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Beneficial Effects and Perspective Strategies for Lycopene Food Enrichment: A Systematic Review

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ABSTRACT

Diets rich in antioxidant compounds are correlated to more favorable health outcomes. Carotenoids are powerful antioxidants, thanks to their effectiveness as scavengers of free radicals. The unique acrylic structure together with the presence of two additional double bonds make lycopene one of the most efficient carotenoids oxygen quenchers. Tomatoes (Solanum Lycopersicum, from which it takes its name) and their derivatives represent the major dietary source of lycopene. Other natural sources of lycopene are melons, guava and pink grapefruits. Cooking food can affect lycopene bioavailability that appears higher in heat-treated compared to raw products. Since lycopene is a lipophilic substance, its intestinal absorption and its distribution in body is related to the presence of lipids in diet and tissues, respectively. For this reason, plasma concentration of lycopene differs widely in individuals, as a result of the influence of different factors. In this review, we provide a complete and up-to-date overview of chemical, biochemical and metabolic properties, addressing the state of art on lycopene as protective molecule and the methods used to produce lycopene enriched foods and supplements from tomato industrial waste.

Keywords: Lycopene; Antioxidants; Cancer; Protective effects; Supplements; Green extraction.

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INTRODUCTION

With more than eighty percent of biomass, plants represent almost the totality of living organisms that populate the world. As any other organism, even the life cycle of the plants is characterized by meticulous sequence of specific phases. Each single stage requires a limited number of macromolecules whose biosynthesis and degradation constitute the primary metabolism. Alongside to what already described, a secondary metabolism exists in plants. This metabolic system uses intermediates and/or final products of primary metabolism in order to generate a large variety of organic compounds named phytochemicals or phytocompounds. Although their functions are still partially unknown, these compounds define the color and organoleptic properties of fruit and vegetables [1]. Secondary metabolism differs from species to species and it is generally conditioned by ecological and genetic factors. In this regard, it has been demonstrated that an elevated atmospheric CO_2 affects the formation of secondary metabolism compounds and nutritional quality of vegetables [2]. Across the years, phytochemicals are receiving more attention thanks to their ability to prevent or attenuate the oxidative stress in several organisms, including humans [3]. The negative redox potential of these molecules gives them the power to become the preferential targets of free radicals and reactive oxygen species (ROS), as superoxide radical (O_2^-), hydroxyl radical (OH.) and hydrogen peroxide (H_2O_2) [4]. Although oxygen is essential for eukaryotic and prokaryotic cells and ROS production represents a physiological process, high doses can potentially pose a threat for cellular components, compromising their effective functionality. However, cells have developed enzymatic and non-enzymatic systems to control ROS production with a view to maintain their levels under pathological range [5]. As opposite sides of the same coin, low physiological concentration of ROS helps cells to prevent pathogens attack, while an excess of the same compound causes a wide range of pathological diseases in human, such as vascular alterations, pulmonary alterations, cataracts, rheumatoid arthritis, neurodegenerative diseases and cancer [6-7]. Even the aging process appears to be related to the accumulation of reactive oxygen species [8]. Due to the presence of one or more unpaired electrons in the outermost orbital, free radicals bind easily and quickly other compounds in order to reach the chemical stability. In contrast to other molecules, which become themselves unstable and free to behave as free radicals, antioxidants block ROS-induced chain reactions keeping their inert status, even after specific interactions with reactive species [9]. Except for plants, animals and humans are able to synthesize only a restricted amount and a small number of antioxidant compounds. In presence of particular enzymatic deficiencies or environment/behavioral adaptive responses, the intrinsic systems designed to neutralize the effect of free radicals and reactive oxygen species, turn out to be not more efficient causing the onset of illnesses. In this scenario, diet intake represents a valid tool to restore the right balance and it may be used as a possible approach to prevent and/or to treat these pathological conditions. Carotenoids (β-carotene, lycopene and lutein, zeaxanthin), ascorbic acid (vitamin C), α-tocopherol (vitamin E), polyphenols and flavonoids are some of secondary metabolites generated in plants, and daily present in human diet, whose antioxidant power has been well characterized [10].

In this current review, we give an overview on carotenoids with particular emphasis on lycopene, starting from chemical and biochemical characterization, going through their putative role in the prevention of several human diseases and concluding with an accurate analysis of the existing and innovative extractive methods/strategies for food enrichment and tomato waste management.

Chemical, biochemical and metabolic features of carotenoids

Carotenoids include a large cluster of plant-related colored pigments that were discovered for the first time in 1831 in *Daucus carota* root [11]. Chemically, they are terpenoids in which it is possible to discriminate a central skeleton, with 22 carbon atoms, and two terminals of 9 carbon atoms each. The terminal units may be acyclic, as in lycopene, cyclic, as in α- and β-carotene, or both cyclic and acyclic, as in γ-carotene. Cyclic units may consist of a wide variety of functional groups such as alcohol, ketone, epoxy and phenyl group [12]. Based on the presence or absence of the oxygen atoms in their carbonic chain, carotenoids are generally divided in xanthophylls and carotenes. Oxygen is a precise hallmark of xanthophylls that includes lutein, zeaxanthin, violaxanthin and auroxanthin. Concerning carotenes, although their molecular structure is quite similar to the xanthophylls, the oxygen deficiency confers them hydrophobic properties. Carotenes include lycopene, β-carotene, α-carotene and many others. Bixin and crocetin are carotene derivative compounds that define a specific subcategory, named carotene acids, which differ from the main one for the presence of carboxylic acid [13].

As mentioned before, carotenoids have been mainly isolated in plants and in marine algae where they participate in photosynthetic process, protecting plant cells against the large number of free radicals that occur during this procedure. Speaking of which, carotenoids have been identified in chloroplasts, together with chlorophyll, generally complexed with proteins and fats [14]. Moreover, depending on the carotenoid molecules that are mainly represented in fruit, they define the relative color; red in tomatoes (lycopene), orange in carrots (β-carotene) and corn (zeaxanthin), yellow in marigold (violaxanthin and auroxanthin) and saffron (crocetin) [11-12]. Even though carotenoids production is a peculiarity of the plant kingdom, similar compounds have also been found in bacteria and in animal organisms, in fact they give the red color to the shell of the lobsters and dye the feathers of numerous birds and the egg yolk [14].

Despite carotenoids being crucial for human life, our body is not able to synthesize these compounds therefore diet represents the only way to guarantee the daily requirement. Vitamin A plays an important role in the biosynthesis of many glycoproteins, which regulate cell differentiation and gene expression. α-, β- and γ-carotenes represent the main source of provitamin A that, at the intestinal mucosa level, is converted in vitamin A [11]. Although more than 600 different carotenoids have been chemically characterized, β-carotene is considered the most biologically active in terms of provitamin A contents [15].

In addition, several studies show how carotenoids are not only an incredible source of vitamin A, but they also possess important protective properties towards human health and diseases [16]. In this respect, zeaxanthin, lutein and lycopene are potent antioxidant molecules.

Lycopene and tomato: more than a union

As a member of carotenoid family, lycopene is an unsaturated aliphatic hydrocarbon that contains 13 carbon-carbon double bonds, 11 of which are linearly conjugated and arranged. The extended polyene conjugated system represents the key to its biological activity and it is responsible for its antioxidant power. Present in tomatoes, lycopene is the last carotenoid that is formed during maturation process and it is responsible for the red color. The proof of this, biosynthesis increases considerably when the chloroplasts, in which chlorophyll is synthesized, switch to chromoplasts, where the synthesis of carotenoid pigments occurs [17]. The skin and pericarp of tomato fruit are particularly rich in lycopene and other carotenoids. While the skin contains 12 mg of lycopene per 100 g, the entire mature tomato only has 3.4 mg per 100 g [18]. Moreover, the lycopene content in tomato may change, reflecting the influence of the variety, the degree of ripeness and both agronomic and environmental growth conditions [19].

Unfortunately, tomato manufactory process can cause lycopene degradation mainly due to isomerization and oxidation. Low storage temperature, low oxygen levels and reduced light exposure are factors that generally reduce the oxidation of lycopene. Moreover, adding antioxidant agents, such as ascorbic acid or sodium acid pyrophosphate, during the processing may limit the above events promoting the quality of the final product [20]. As for isomerization, in fresh tomatoes lycopene has been found in all-trans configurations, while mono- or poly-cis isomerization forms can occur as a consequence of the manufactory process. Nevertheless, isomerization affects not totally lycopene content both because the storage facilitates re-isomerization, especially from cis- to trans, and because cis- isomers are better absorbed at intestinal levels thanks to their higher solubility grade in mixed micelles [21].

Special reference needs to be made for the temperature used during the transformation process, especially because heat is capable of inducing both degradation and lycopene isomerization. It has been proven that temperatures between 90° and 150°C cause a dramatic decrease in all-trans lycopene content and a contemporary increase in cis-isomer concentration [22]. On the other hand, practices in which a physical destruction or a softening of the cell membranes of the plant is produced, such as cooking or grinding, may rise lycopene bioavailability due to the breakup of lycopene-protein complexes [23]. Furthermore, because lycopene is a lipophilic compound, in aqueous systems it can aggregate and precipitate in crystals. In this regard, a well-performed study shows that adding olive oil during cooking of tomatoes greatly increases the absorption of lycopene. The authors reported an increase of 82% in blood concentration of all-trans-lycopene and 40% of cis-lycopene, comparing 11 subjects who consumed tomatoes in olive oil *vs* 12 subjects who consumed tomatoes without it [24].

Protective effects of lycopene in human diseases

Several studies have highlighted the importance of the daily consumption of fruit and vegetables in order to reduce the risk of developing diverse pathologic conditions, including cardiovascular diseases and different cancer types [25, 26].

Beneficial effects that result from their consumption are mainly due to the high content in carotenoids, vitamin E, isoflavones and polyphenols, which principally operate as antioxidant agents [27]. Notably, it has been demonstrated that the capability of lycopene to neutralize free radicals is above the average (2 times more than β-carotene and 10 times more than α-tocopherol), making it a very interesting substance for its applications as a multiple therapeutic agent [28]. On this subject, it has been proved that lycopene inhibits the growth of cancer cells blocking cell cycle progression and affecting specific signal reception factors [29]. It has also been estimated that regular intake of tomato, and hence lycopene, reduces the risk of the onset of many tumors by 43%, in particular to lungs, stomach, colon, mouth, pharynx and prostate tumors [30]. Moreover, with regard to mutagenicity, in lycopene-pretreated mice the micronuclei numbers were significantly reduced after individual mutagens administration [31]. Other studies have underlined the relationship between lycopene and heart/artery wellness; in fact, lycopene-contained foods consumption limits oxidation of LDL-cholesterol, reducing the risk of cardiovascular disease by 50% [32]. In addition, in a recent paper Langella et al. show the ability of diets enriched in acidic components, including tomato, to reduce symptoms that are related to gastritis and gastroesophageal reflux [33].

Carcinogenesis, atherogenesis and cardiovascular diseases are just some pathological conditions in which lycopene may have positive effects in terms of prevention and treatment. In this specific section, we point out the protective role of lycopene in several human illnesses.

Cardio protective and anti-inflammatory properties

High LDL-cholesterol serum levels, cigarette smoking and elevated systolic blood pressure are the main risk factors for the outbreak of atherogenesis and other cardiovascular diseases. The oxidative stress, however, represents the mechanism by which these etiological causes are connected [34]. In the last years, several original articles and reviews have provided evidence in favor of lycopene as a useful cardioprotective agent [35-36]. Lately, Ried and Fakler performed a meta-analysis, using a random effect model of all studies available on PubMed and Cochrane databases, in order to evaluate the effect of lycopene on blood lipids or systolic blood pressure. They observed that lycopene was capable of reducing systolic blood pressure in all trials analyzed, whereas the reduction of total and LDL-cholesterol was significant only in a specific subgroup of trials in which a daily dosage of 25mg or more was used [34]. Furthermore, adding tomato extract to patients treated with ACE inhibitors, calcium channel blockers or their combination with low dose diuretics, caused a decrease of 10 mmHg or more in systolic and 5 mmHg or more in diastolic pressure [37].

In a recent paper, Petyaev et al. focused on the different types of nutraceutical formulation of lycopene used for supplementation and their relative effects on cardiovascular variables. Although they did not disprove the promising union of lycopene and cardiovascular benefits, they showed how a different lycopene source had a dissimilar outcome in patients with coronary vascular disease [38]. Notably, they demonstrated that lycosome formulation led to a higher increase in serum lycopene levels, FMD and StO_2 values, and a more prominent reduction in oxidized LDL compared to lactolycopene. However, preventing LDL oxidation is not only an exclusive quality of lycopene, since other plant-related pigments have been established to have similar outcome [39]. Zeng et al. proved that lycopene prevents cardiac hypertrophy, suppressing ROS production and blocking ROS-dependent MAPK and Akt/GSK3β signaling [40].

Hypertension, cardiovascular diseases and smoking are also the leading causes of chronic kidney disease (CKD). Hirahatake et al. observed a strong inverse association between higher concentration of serum carotenoids, including lycopene, and rapid eGFR decline over 5 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study [41].

Several reports provide evidence on the ability of lycopene supplementation to modulate both allergic and inflammatory processes [42]. Hazlewood et al. evaluated the effects of lycopene on allergic inflammation in a mouse model presenting the allergic airway disease (AAD). They observed that lycopene supplementation was able to affect the cytokine production and therefore allergic and inflammation responses [43]. In addition, tomato powder (TP) decreases high fat diet-induced proinflammatory cytokine in liver and in the epididymis adipose tissue of C57BL/J6 mice. The anti-inflammatory effect of lycopene in this experimental study was related to IκB and p65 dephosphorylation [44].

Photo protective activities on skin diseases

Ultraviolet (UV) rays induce formation of reactive oxygen species, oxidative stress and free radicals in skin tissue, causing short and long-term effects. In order to verify the photoprotective effect of lycopene on cutaneous erythema, a well-controlled and randomized study exposed 20 adult women (phototype I and II) to 55 g/day of tomato sauce for 12 weeks. After supplementation, the authors showed that the minimum dose of UV radiation that caused cutaneous erythema was significantly higher in the supplemented group compared to the control. Moreover, histological analysis of UVR-induced skin biopsies exhibited a decrease of metalloprotease-1, an early marker of skin damage, and mitochondrial DNA 3895bp deletion, as an index of nucleotide damage, in the treated group [45]. In another paper, Chen et al. display how lycopene pretreatment attenuated UVB-induced cell hyper-proliferation and promoted apoptosis in both human keratinocytes and SKH-1 hairless mice. In details, they demonstrated that lycopene-induced photoprotective effects were mediated by a negative regulation of FOXO3a and by an involvement of the mTORC2/AKT Signaling Pathway [46]. More recently, it has been estimated that lycopene plasma levels of atopic dermatitis (AD) patients are comparable to healthy volunteers, while the percentage of 13-cis-lycopene isomers has significantly increased in the same individuals [47]. These alterations might indicate a specific consequence of the above chronic skin inflammation disease, representing a possible biological marker to evaluate the therapeutic efficacy and to monitor the disease progression. A preliminary study indicates how the daily facial use of Lycogen™, a supplement containing a high lycopene percentage, reduces the oxidative processes and prevents aging of the skin [48].

Beneficial effects on nervous system

The oxidative damage caused by free radicals on neurons can lead to an increase in the incidence of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD) [49]. Food and diet can represent a powerful ally to contrast these pathological conditions. In this regard, Scarmeas et al. investigated the association between the Mediterranean diet and Alzheimer's disease. Notably, they demonstrated that this specific feed intake in which red tomatoes are highly represented, characterized by high antioxidants content, reduced the risk of developing AD [50]. Moreover, it has also been verified that lycopene reduces Aβ1-42-induced mitochondrial dysfunction as well as the expression of different neuroinflammatory cytokines in rat brain [51]. In another *in-vivo* study, lycopene assumption reverted neurochemical defects, apoptosis and abnormalities in PD mice, representing an adjuvant strategy for the treatment of this neurodegenerative disease [52].

Numerous are the proofs that support the clinical relevance of lycopene as a protecting agent not only against neurodegenerative diseases, but also towards nervous system well-being in general. At this regard, Zhang et al. aimed to assess the potential effects of lycopene on LPS-induced depression-like behaviors. They verified how lycopene reduced LPS-induced expression of IL-1β and HO-1 in hippocampus, as well as IL-6 and TNF-α plasma levels. These phenomena were accompanied by improvement of neuronal cell injury in hippocampal CA1 regions and depression-like behaviors [53]. In another study lycopene administration attenuated the effects of 3-nitropropionic acid (3-NP), a chemical irreversible inhibitor of succinic acid dehydrogenase (SDH) used to induce neurodegeneration similar to Huntington's disease (HD) in mice [54].

Lycopene and bone tissue

Osteoporosis is the most widespread pathological condition affecting skeletal system, which leads to bone mass reduction, skeletal fragility and microarchitectural deterioration. It occurs mainly in the post-menopausal period in women as a consequence of the decreased estrogens production [55]. Modulation of osteoblast and osteoclast functions represents one of the possible pharmacologic approaches currently available in clinic for the osteoporosis treatment. In a recent study, Oliveira et al. demonstrated how daily intake of 10 mg/kg of lycopene for 60 days decreased bone loss in femur epiphysis in ovariectomized (OVX) rats. Notably, they showed that lycopene intake induced a significant upregulation of genes involved in osteoblast differentiation and bone formation, such as Sp7, Runx2, Bsp and Bglap [56]. In addition, in another *in-vivo* study, it has also been proved that lycopene treatment suppressed the OVX-induced bone turnover, as indicated by changes in biomarkers of bone metabolism, including serum osteocalcin (s-OC), serum N-terminal propeptide of type 1 collagen (s-PINP), serum crosslinked carboxyterminal telopeptides (s-CTX-1) and urinary deoxypyridinoline (u-DPD) [57].

Mackinnon et al. performed a detailed human study in which more than sixty menopausal women were exposed to a diet absent in tomato and tomato-derived foods for one month in order to evaluate N-telopeptide serum concentration, as a specific marker of bone fracture. The results of this research showed a significant increase of N-telopeptide in presence of tomato deprivation status, while the administration of tomato juices or a drink containing an extra quota of lycopene induced a decrease of the same marker [58]. Rao et al. have also obtained similar results in a cross-sectional study reported in a previous paper [59].

Eye tissue protection

The antioxidant properties by lycopene have displayed protective effects even towards eye tissue. In this regard, Vachali et al. declared that the progression of some eye's diseases, such as age-related macular degeneration and cataract, could be delayed by increased dietary carotenoid consumption and/or supplementation [60]. Notably, comparing the carotenoids' concentration of 34 patients affected by macular degeneration with 21 healthy subjects, the authors showed that lycopene levels were significantly lower in those affected by macular degeneration. A preclinical study shows that lutein or lycopene pre-incubation of ARPE-19, a representative model of human retinal pigment epithelial cells, protects from tert-butyl hydroperoxide-induced oxidative stress [61]. In addition, Inoue et al. proved the evidence that carotenoids, including lycopene, defend 661W murine photoreceptor cells against death-induced light exposure. A clear involvement of Ho-1, Nqo-1, Gclm and Nrf2 genes has been described [62].

In the era of gene therapy, finding more effective and safety methods capable of delivering specific genetic targets, represents an important aim in medicine and more specifically in ophthalmology. As drug delivery system, niosomes have gained growing attention for being osmotically active and chemically stable formulation [63]. A present study, aimed to evaluate the incorporation of the natural lipid lycopene into niosomes formulations, demonstrates that the incorporation of the carotenoid compounds clearly increased transfection efficiency in ARPE-19 cells, without affecting cell viability. Furthermore, *in-vivo* administration shows that lycopene-containing niosomes are able to transfect the outer segments of the rat retina, offering reasonable hope for the treatment of various retinal diseases [64].

A particular focus on cancer

Numerous studies show how the daily intake of the antioxidants contained in tomatoes reduces the risk of developing tumors [65]. Among the others, lycopene represents an intriguing anticarcinogenic compound both because it has antiproliferative effects against tumor cells and because it protects normal cells from chemo- or radio-therapy [66].

In gastrointestinal cancer, a second most common cause of cancer-related death, a case-control study provides strong evidence about protective effects induced by tomatoes, tomato-rich foods and lycopene against the upper aero digestive tract [67]. In addition, it has been estimated that high concentrations of lycopene in blood reduce the risk of developing gastric mucosal cancer [68].

Encouraging results have also been obtained in pancreatic cancer, a tumorigenic condition characterized by poor prognosis, lowest 5-year survival rate and in which no effective therapies are currently available. It has been proved that in subjects in whom the blood levels of lycopene were very high, the risk of developing pancreatic cancer was three times lower [69]. In addition, Jeong et al. investigated the anti-cancer mechanisms of lycopene in human pancreatic cancer cells. The results indicated that lycopene induced apoptosis in pancreatic cells, suppressing the expression of IAP proteins such as SURVIVIN, cIAP1 and cIAP2 [70]. Although several research has reported the lycopene-induced anticancer effects in prostate, describing even the possible molecular mechanisms, the role of lycopene in prostate cancer prevention remains controversial [71, 72]. In particular, two recent meta-analysis, analyzing both dietary and circulating concentrations of lycopene, underlined how lycopene concentrations were inversely related to the risk of developing prostate cancer, but they did not reduce the advanced prostate cancer risk [73, 74].

Bi et al. assessed the biological effects of lycopene in the human cutaneous squamous cell carcinoma COLO-16, human epidermal keratinocytes (HEKs) and the immortalized human keratinocyte cell line HaCaT. The authors showed that carotenoid compounds inhibited the cell proliferation and migration of COLO-16 cells but not normal keratinocytes. These phenomena were partially mediated through the activation of ERK, JNK and MTORC1 as well as the inhibition of autophagy [75].

Other findings concerning the protective effects of lycopene in cancer are present in literature, for instance kidney, lung and cervical cancer [76, 77].

In the last decade, naturally occurring molecules are receiving more attention for their potential anticancer effects [78]. Forskolin, for example, a cAMP elevating agent extracted from the roots of the Indian plant Coleus forskohlii, is emerging as a fascinating compound thanks to its distinctive antineoplastic properties both as a single agent and in combination with specific drugs. In a recent review, Sapio et al. have assembled cAMP signaling characteristics that are relevant for cancer biology to support the putative role of forskolin as an effective anticancer agent [79]. Promising and similar results have also been shown by lycopene in chemotherapy combination. In this regard, Ko and Moon showed that lycopene reduces side effects and improves the efficacy of different drugs in human breast cancer, maintaining high selectivity and low toxicity [80]. Moreover, lycopene-loaded liposomes (L-LYC) enhance doxorubicin-induced cytotoxicity in B16 melanoma cells both *in-vitro* and *in-vivo*. Doxorubicin-induced cardiotoxicity is clearly relived in combination with L-LYC. [81].

Perspective strategies: extractive methods, food enrichment and waste management

The waste materials, deriving from the transformation of plant products, represent an extremely valuable resource for their relative contents in nutrients and still bioactive compounds [82]. The low extractive yield of the current processing methods denotes the main cause of the nutrients' wastage. In this regard, it has been quantified that only a percentage between 10 to 40% of the raw materials is preserved through the manufactory processes, while the rest, that often has a "nutritional value" greater than the main processed products, becomes waste [83]. Although alternative applications have been found for some of these waste products, innovative and more effective processing methods are needed in order to increase the extractive capacities and promote the environmental and the economical sustainability. In a recent review, it has been analyzed how compounds and extracts, deriving from agronomical disposable waste, can be used in the cosmetic field [84]. In this paper, Barbulova et al. asserted that these types of products are effective, inexpensive and bio-sustainable, representing a valid alternative to the regular plant-derived extracts. In addition, the use of organic farming waste could eliminate the potential safety problems due to any residual pesticides or toxic chemical compounds utilized in non-biological plantations.

The gastronomic versatility, combined with flavor and countless health benefits, makes tomatoes one of the most used plants in the food transformation industry. Across the years, several studies have carried out their findings on tomatoes extracting methods [85, 86]. Speaking of which, a recent report has shown that individual and interactive effect of operating high hydrostatic pressure (HHPE) and solvent polarity may significant influence the extraction yield of flavonoid and lycopene content. In particular, the authors described 450 MPa and 60% hexane as the optimal HHPE extracting condition, providing the maximum flavonoid yield (21.52 ± 0.09 mg QE/g FW) and lycopene content (2.01 ± 0.09 mg QE/100 g FW) [85]. Alongside the traditional solid-liquid extraction techniques that involve the use of large amounts of solvent, more and more eco-compatible processes are being developed, such as supercritical extraction, ultrasonic, microwave, pulsed electric, enzymes- or microorganisms-extraction. In this scenario, the dynamic liquid solid rapid extraction (RSLDE) performed by Naviglio extractor has found various applications in the food industry [86-92]. Moreover, RSLDE has also been used to extract lycopene from the waste tomato processing, thus increasing the extraction yield and reducing both the procedure time and the use of organic solvents [93-95].

Another promising green technique, capable of substituting organic solvents used for lycopene extraction in the food industry, has already been published [96]. Notably, Amiri-Rigi and Abbasi have proposed lecithin-based olive oil microemulsion as a highly effective compound for lycopene collection. In addition, even though the usage of enzymatic extraction processes is quite complex, it is possible to obtain a quantity of lycopene that is 5 times greater in discarded tomatoes peel than in the pulp [97]. Actually, almost all lycopene on market comes from extraction from the pulp of fresh fruit because chemical synthesis is very expensive. Therefore, the use of genetic and breeding tools may represent a hypothetical approach to enrich the relative fruit content and to make biological lycopene more available. CRISPR/Cas9 is a site-specific genome editing technology that has been demonstrated to be a simple and effective system to manipulate DNA in various species, even in plants [98]. Newly, Li et al. used multiplex CRISPR/Cas9 technique to promote the biosynthesis of lycopene and to inhibit its relative conversion to β- and α-carotene in tomato fruits [99]. The authors identified five different genes, involved in carotenoid metabolic pathway, whose activity was related to lycopene accumulation. Surprisingly, CRISPR/Cas9-induced knockdown of those selected genes increased lycopene content in tomato fruits to about 5.1-fold.

Several million tons of tomatoes, used by the food industry every year in the world, produce a large amount of solid processed waste that needs to be arranged. Knoblich et al. assessed the possibility of using discarded tomatoes waste in feeding chickens with a view to increase the carotenoids content in eggs [100]. Although no nutritional qualities can be attributed to tomato waste, a small amount of seeds and peels in the diet of hens could increase the pigmentation of the egg yolk and lead to a detectable increase in lycopene content. Another valid alternative strategy for tomato processing waste re-engaged is represented by Biomass, a renewable resource to produce electricity. In this regard, the available findings, aimed to characterize the tomato waste as an energy source, show low sulfur and ash values, high contents in volatile substances and an elevated calorific power, probably due to the oil content [101]. Moreover, another study takes into consideration the exploitation of anaerobic fermentation as a source of methane gas, establishing a possible relationship between chemical composition and methane yield [102]. The possibility of recovering from processing waste natural polymers, and in particular polysaccharides, constitutes an additional future perspective. Procedures for purification of the polysaccharide fraction from products of the tomato industry have been developed [103]. In this paper, the authors determined both the anticytotoxic activities of tomato-derived exopolysaccharides and their chemical composition, rheological properties and primary structure. Potential applications of these biopolymers have been checked in agriculture and pharmacological field [104]. Taken together, the above cases represent a significant contribution towards sustainable agriculture and provide alternative extracting approaches to the food, nutraceutical, pharmaceutical and cosmetic industries.

CONCLUSIONS

In recent decades, a wide variety of plant-related substances, including lycopene, has been identified as protective agents against various human diseases [25, 26]. These molecules, that are often responsible for the organoleptic properties of plant products, are capable of modulating numerous biological activities and cellular functions, such as antioxidant and anti-inflammatory reactions, immune and hormonal responses, antibacterial/antiviral properties, enzymes activities [42-45, 65]. The rapid increase in supply of phytochemical compounds in nutraceutical and in functional foods, constitutes a new intriguing challenge for the industry. Efficacy and safety, as well as quality and quantity of supplements and foods containing phytocompounds, represent just some of the issues that need to be faced by manufacturing-related sector. In a world in which the waste and waste production are becoming increasingly problem, enough to be a real threat for mammalian survival on this earth, identifying valid alternative methods for waste management and recycle is the only way forward to withstand a sustainable economy. In spite of increasing number of studies that support the beneficial effects of phytochemical, extensive studies are required to define the precise daily diet intake of these molecules for each pathological condition, in terms of both morbidity improvement and prevention. In conclusion, based on current knowledge, it is not reasonable to formulate specific nutritional recommendations for phytocompounds, nevertheless we believe that their relative consumption in a varied diet, rich in plant-based and well-balanced foods, represents the best strategy to maintain and promote our wellness.

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