its interactions with other antioxidants (50,51). Lycopene, as pro-oxidant, not only can generate either beneficial or harmful effects in biological systems, but can also influence the progress of human diseases (50,51).

If lycopene promotes an inappropriate prooxidant activity in normal cells, harmful results might be obtained with cell damage induced through the production of ROS (50,51). As a result, the normal regulatory functions are modified and, consequently, cellular integrity will be damaged and/or neoplastic transformation might be induced (50,51). On the other hand, if lycopene acts as prooxidant in already transformed cells, beneficial results might be obtained with the growth and development of malignant lesions´ inhibition and/or the tumour cytotoxic effects (50,51). Moreover, associations of antioxidants can restrict the prooxidant property of carotenoids and, as a result, potentiate the antioxidant characteristics of these bio-actives (50,51).

2.2. Modulation of detoxifying enzymes

The **electrophile response element transcription system** (EpRE) or **antioxidant response element transcription system** (ARE), corresponds to the cis-regulatory sequences in the promoter region of the detoxifying enzymes (5). Lycopene can activate this ARE transcription system, influencing the xenobiotic metabolism (5). Firstly, lycopene breaks the cytosolic interactions between the main ARE-activating Nrf2 and its inhibitor (Keap1) (5). Once free of Keap1, Nrf2 translocates itself to the nucleus, inducing the expression of phase II enzymes (5). Consequently, mRNA and protein levels increase (5).

2.3. Induction of Gap-junctions Communications

The gap junctional communication is achieved by channels composed of gap junction proteins such as connexin 43 (Cx 43) (3,23). GJC allows the exchange of signalling molecules and nutrients among neighbouring cells (5). GJC is also involved on the epithelial polarization and plays an important role in the formation of more stable biological membranes, including various types of epithelia and the skin (52).

One of the characteristics of carcinogenesis is loss of GJC (5,23). Thus, the proliferation of tumor cells is not inhibited (18). Lycopene **can induce GJC** through a differential and dose-dependent mode, inhibiting the carcinogen progression of initiated fibroblasts to transformed ones by a reversible way (5,18,23).

Various authors report a positive relation between GJC or Cx 43 expression with lycopene consumption. For instance, a study with **rat liver epithelial cells** supported that a lycopene oxidation product, 2,7,11-trimethyltetradecahexaene-1,14-dial, enhances GJC (53,54). Other study in **human keratinocytes** suggested that the oxidative metabolite, lycopene-5,6-epoxide, can increase Cx 43 expression (51,55).

2.4. Retinoid-like Activity

Vitamin A performs a prophylactic effect on the development of carcinogen induced epithelial tumours (56,57). In fact, some animal studies reveal that vitamin A deficiency is related with increased tumour formation (56). Considering the distribution and possible toxicity of vitamin A, the supplementation with retinoids seems to be an alternative as prophylactic agents (56,57) .

Retinoids are the oxidative products of provitamin A carotenoids, modulating the gene expression at specific target sites, and inhibiting the cancer cells´ growth (23) acting on differentiation, proliferation, apoptosis, and cell cycle control (56).

Unlike other carotenoids, lycopene does not have a beta-ionic ring, and therefore, it lacks vitamin A activity (18). On the other hand, this molecule is an important **intermediate in biosynthesis of vitamin A precursor carotenoids** like β-carotene and β-cryptoxanthin (7,23). In fact, **lycopene has a partial pro-vitamin A activity** due to retinoic acid receptors (RARs), particularly the retinoid-X receptors (RXRs) activation pathways (58). Accordingly, a study with animals fed with vitamin A deficient diet supported that lycopene supplementation can up regulate signalling pathways mediated by retinoic acid response in many organs probably through its metabolites with a similar structure to retinoic acid (59). Thereby, lycopene can re-establish vitamin A deficiency (59).

2.5. Cell Proliferation and Apoptosis Regulation

Lycopene do not induce DNA-fragmentation in tumour cells, but it significantly induces the apoptotic way, even though these results are dependent on the cell line, time of treatment and dosage used (38).

Overall, lycopene has many chemopreventive mechanisms. Firstly, it has a "reactive oxygen species scavenging activity", **decreasing susceptibility to oxidative stress** and **preventing lipid peroxidation and DNA damage** (5,23,49). Secondly, it **induces phase II detoxifying enzymes** at the transcriptional level, protecting the cells from ROS and electrophilic molecules (5,23,49). Thirdly, it **enhances GJC**, which is suppressed during carcinogenesis (5,23). Moreover, it **modulates the cell cycle progression**, and **induces apoptosis in cancer cells** (5,23,49) as well as **inhibits insulin-like growth factor 1 receptor (IGF-1R) signalling pathway** and the **correspondent Ras signalling cascade** (18,23,49). Since insulin-like growth factors (IGF) are the main autocrine paracrine regulators of mammary and endometrial cancer cell growth, lycopene suppression in IGF-1R signalling pathway can have an important role in the regulation of endometrial cancer, among other tumours (15,60). Among all these mechanisms, the human health benefits are mainly due to lycopene antioxidant activity (8).

On oestrogen-positive **breast cancer** cells (MCF-7), the major mechanism behind the anti-proliferative activity of lycopene is the inhibition of the IGF-1R pathway (5). On the other hand, in **prostate and colon carcinoma** cells, lycopene influences Ras signalling through inhibiting the expression of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (5).

Despite inhibiting cancer cells growth, **human fibroblasts appear to be less sensitive** to lycopene action (23) due to the gradual escape of cells to growth inhibition over time (15,60). Thereby, lycopene may act as anticancer compound without significantly disturbing these normal cells (15,60).

The **platelet-derived growth factor BB** (PDGF-BB), which favours the growth, invasion and metastasis of melanoma, can be blocked through the linkage with lycopene, being interrupted the **melanoma** progression (23).

An association of lycopene and 1,25-dihydroxyvitamin D3, at low concentrations similar to their physiological levels, has a synergistic effect in proliferation and differentiation and an additive effect in cell cycle progression with accumulation of cells in the Go/G1 phase (61,62).

There are evidences that combination of different carotenoids can inhibit oxidative damage more efficaciously than the pure compounds, probably due to their differential membrane localization and/or physicochemical properties (4). Thus, the **synergistic interaction** of lycopene with other compounds is critical to reach its optimal function in human health (3).

3. LYCOPENE EFFECT ON DISEASES CONTEXT

Increasing evidence suggests that a lycopene-rich diet can prevent or reduce the risk of CVD and some cancers (8,12). Some authors suggest that a daily intake of 5-7 mg lycopene might be enough to obtain the benefits of this nutrient (31).

3.1. Cancer

In addition to prevent some cancers (63) such as **prostate**, **bladder**, **cervical**, **leukemia** (3), **oral**, **esophageal**, **pancreatic**, **rectal**, **colon**, (or digestive tract), **lung** and **breast** (23), lycopene also retards the growth of tumours and inhibits tumorigenesis (49). Notwithstanding, some authors believe that beneficial effect of lycopene may be specific for certain organs (4).

Epidemiological studies reveal an inverse correlation between dietary intake of lycopene and the risk of certain types of cancer (5). In **prostate cancer** patients, a lycopene rich diet reduces oxidative stress and, as a result, decreases damage of the plasma lipoproteins, serum proteins and lymphocyte DNA (5). In this way, lycopene inhibits cancer development and reduce the aggressiveness of prostate tumours (5). A study with laying hen **ovarian cancer** cells demonstrated that lycopene significantly down regulates the ovarian expression of signal transducer and activator of transcription 3 (STAT3), which can provoke mutations that promote tumorigenesis due to the deregulation of cell cycle and apoptosis in ovarian cells STAT3 (62). Furthermore, it was evidenced that lycopene up regulates the expression of the protein inhibitor of activated STAT3 (PIAS3), contributing to inhibition of activated STAT3 and, as a result, suppressing tumour growth (62). Other study in ferrets suggested that lycopene may inhibit the growth of **lung cancer** cells and prevent lung tumorigenesis (64). However, epidemiological studies and standardized methodologies are indispensable to evaluate lycopene bioactivity with maximum rigor (49).

On the contrary, other studies showed no beneficial effects of lycopene intake among others which have a poor study design based only on a food frequency questionnaire (4). Some authors even suggest that there is an inverse association between lycopene and the risk of certain advanced diseases (4). **Table 1** summarizes different studies regarding the effect of lycopene on several types of cancer.

Table 1 - Reported effects of lycopene in some types of cancer.

Type of cancer	Type of study	Lycopene effect	References
Colorectal cancer	Prospective cohort study	The high consumption of green-yellow vegetables, which are responsible for serum levels of lycopene, can reduce the risk of colorectal cancer mortality in rural Japanese.	(19,65)
	Case-control study	There is not a relation between lycopene and the risk of colorectal cancer.	(19,66)
Lung Cancer	Cohort study	Lower risks of lung cancer are observed for the highest *versus* the lowest quintiles of lycopene.	(49,67)
Ovarian cancer	Case-control study	Intake of lycopene is significantly and inversely associated with risk of ovarian cancer, predominantly, in premenopausal women.	(62,68)
Pancreatic cancer	Case-control study	The consumption of tomatoes and tomato-based products, which have high lycopene content, can help to decrease pancreatic cancer.	(49,69)
Prostate cancer	Meta-analysis	The consumption of lycopene or lycopene-containing foods decreases the risk of developing prostate cancer.	(56,70)
	Prospective observational study	Lycopene intake is associated with a reduced risk of prostate cancer.	(4,71)
	Prospective cohort study	A higher lycopene intake as a food or a supplement reduces (in 18%) the risk of benign prostatic hyperplasia in men.	(19,72)

3.2. Inflammatory Diseases

Lycopene has positive effects on inflammation and redox imbalance due to its capacity to activate the expression of antioxidant genes and regulate signalling pathways liable for the induction of inflammatory mediators (31). Thus, lycopene activates the expression of antioxidant genes, being responsible for the nuclear translocation of Nrf2 (31). Besides, lycopene inhibits tumour necrosis factor (TNF)-α releasing and stimulates interleukin (IL)-10 production (23).

The several anti-inflammatory effects of lycopene can be summarized into: a) modulation of cyclooxygenase and lipoxygenase expression; b) regulation of inducible nitric oxide synthase; c) interference NF-kB as well as with activator protein-1 (AP-1) and with signalling of MAPK (5).

For example, a study with male mice concludes that, after intraperitoneal lipopolysaccharide injection, lycopene can significantly decrease the up regulation of plasma interleukin (IL)-6 and TNF-α avoiding an **inflammation damage on brain tissue** at 6 hours (73).

Since the pathogenesis of **insulin resistance and type 2 diabetes** involves an increase of interleukin (IL)-1β, TNF-α and C-reactive protein levels, these disorders are intimately associated with inflammation (74). A study using mice fed with high fat diet indicated that lycopene improves inflammation by preventing the increase of IL-

1β, TNF-α and C-reactive protein levels (74). Thereby, lycopene prevents the insulin resistance, inflammation and lipid accumulation (74).

3.3. Skin Diseases

The skin protection mechanisms can be increased by lycopene due to the synthesis of prostaglandins and phospholipids components of cell membrane (23). Thereby, topical application of lycopene may reduce inflammatory infiltrate (23). In fact, anthralin induced edema and erythema on the mice ears proved to be significantly attenuated by the epicutaneous application of 0.05% lycopene comparable to the treatment with 1 mg/g betamethasone solution (44).

Some authors suggest that the lifestyle conditions of individuals influence the carotenoid concentration in human skin (75). Indeed, while the concentration of the cutaneous lycopene is lower in smokers, it is higher in the vegetarian people (75).

Lycopene protects and prevents acute ultraviolet (UV) B induced photodamage by inhibiting epidermal ornithine decarboxylase, reducing inflammatory responses, keeping normal cell proliferation and preventing DNA damage (23,76). In fact, a study, using a nontumorigenic human immortalized keratinocytes (HaCaT) cell line, supported that lycopene may have a **corrective function in irradiated cells** depending on the level of photodamage (51). Another study suggested that an increase in plasma isomers of lycopene can change activation of nuclear hormone receptor signalling pathways, thereby being relatively responsible for the **atopic dermatitis** (AD) phenotype (58). Moreover, a study with hairless mice revealed that, after p.o. administration, lycopene can improve AD symptoms such as visual appearances, moisture levels of the skin, inflammatory cells in the dermis and skin thickness (77).

Regardless of a range of potential antioxidants naturally present in skin, the excessive ROS production often surpasses the skin antioxidant ability (51). Therefore, the photoprotection can be enhanced by topical or systemic administration of carotenoids (6). The concept of oral **photoprotection** by antioxidant micronutrients is becoming more relevant (78). In fact, after antioxidant micronutrients supplementation including lycopene, the skin roughness decreases (75), reducing skin aging and the formation of furrows and wrinkles (79). However, an increase in plasma levels of lycopene from nutritional supplementation not always correlates with a significant photoprotection (78). Even though it does not be comparable to the use of sunscreen formulations, diet lycopene can provide a basal protection against ultraviolet (UV) radiation (80). However, some authors suggest that lycopene does not exhibit photopreventive properties and get worse DNA damage induced by UV radiation due to the instability of lycopene under sun exposure generating pro-oxidant effects (80).

A study administered topical formulations containing lycopene and/or dexamethasone to mice previously exposed to UV radiation (81). Taking into account the morphological and biochemical assessments, the lycopene gel granted a higher

protection against **photoaging**, while the dexamethasone gel probably failed due to its capacity to generate oxidative stress (81).

Unfortunately, lycopene is more sensitive to UV radiation than other carotenoids (30). At the skin level, during UV exposure, there is a radical quenching that consumes lycopene (4). In fact, in the first 30 minutes after irradiation, the values of lycopene fall very quickly (75). The lycopene photodegradation can be prevented with deoxygenation of the system, avoiding the dissolved oxygen consumption (82).

3.4. Others

Lycopene reduces **cholesterol** levels (3), contributing to the improvement of cardiovascular disease (CVD) due to atherosclerotic plaque reduction (18).

The 7-ketocholesterol (7-KC) appears to have an important role in **atherosclerosis** (83). Fortunately, some authors suggest that lycopene can prevent the detrimental effects of the 7-KC by reducing both oxidative stress and apoptosis in human macrophages (83). The mesenchymal stem cells transplantated in ischemic diseases and pretreated with lycopene can be used in the treatment of certain tissue injuries since the lycopene prevents **ischemic injury** through the suppression of apoptosis-associated signal pathway and enhancement of antioxidant protein (84).

High lycopene serum level may be also associated to a lower risk of **age-related macular degeneration** (5) due to the greater ability of lycopene to quench singlet oxygen present in the eye, as well as, to the influence on atherogenic processes that indirectly affect the macula (37,85).

The lycopene can activate the adaptive immune response, maintaining an adequate defence against microorganisms (31). Thus, it protects against **bacterial infection** and **radiation** (23).

In addition, serum lycopene is inversely associated with plasma glucose and fasting insulin concentrations (4). A cross-sectional study supports that dietary lycopene intake can reduce the risk of **gestational diabetes mellitus** due to the reduction of fasting blood glucose (86). In fact, an increase of 1 mg in lycopene consumption reduces in 0.005 mmol/L fasting blood glucose and, consequently, decreases 5% the gestational diabetes mellitus risk (86).

The oxidative stress can affect sperm viability, motility and DNA, which are primary causes of **infertility**, mainly by idiopathic male factor (18). Lycopene is able to decrease lipid peroxidation and DNA damage of spermatozoa as well as enhance immunity through the increasing of antioxidants such as catalase and glutathione peroxidase (18). Thus, lycopene can improve sperm count and viability (18). In fact, a study assessed the effect of lycopene **on the cryopreservation of rooster sperm in Beltsville extender** and revealed that supplementing the freezing extender with lycopene or with lycopene nanoliposomes enhances sperm quality, mainly the motility and mitochondrial activity, probably because of the ameliorating on redox balance, the cells energetic metabolism, and membrane protection (87).

A study developed with rats treated with colchicine propose that lycopene can **reverse neurobehavioral deficits** and **increase cognition** due to acceleration of brain antioxidant defence mechanisms and down regulation of nitric oxide pathways (88).

The **Alzheimer disease** is marked by the accumulation of β-amyloid in the brain, mainly the β-Amyloid$_{1–42}$ (A$\beta_{1–42}$) (89). A study in rats injected with A$\beta_{1–42}$ peptide suggested that lycopene treatment can significantly decrease the Aβ_{1-42}-induced mitochondrial dysfunction, the inflammatory cytokine mediators such as NF-κB, IL-1β, TNF-α, and transforming growth factor (TGF)-β besides the caspase-3 activity within the brain (89).

The oxidative stress can have an important role on pathogenesis of **Parkinson disease** (90). A study in rotenone treated rats suggested that lycopene can prevent not only rotenone-induced alterations in antioxidants, but also induced oxidative stress and neurobehavioral deficits (90). Thereby, the supplementation of lycopene can be involved in **neurodegenerative diseases** involving accentuated oxidative stress (90).

4. FORMULATIONS OF LYCOPENE

4.1. Oral Formulations with Lycopene

The food preparations of lycopene are formulated as suspensions in edible oils or as water dispersible powders, being stabilized by antioxidants (91). In fact, the presence of oil improves the bio accessibility of lycopene due to the free fatty acids that increase the solubilisation efficacy of the lycopene, during the digestion process (92). A recent study encapsulated lycopene powder (> 10%) in an orange oil beverage emulsion (pH 3.2) with **different long- and short-chain triglyceride ratios**, revealing that lycopene bio accessibility increases (2.7%) when the ratio of long and short- chain triglycerides is 75:25, respectively (92). This can be explained by the formation of colloidal structures from the long chain triglycerides digestion, which accommodate the lycopene, increasing the lycopene solubilisation capacity before the absorption; however, more research is needed on this subject (92).

Blakeslea trispora is a **fungus capable of synthesis large quantities of lycopene** (93). A study used two lycopene-based products - tomato (oleoresin 6%) and *Blakeslea trispora* (sunflower oil suspension 6%) (93). Even though these formulations seem to be similar relative to the lycopene bioavailability, the results were not significant from a physiologic/nutritional point of view (93). Thus, it is not possible to extrapolate whether the regular consumption of the mentioned formulations could provide comparable lycopene plasma levels (93).

The arabinoxylan gels can act as lycopene carriers, protecting it from the gastric environment and **liberating it into the intestinal lumen** (94). A study formulated lycopene from tomato in arabinoxylans gels at 3% and 4%, and, consequently, investigate the release of lycopene from the gels formed, during 4h, which corresponds to the average transit time from oral intake to the colon (94). Once in the colon, the arabinoxylans gels can be converted in oligosaccharides by the colonic bacteria (94). As a result of the network degradation, the lycopene is released and, consequently, absorbed (94).

4.2. Intravenous Formulations with Lycopene

A study in rats revealed that lycopene encapsulated in nanoliposomes presents a higher degree of recovery from structural changes of **kidney tissue induced by methotrexate**, reduced it more efficiently than lycopene dissolved in corn oil (21). Therefore, the formulation with nanoliposomes avoid the rapid interaction between lycopene and highly reactive compounds, such as plasma proteins and/or metal ions (for instance, K^+, Ca^{2+}, Mg^{2+}, Al^{3+}, or Cu^{2+}), prolonging its presence in circulation and, as a result, allowing lycopene to achieve the targeted damaged tissue (21).

4.3. Topical Formulations with Lycopene

In the last years, dermal delivery after topical application of actives compounds, including lycopene, has gained crescent importance and development because of the lower risk of systemic side effects compared to oral delivery (23). Lycopene is being widely used in cosmetic products as age-defying, facial moisturizers and eye creams in order to protect the skin from potential damages of UV radiation and prolong the tan (17).

There are several advanced drug delivery systems such as nanoparticles, liposomes and cyclodextrins, nano/ microemulsions, among others (23). Firstly, topical application of lipid **nanoparticles** allows the lipid interaction between epidermal lipids of the stratum corneum and the carrier (23). Relatively to **liposomes**, they are usually hollow spheres ringed by a lipid bilayer (23). Finally, **cyclodextrins** are water soluble and non-reducing cyclic carbohydrate polymers (23). In topical formulations, the derivatives commonly used are β- and methylated-β-cyclodextrins (23).

The *in vivo* delivery of lycopene can be considered a challenge (95). In fact, there already are several strategies to deliver the lycopene, such as the carriers already mentioned, besides **oil-in-water (O/W) emulsions stabilized by plant and lacteal proteins** (soy, pea, whey and sodium caseinate), having the plant proteins a better performance on lycopene stability in colloidal systems than lacteal proteins (95).

4.3.1. New Lycopene Formulation Techniques

Lycopene release can be improved by a solid dispersion technique - the **dripping pill preparation** in water-soluble carriers, increasing its solubility (27).

Encapsulation techniques of lycopene can enhance its stability through the conversion of the liquid form to the solid one in order to favour the lycopene manipulation and use (96). The encapsulation can be performed by spray-drying, freeze-drying, complex coacervation (96), phase separation, co-crystallization, interfacial polymerization, microwave-assisted, supercritical fluid extraction, among others (97).

There are several agents that can be used in encapsulation process, like maltodextrin, whey protein isolate and octenylsuccinate-modified starch (98). A

study, using these three encapsulating agents, showed their effect on the physicochemical properties as well as the evaluation of lycopene stability from tomato concentrate microencapsulated by spray drying (98). The encapsulating agents that proved to be the most adequate to protect lycopene during spray drying and storage were the maltodextrin and the modified starch since the highest retention of lycopene immediately after drying besides an improved antioxidant capacity and lower degradation rates of lycopene were observed with those agents (98).

4.3.2. Lycopene-loaded Advanced Delivery Systems

Regarding the topical application of lycopene, it should be noted its strong affinity for stratum corneum components, being retained in the outermost skin layer (44). Consequently, the penetration of lycopene into deep skin layers can be difficult (44). Once applied on the skin, **lipid nanoparticles** form films with good adhesiveness to contact surface, increasing skin hydration (22). Lycopene-loaded lipid nanoparticles demonstrates an occlusive property through the lipid film formation and nanocrystalline characteristics of lycopene besides the lipid matrix (22).

Over the last years, advanced carriers have been designed to penetrate the skin in intact form, and allow the percutaneous absorption of the active within the skin (23). To move freely into the skin and deliver loaded actives into the systemic circulation, this carrier must have the ability to deform itself due to the highly flexible membranes (23). Thereby, to distinguish from the conventional liposomes, these new carriers were called as transfersomes or **deformable vesicles** (23). For instance, polysorbate, a common surfactant present in transfersomes, as well as ethanol present in ethosomes, can facilitate lycopene solubilisation and incorporation efficiency (44).

Microemulsions with medium chain glycerides (mainly mono- and diglycerides) are important delivery systems to promote the cutaneous delivery of lycopene and improve the antioxidant activity in the skin (79). A microemulsion containing mono/diglycerides as oily phase has a higher increase in the penetration of lycopene into viable layers of the skin, than a microemulsion containing triglycerides (79). Therefore, the substitution of triglycerides for mono/diglycerides in microemulsions not only influences the structure of the system and its potential to modulate the barrier function of the skin, but also increases the delivery of lipophilic compounds into the skin (79). A microemulsion is not an inert vehicle since the addition of compounds to the microemulsion may affect its phase behaviour (79,99). In fact, lycopene appears to disturb the flexibility of the micelle and its spontaneous curvature (79,99).

4.4. Other Formulations with Lycopene

It seems that scaling and root planning alone were not effective to neutralize the ROS action on periodontal tissues (100). Thereby, a study assessed the important role of **lycopene on chronic periodontitis**, revealing that the delivered lycopene by solid lipid microcapsules associated with scaling and root planning may present a

protective effect on periodontal tissues through the locally reduction of proteins oxidative damage (100).

5. FUTURE HEALTH PERSPECTIVES

The **resonance Raman spectroscopic** method is useful for *in vivo* analysis of the carotenoids in human skin (75), being an alternative to skin microtopography, which only supplies superficial skin architecture data, and to invasive measurements as histologic biopsies (23). This non-invasive method involves a laser that emits two wavelengths (488 nm and 514.5 nm) (75). While the 488 nm wavelength is absorbed not only by lycopene but also by β-carotene, the 514.5 nm wavelength is absorbed mainly by lycopene (75). Thus, knowing the absorption spectra of carotenoids, the quantitative concentration of lycopene can be determined (75). In carotenoids, there are three salient Raman lines due to many factors like the rocking motions of the methyl groups (C-CH3), the carbon–carbon single bond (C-C) and carbon–carbon double-bond (C=C) stretch vibrations of the conjugated backbone (75).

Currently, it is possible to observe lycopene deposition in cultured cells and some tissues through a new noninvasive immunohistochemistry method that uses a monoclonal antibody (mAb) against lycopene (101,102). Recently, a study conjugated the mAb against lycopene with fluorescence, to colour the lycopene present in corneocytes and sebum, after the daily intake of lycopene capsules (7 mg) during 4 weeks (101). In the future, **new lycopene quantification assays** might be performed from lycopene-specific monoclonal antibody in order to identify individuals with lycopene deficiency as well as to monitor, optimize and personalize the lycopene supplementation of risk groups in the general population (101).

6. CONCLUSION

In general, consumption of lycopene is strongly recommended considering the numerous preventive strategies to decrease the risk of diseases mediated by oxidative stress, such as hypertension, atherosclerosis, cardiovascular disease, neurodegenerative disorder, cancer, among others.

Depending on the population studied, the dietary intake of lycopene varies mostly due to inter-individual difference. Furthermore, the lycopene intake may not be enough to prevent or surpass a lycopene deficiency, mainly in elderly people as well as in overweight, obese or with metabolic syndrome people. Thereby, lycopene mostly extracted from tomato exerts an important role in human health, including skin diseases. Notwithstanding, there is certainly an additive or synergistic action of other bioactive phytochemicals present in the tomato matrix or in the diet in general that can be responsible for the health effects previously suggested. Additionally, considering that different antioxidants have a specific location in cell membranes, the combination of lycopene with other antioxidants will offer a large potential for human health.

More robust research work and clinical trials following a standard design remain to be performed at higher extent to evaluate the lycopene biological function at cellular level as well as to explore whether there are differences between all-trans and various cis isomers of lycopene regarding this activity. The purity, safety and lycopene content on tomato matrix as well as its bioactive stability while formulated are also of great importance.

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ANNEX 1 – Mechanisms behind biological properties of lycopene

Lycopene			References
Mechanisms	**Main action**	**Consequences**	
Free radicals scavenger	Antioxidation	• Decrease susceptibility to oxidative stress • Protect against photosensitized oxidation • Prevent lipid peroxidation and DNA damage • Reduce fasting blood glucose, preventing insulin resistance and reducing the risk of gestational diabetes mellitus • Improve sperm count and viability • Revert tumour initiation • Regenerate the non-enzymatic antioxidants • Reduce indirectly age-related macular degeneration	(5,18,23,37,47,49,74,85,86)
Phase II detoxifying enzymes inducer Phase I detoxifying enzymes inhibitor	Modulation of phases I and II enzymes	• Protect tissues, cells and low-density lipoprotein from reactive oxygen species and electrophilic molecules	(5,17,23,49,103)
ARE transcription system activator	Antioxidation	• Xenobiotic metabolism	(5)
Activator of antioxidant genes expression Decrease inflammatory mediators (as NF-κB, IL-1β, TNF-α, TGF-β, …) IL-10 stimulator Modulate cyclooxygenase and lipoxygenase expression Decrease $A\beta_{1-42}$-induced mitochondrial dysfunction	Anti-inflammation	• Reduce liver injury induced by ischaemia– reperfusion model • May attenuate ventricular remodelling post-myocardial infarction • Prevent insulin resistance, type 2 diabetes, and metabolic syndrome in general • Repair learning and memory deficits	(5,23,74,88,89,104–107)

Attenuate p53 and caspase-3 mRNA expression
 	
HMG-CoA inhibitor
	Hypocholesterolemic action	• Prevent lipid accumulation
		  ○ Reduce atherosclerotic plaque
		  ○ Prevent/Reduce CVD (as atherosclerosis) and some cancers
			(18,108)

IL-12 secretion and IFN-γ up-regulator	Anti-angiogenesis	• Suppress growth and metastasis of cancers	(109)

Cx 43 mRNA stabilizer	GJC induction	• Inhibit the carcinogen progression	(5,18,23)
Intermediate in biosynthesis of vitamin A precursor carotenoids	Modulation of nuclear receptor superfamily (RARs, RXRs, …)	• Prevent the development of carcinogen induced tumours	(7,56)
IGF-1R signalling pathway suppressor	Anti-proliferation	• Inhibit proliferation of cancer cells through: o Arrest G1/S phase of cell cycle o Lead to apoptosis in cancer cells • Induce cell differentiation	(5,18,23,49)
Adaptive immune response activator	Immune modulation	• Protect from bacterial infection and radiation	(23,31)