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Integral valorisation of tomato by-products towards bioactive compounds recovery: Human health benefits

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ABSTRACT

The tomato processing industry is one of the world's most important markets. This industry aims to optimise production, minimise energy costs and waste streams while ensuring high-quality products. This sector produces substantial amounts of by-products frequently disposed of as waste rather than reintroducing them with a new intent into the supply chain. However, these by-products are rich in bioactive compounds (BC), including carotenoids, fibre, which exhibit antioxidant, anti-inflammatory and chemopreventive properties, and cardiovascular protection. Reusing these compounds is favourable to reducing the environmental impact and enables the development of added-value products with various possible uses such as food and feed additives, nutraceuticals, cosmeceuticals, etc. This review summarises relevant issues towards the recovery and valorisation of BC from industrial tomato by-products within a circular economy context.

1. Introduction

Around 1.3 billion tons of food are wasted or destroyed worldwide (FAO, 2019), being fruit and vegetables one of the most generators of industrial by-products (Gustavsson, Cederberg, Sonesson, van Otterdijk, & Meybeck, 2011). The losses and waste of fruit and vegetables (the final products not reused or used for other purposes) constitute up to 50 % of production in the processing and post-harvest periods (de Brito Nogueira, da Silva, de Araújo Luiz, de Andrade, de Andrade, Ferreira, & Fai, 2020; de Brito Nogueira et al., 2020; Sogi & Siddiq, 2011; Sogi & Siddiq, 2011). According to the International Fresh-Cut Produce Association (IFPA), the fruit and vegetable industry consists of products that undergo cleaning, cutting, mixing and packing. They are the non-product flows of crude materials, which have a trade value lower than collection and restoration costs and are consequently disposed of as waste (Table 1). The preparation of fruit and vegetables (canning, drying, freezing, juices, jams and jellies) prolongs the shelf-life of the products. An example is the process used during tomato processing paste where is crucial to obtain products with higher viscosity and higher levels of lycopene. Hot-break process (higher temperatures used during processing, 94–97 °C, followed by the cooling process 77 °C, allows: a) a rapid deactivation of pectolytic enzymes that are essential to prevent demethylation and break-down of pectin molecules; b) obtain products with higher viscosity –the efficient extraction of pectin and hemicellulose (compounds with higher viscosity due to their high molecular weight) depends on their solubility from the cell wall into the extract and increase with hot treatments; c) the lycopene is retained (Mirondo & Barringer, 2015; Zuorro & Lavecchia, 2010). This approach can produce better flavor and color retention products (Xu, Adyatni, & Reuhs, 2018).

According to Eurostat, almost 2.2 million hectares of vegetables were consumed and processed in the European Union (EU) in 2017. The most valuable was the tomato crop, representing 11.7 % of the total EU planted area (EC, 2017). In the 2018 global tomato market, 184 million tons were predicted to rise more in the Compound Annual Growth Rate (CAGR) of 3.1 % to attached 221 million tons over 2019 to 2024. The growth of the tomato market and the improvement of tomatoes also fuel the industry's progress. It has a heavy focus on the tomato industry, and the ten biggest developing countries account for 83 % of the world's annual production.

Nevertheless, the indicators processed outside of those ten countries

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Table 1
Main BC present in tomato processing by-products and associated bioactivities.

BC			Bioactivities	References
Classes	*Subclasses*	Concentration of BC (g/100 g)		
Carotenoids	Lycopene	Peels 0.10 to 0.15 Seeds 0.013 to 0.020	Antioxidant activity Prevention of heart diseases Anti-cancer Immune defences	Singh, Ahmad, & Ahmad, 2015 Szabo et al., 2018 Young, Donkena, Yuan, He, & Zhang, 2014 Zhao et al., 2020 Górecka et al., 2020 Wu et al., 2015 Kaboré et al., 2022
	β-carotene	Peels: 0.0311 to Seeds: 0.0063	Antioxidant capacity Improve immune defences Prevention of cardiovascular diseases	Martí et al., 2016 Domínguez et al., 2020 Domínguez et al., 2020 Kaboré et al., 2022
Dietary fibre		Tomato peels: 43.98 to 59.03 Seeds: 21.55 to 22.26	Control glucose absorption Decrease the risk of cardiovascular diseases Decrease the probability of colon cancer	Jones 2014 Szabo et al., 2018 Coelho et al., 2020; Ribeiro et al., 2020 Kaboré et al., 2022
Fatty acids	linoleic acid oleic acid palmitic acid	Tomato Peels: 5.4 to 21.55	Emollient UV protection	Giannelos et al., 2005; Persia et al., 2003; Kaboré et al., 2022
Proteins		Tomato peels: 11.71 to 21.90 tomato seeds 15.18 to 38.7	Antimicrobial activity against Gram-positive bacteria	Taveira et al., 2010

have slowly risen in recent years. Over the 2017–2018 trading year, seven primary manufacturing and trade countries shipped nearly 6.34 million tons of finished goods in Europe, China, the US, Turkey, Iran, Chile and Ukraine. Almost a third (40 million tons of valued tomatoes out of 130 million tons) of tomatoes turned out to be processed worldwide. About 10 % of overall tomato production fails to meet the customers' requirements, leading to essential losses during harvest and minimal processing (Coelho, Pereira, Rodrigues, Teixeira, & Pintado, 2019). On a technical basis, most tomatoes are produced for processing into food products, namely sauce, paste, juice and canned tomatoes, generating a large volume of by-products (Fig. 1). In addition, the by-products generated, containsvarious biologically active substances that mostly are lost as waste (or may be used in animal feeding) despite being a promising source of dietary fibres, proteins, carotenoids, tocopherols, polyphenols, vitamins and other compounds (Chaudhary, Sharma, Singh, & Nagpal, 2018; Viuda-Martos, Sanchez-Zapata, Sayas-Barberá, Sendra, Pérez-Álvarez, & Fernández-López, 2014). These biochemical properties includ anti-inflammatory, anti-allergenic, antimicrobial, vasodilatory, coronary and antioxidant effects (Szabo, Cătoi, & Vodnar, 2018; Viuda-Martos et al., 2014). However, the knowledge regarding how specific tomato BC's concentration, structure, and ratios affect their activity and uptake in the human body is still limited. Thus, due to their high BC content, the growing interest in using tomato waste is explored through modern extraction methods to obtain new value-added compounds.

This review aims to present an overview of the functional and biological properties of the principal BC present in tomato by-products, their bioavailability and their integral valorisation.

2. Research published in the previous two decades

The research papers on tomato processing by-products published in each year of the last two decades were gathered by doing a search on Web of Science with the key words "tomato", "processing", "paste", "by-products" and choosing the options "all data bases" and "subject".

This implies that any articles that were available in Web of Science databases and had the above indicated terms in their title, abstract, or key words were examined.

All article abstracts were examined and classified into one of six categories: tomato processing by-products, nutritional and phytochemical content, bioactivity qualities, bioaccessibility, extraction and characterisation of carotenoids, and scale-up extraction procedure. Review papers, meeting abstracts, patents, and studies that were not written in English or did not address tomato paste manufacturing as a by-product were eliminated.

According to our search, since 2000, 135 papers (2000–2005: 4; 2006–2010: 6; 2011–2015: 27; 2016–2020: 72; 2021–2022:36) were published, which reveals that the characterization and reuse of tomato paste by-products are a growing research area.

The nutritional and phytochemical characterization of tomato by-products during processing paste has been extensively studied. However, more research studies about bioacessibility and bioavailability of bioactive compounds like carotenoids from tomato peels and pomace are needed.

3. Industrial tomato by-products

The question is, "how much tomato is wasted along the food supply chain to produce a tomato sauce?". Tomato pomace is the most critical tomato by-product (Fig. 1). Dried tomato pomace consists of 33 % seed, 27 % skin and 40 % pulp (Allison & Simmons, 2017; Viuda-Martos et al., 2014). When 344 g of tomato sauce are obtained, about 80.5 g of losses and waste are generated (Secondi, Principato, Ruini, & Guidi, 2019).

Some steps are associated with processing tomatoes. After harvest, tomatoes enter a sorting station, where extraneous materials are removed and discoloured, green and damaged tomatoes. The ideal tomatoes are chopped, and then their pulp can undergo a cold (pre-heated from 65 to 75 °C) or hot (pre-heated from 85 to 95 °C) break, depending on the type of paste desired. The pulp obtained, comprising fibre, juice, pores and skin and seeds, passes through different sieves, allowing the pulp to end up either coarser or smoother. Usually, 95 % of pulp pass through sieves and only 5 % corresponds to bagasse by-product (fibre, seeds and skin), used as feed for livestock or others applications. The evaporation step is the most energy-intensive of the tomato paste process. In this step, water is removed, and the juice, which is still 5 % solid, becomes 28 to 36 % concentrated tomato paste. Finally, the pulp is aseptically packaged. Tomato bagasse's average composition (in dry weight) is 59.03 % fibre, 25.73 % sugars,19.27 % protein, 7.55 % pectin, 5.85 % fat, and 3.92 % minerals chemical characterisation in various stages of the industrial production process. Regarding these results, tomato bagasse could be used as a potential source of fibre and protein. The tomato fibre can provide up to 80 % of all dietary fibre, which means that it is much better than other vegetable by-products on a dry weight basis.

Thus, by-products with high potential are generated during tomato processing (Fig. 1), with potential added value and health benefits.

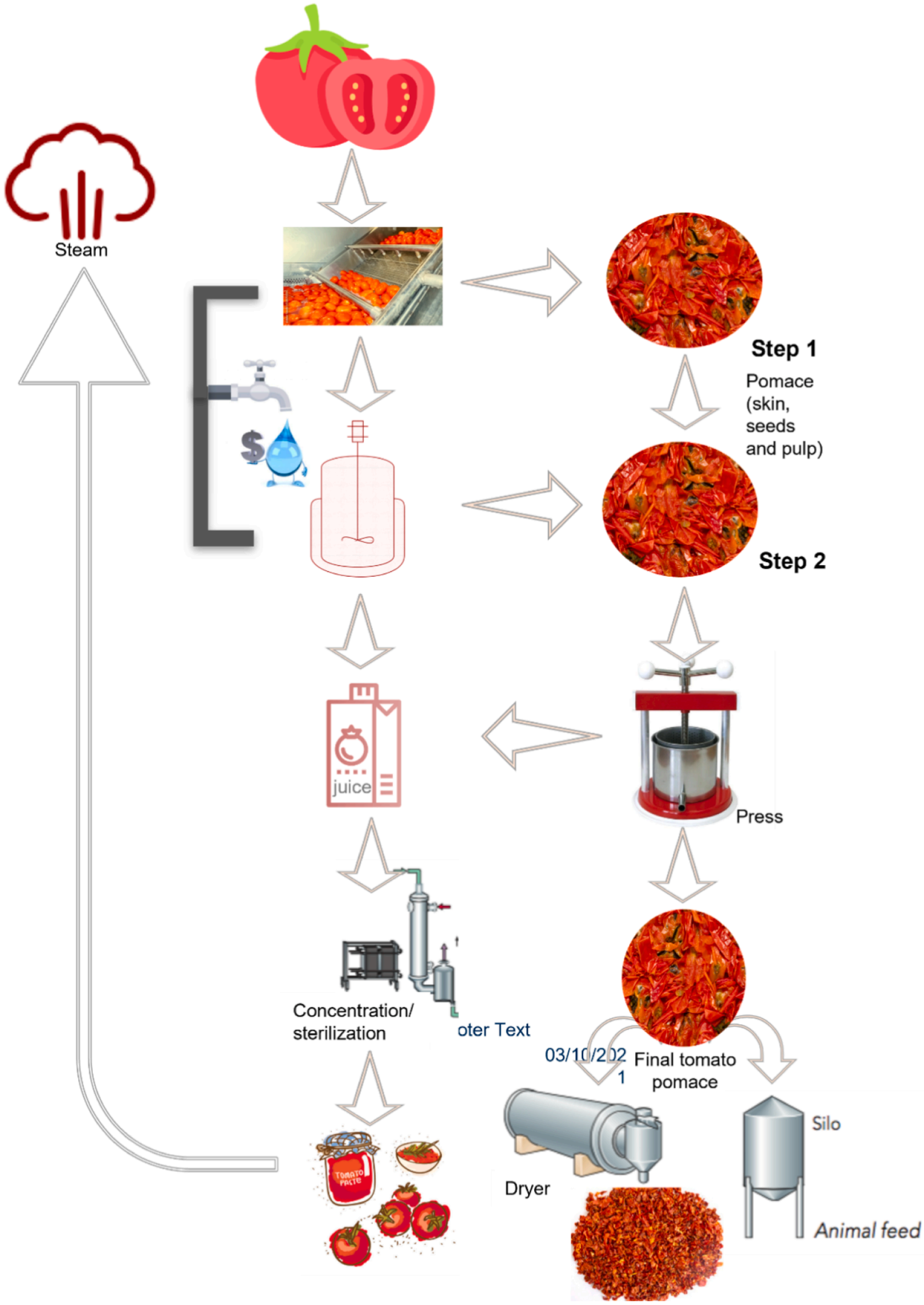


Fig. 1. By-products generated during tomato processing.

4. Valorisation approaches to tomato by-products

The diverse composition and diversity of components of fruit and vegetable wastes imply a highly multidisciplinary task when the beneficial recovery of those molecules is expected and suited to the circular bio-based Europe (CBE) and public policies (FAO, EFSA, WHO). As stated earlier, these wastes are rich in BC and can be used to obtain new valuable products instead of disposing of them with environmental impact (Coelho, Pereira, Rodrigues, Teixeira, & Pintado, 2020; de Brito Nogueira et al., 2020). The utilisation of fruit and vegetable wastes has included extraction of BC for food, nutraceutical and cosmetic applications, animal feed production, fertilisers, and bioenergy production.

There are few studies based on tomato by-products valorisation under the CBE approach. Generally, the tomato-bagasse is used as cattle feed or spilt into controlled sites, causing significant shipping costs, environmental impact, consisting of around 60 % seed and 40 % peel. Secondi et al. (2019) described the leading factors for tomato losses and waste in the supply chain for tomato sauce and the reuse of these by-products according to the CBE method. In this report, 85.9 % of overall losses and surplus are priced in alternate industries. All the destinations mentioned have been treated as low to medium value uses according to the CBE approach: feed and treatment of livestock (14.5 %); recovered for energy (12.5 %); not harvested/plowed-in (57.9 %), and for human consumption (0.7 %) of overall tomato losses and waste are used.

Many researchers investigated a potential high-quality, total recovery solution by applying tomato bagasse and its fractions as powder as a whole in food. Tomato bagasse, which is a rich food in lycopene, peroxides, dietary fibre, unsaturated fatty acids and essential amino acids with no harmful effects on the sensory and textural properties, has been integrated as ingredients into meat products, wheat flour-based foods and into the tomato paste (Lu, Wang, Gao, Ye, & Zhao, 2019). For example, it is possible to add tomato bagasse powder (2 g/100 g) or crude lycopene (50 and 100 mg/100 g) to whole wheat flour cookies. Another example reports the use tomato bagasse in the manufacture of tomato ketchup, with an improved amount of food fibre (3.8 g/100 g) (Torbica et al., 2016).

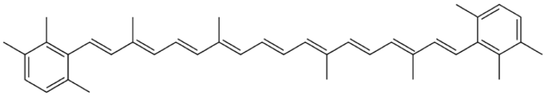
To avoid the harmful influence of food on the sensory characteristics is essential to use lower tomato bagasse powder content, reduce its powder particle size, and avoid extensive warming or use lyophilisation techniques (Belović, Pajić-Lijaković, Torbica, Mastilović, & Pećinar, 2016; Bhat, Wani, & Hamdani, 2020; Torbica et al., 2016).

Besides using tomato bagasse in food as a whole, its bioactive fractions can be obtained, such as lycopene, dietary fibre, pectin, protein and oil. Usage of conventional and novel approaches for extraction of lycopene has been the subject of tomato by-products' recovery (Løvdal, Eroglu, & Agati, 2019). In the last years, the importance of tomato bagasse valorisation has also been reported. This valorisation includes, for example, the lycopene sequential recovery and anaerobic digestion [8]. Allison and Simmons (2017), valorised tomato bagasse with sequential lycopene recovery and anaerobic digestion. The authors used mixed and organic solvent processes constituted by hexane, acetone, and ethanol to obtain lycopene. After lycopene recovery, the authors also bioconvert methane via anaerobic digestion, using pre-treatments with ionic liquids. They verified extraction yields of lycopene above 293 to 476 mg g^{-1} DW. In another study, in 2018, the researchers have highlighted the use of tomato bagasse as a raw material for the manufacture of biomaterials. The authors produced a mixture of unsaturated and polyhydroxylated fatty acids through hydrolysis of tomato pomace by-products; and a non-hydrolysable secondary residue. The authors showed a yield of approximate 31 % w/w, which is compatible with the lycopene and proteins recovery by standard process (alkaline hydrolysis at medium temperatures followed by neutralisation) (Benítez et al., 2018).

5. Bioactive compounds

The central tomato BC are carotenoids (e.g., lycopene), tomato fibre, tomato seed oil and enzymes (Table 2.2). They can be recycled into the food chain as functional ingredients/additives for different products and applications (Coelho et al., 2020; del Valle, Cámara, & Torija, 2007; Shi & le Maguer, 2000; Taveira et al., 2010). Both polyphenols and carotenoids represent essential metabolites abundantly present in fruits and vegetables. Their antioxidant properties play a crucial role in preventing chronic illnesses, mainly cancers or cardiovascular diseases (Coman et al., 2019).

(i) Carotenoids



The carotenoid's general structure is a polyene chain with 9–11 double bonds that may terminate in rings. They are a class of fat-soluble plant- and microorganism-based pigments that produce various colours such as purple, orange and red. To date, more than 750 natural carotenoids have been reported, but only 20 have been identified in the blood and tissue of humans. Carotenoids are phytochemicals with antioxidant properties, and they serve as important dietary sources of vitamin A. They interact synergistically with other antioxidants to protect cells and tissues from oxidative damage (Szabo et al., 2018).

Carotenoids are grouped according to their chemical constituents into two categories, namely xanthophylls and carotenes. Oxygenated derivatives are known as xanthophylls; additionally, aldehyde groups (*β*-citraurin), epoxide groups (neoxanthin, antheraxanthin, and violaxanthin), oxo/keto groups (canthaxanthin and echinenone), and oxygen substituents (zeaxanthin and lutein) are categorised as complex xanthophylls. At the same time, hydrocarbon derivates only carotenoids (lycopene, α-carotene, and β-carotene) are named carotenes (Tan & Norhaizan, 2019).

Thanks to the association of carotenoids to human wellbeing, numerous recent experiments have been conducted to revaluate tomato industrial by-products by extracting carotenoids. The method of extraction applied can strongly affect the amount and quality of this BC.

Tomato pomace drying conditions, light exposure and tomato cultivar may also be of significant value in the recovery of carotenoids. Due to these reasons, to reduce losses, carotenoids should be extracted/used directly after treatment or for a limited period after drying (Szabo et al., 2018).

Lycopene

Lycopene is the most common tomato carotenoid (lycopene, phytoene, phytofluene, β-carotene, γ-carotene; δ-carotene; lutein; neuroporene, and α-carotene). It is a photosynthesis and photoprotection red carotenoid (Caseiro et al., 2020; Martí, Roselló, & Cebolla-Cornejo, 2016). The acyclic carotenoid $C_{40}H_{56}$ is unsaturated, and its optimum pH stability is 3.5–4.5. Several studies have demonstrated the possible health benefits of lycopene (Nagao, 2011; Szabo et al., 2018, 2019). This antioxidant compound (Coelho et al., 2019; Navarro-González, García-Valverde, García-Alonso, & Periago, 2011) lowers the likelihood of coronary disorders (Szabo et al., 2018), cancer (primarily the prostate) (Boileau et al., 2003) and immunological illnesses (Zhao et al., 2020). Since 1997 lycopene may be used as a colouring in food and drinks and is classified as E160d. It can be used as a dietary supplement in the food industry (Faustino et al., 2019). However, this compound is highly hydrophobic and can be deficient in the human body's bioavailability. It is insoluble in water and methanol, typically solvent-solubilised in organic solvents such as chloroform, hexane, carbon disulphide, acetone, petroleum ether and gasoline (Caseiro et al., 2020). Thus, it is necessary to apply different technologies to increase its solubility and bioavailability (Caseiro et al., 2020).

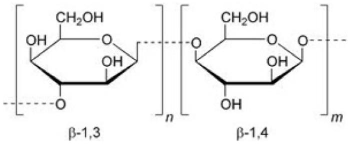
Tomato by-products may contain lycopene in a range of 80 to 150 mg/kg, while the tomato pulp contains 110 mg/kg and the tomato peel contains 540 mg/kg. Tomato cooking and processing improve the bioavailability of lycopene (Kalogeropoulos, Chiou, Pyriochou, Peristeraki, & Karathanos, 2012; Navarro-González et al., 2011; Nour et al., 2018).

β-Carotene

β-Carotene is a regularly used plant pigment and is one of the most studied in the carotenoid family. Often, Vitamin A has been the main nutritional precursor. Linear lycopene is turned into β-carotene by adding beta-ionone rings at both ends of the molecule, under the enzyme lycopene-cyclase (β-Lcy) (Rosati et al., 2000; Strati & Oreopoulou, 2016). β-carotene dietary origins are black and light green vegetables found in carrots, orange, kale, spinach, turnip greens, apricot, and tomatoes. β-carotene is the second most widely detected carotenoid in industrial tomato waste after lycopene, as indicated by the latest biological research (Urbonavičienė, Bobinaitė, Trumbeckaitė, Raudonė, Janulis, Bobinas, & Viškelis, 2018). A study reported that the tomato by-products, constituted mainly by skins and seeds, contain higher amounts of β-carotene 149.8 ± 6.4 mg dry weight) than the whole Heinz hybrid tomatoes (86.1 ± 4.4 mg dry weight) (Kalogeropoulos et al., 2012). Various epidemiological studies have revealed that β-carotene may improve immune function and have antioxidant capacity. β-carotene blood levels in humans are reversely associated with the risk of Type 2 diabetes and obesity, which are significant cardiovascular risk factors. However, these benefits seem to disappear when β-carotene is administered as a pharmacological supplement in high doses (Martí et al., 2016; Satia, Littman, Slatore, Galanko, & White, 2009).

The most clearly shown feature of β-carotene is provitamin A development in humans. Because of its chemical composition, β-carotene can be hypothesised to create two retinol molecules through the enzyme β-carotene-15,15′–oxygenase, whereas the other provitamin A carotenoids can produce only one molecule (Satia et al., 2009). In a study by Weber and Grune (2012), the importance of β-carotene to human vitamin A generation has been addressed in depth. Because of different factors influencing bioconversion and bioavailability of provitamin A carotenoids, it is difficult to evaluate the recommended dietary dose to achieve maximum vitamin A absorption. In terms of nutrients, one of the main measures to avoid vitamin A deficiency is to improve the food supply containing vitamin A in the least developed areas (Weber & Grune, 2012). Industrial tomato waste is a cheap source of BC, meaning that the issues associated with vitamin A deficiency can be minimised.

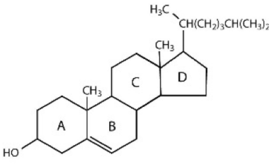
(ii) Dietary fibre



Dietary fibres (DF) consist of polymers of 10 or more monomeric carbohydrates such as polysaccharides, oligosaccharides and lignin. These food components are resistant to digestive enzymes (Coelho et al., 2020). Insoluble and soluble fibres can control glucose absorption and reduce plasma cholesterol, thereby avoiding obesity, decreasing the risk of cardiovascular disorders, colon cancer and enhancing the digestive process (Jones 2014; Szabo et al., 2018; Coelho et al., 2020; Ribeiro et al., 2020).

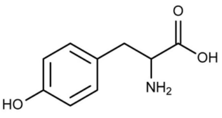
The content of tomato DF reported in the literature ranges between 50.74 and 59.03 g/100 g (Silva et al., 2019; Szabo et al., 2018), from which 40.5 g/100 g were insoluble fibre (Alvarado, Pacheco-Delahaye, & Hevia, 2001). Therefore, this by-product could be applied in the food industry as an excellent source of fibre. In food labelling, it can be referred "source of fibre," when it has at least 3 g/100 g or 1.5 g/100 g dietary fibre, under Regulation 1169/2011/EU (The European Parliament and the Council of the European Union. (2011), 2011).

(iii) Lipids



Tomato by-products contain a lipid content in the range of 32 to 60.0 g/kg for peel and between 40.4 and 63.7 g / kg for seed (del Valle et al., 2007; Giannelos, Sxizas, Lois, Zannikos, & Anastopoulos, 2005; Porretta et al., 2009; Rossini et al., 2013). Authoritative researchers reported that such by-products are rich in unsaturated fatty acids (77.04 %), with only 22.72 % of saturated fatty acids. The only main fatty acids present in this by-product is linoleic acid, followed by oleic and palmitic acid (Giannelos et al., 2005; Persia, Parsons, Schang, & Azcona, 2003). The tomato seed oil is used in cosmetic formulations as emollient and UV protection.

(iv) Protein



The three-dimensional arrangement of atoms in an amino acid-chain molecule is known as protein structure. Proteins are polymers, especially polypeptides, that are made up of amino acid sequences. Defatted tomato seeds have been ascribed with hypocholesterolemic properties and can be used as a food product (Knoblich, Anderson, & Latshaw, 2005; Szabo et al., 2018). The mean protein level reported in tomato pomace was 21.9 % for dried weight and 38.7 % for defatted tomato seeds. After hexane extraction, comparable protein content in tomato seeds was reported as more than double the protein content of tomato seeds found in most wheat varieties (Sarkar, Kamaruddin, Bentley, & Wang, 2016).

Several studies were centred on tomatoes and pomace recycling ability, but few assessed the potential for tomato seeds reuse. The truth is that during industrial production, the additional step in the method of recovery of the seeds and the results of the protein content in tomato seeds shows their nutritional value and their functional applicability (Szabo et al., 2018).

5.1. *Extraction of BC from tomato by-products*

Tomato by-products are good sources of BC. The efficacy of the extraction of BC can depend on the implementation of crucial steps: I) pre-treatment; II) extraction; III) purification; and IV) drying (Coelho et al., 2020) (Fig. 1, Table 2).

5.1.1. *Pre-treatment*

Tomato by-products contain high moisture, making them perishable due to contaminations with microorganisms, aerobic rot and nutrient losses (Méndez-Llorente et al., 2014). The drying process may be appropriate depending on the extraction technique; also, dehydration allows the transport and storage of waste. Tomato dryers, drum dryers and fluid bed dryer types are among the big dryers used in the tomato industry. The extraction method is enhanced by homogenisation and the reduction of the particle size of these wastes. On the other hand, OH could be used before the extraction, as a pre-treatment since it may improve the extraction. In this method the current passes through the food matrix, decreasing the microbial biomass and enhancing the extractions process by electroporation effects (Coelho et al., 2020).

5.1.2. *Extraction*

BC from tomato by-products, including mainly carotenoids and fibre, can be commonly recovered by solid–liquid extraction. However, this process involves using toxic chemicals solvents, such as benzene, chloroform, and methylene chloride. Thus, the interest in environmentally friendly processes for industrial BC production has grown. This extraction includes dissolving BC in a suitable solution, followed by a separation process that aims to isolate soluble materials from insoluble or less soluble constituents. This step is critical because BC must be extracted without destroying its beneficial properties (Coelho et al., 2020). The principal techniques used in the recovery of BC are traditional solid–liquid extraction, sonicated extraction and microwave-assisted extraction (Coelho et al., 2020). Many conditions used to extract BC from food by-products have been thoroughly evaluated. Some studies suggest that the most efficient carotenoid extraction method from tomato seeds and peels is organic solvents, including hexane and ethyl acetate. Indeed, the yields of cis isomers are increased as the solid–liquid ratio declines and the proportion of ethyl acetate increases. The conventional method of carotenoids extraction generally consumes large quantities of costly, toxic and dangerous organic solvents (Lazzarini et al., 2022; Luengo, Condón-Abanto, Condón, Álvarez, & Raso, 2014).

Coelho et al. (2019), used OH extraction to recover different compounds from tomato by-products is studied. It showed not only that the new technology enables recovery of phenolic compounds such as rutin, kaempferol and naringenin at superior yield, but also that these same extractions can be selective for other compounds, like carotenoids.

Table 2
Advantages and Limitations of using new technologies in the extraction of BC from tomato by-products.

Technology	Advantages	Limitations	References
Ohmic Heating	Colors, flavors, and nutrients are preserved Reduce the cooking time, fouling, and consumption of energy The requisite temperature was rapidly attained Heating liquid quickly and uniformly at higher heating rates Decreased surface fouling issues No heat transmission when the current has been cut Low upkeep costs and excellent energy conversion rates System shutdown without delay Lower maintenance expenses as a result of the lack of moving parts An environmentally friendly system that is quiet Lowering the possibility of heat transmission surface fouling;	Absence of generalized knowledge Requested modification based on the dairy liquid's conductivity narrow frequency band Challenging to govern and monitor Temperature and electrical field distribution have a complex connection.	Fadavi et al., 2018; Coelho et al., 2020
Pulsed electric fields	No toxicity; Short treatment time; Preserve color and flavor:	Use with conductive materials is challenging Only appropriate for liquids Heat is effective when combined; scaling-up issues are possible	Baiano, 2014; Barba, Zhu, Koubaa, Sant'Ana, & Orlien, 2016
High Pressure	Preserve bioactive compounds, colors, and flavors;	Expensive equipment	Karacabey & Mazza, 2008; Burin, Ferreira-Lima, Panceri, & Bordignon-Luiz, 2014
Microwave extraction	Shorter extraction times; reduced solvent volumesHeating speed homogeneity (in some circumstances, this uniformity may be diminished) Selective heating (while more efficiency can be obtained, temperature profiles can evolve in multi-component food systems) Can be instantaneously turned on or off	Inadequate experimental data to model MW heating The requirement for engineering intelligence to comprehend and reduce uneven heating or thermal runaway	Li, Skouroumounis, Elsey, & Taylor, 2011; Liazid, Guerrero, Cantos, Palma, & Barroso, 2011; Varadharajan, Shanmugam, & Ramaswamy, 2017
Supercritical Fluid Extraction	It has a low critical pressure and temperature (31°C and 7.3 MPa), is non-toxic, non-flammable, and nonexplosive, and is classified as a food-grade solvent (GRAS). CO2 is non-reactive, non-toxic, abundant, and less expensive. Outstanding mass transfer characteristics There are no residues in the treated product. Process that is both environmentally benign and energy efficient Sustainable solvent is simple to obtain, inexpensive, and enables for solvent-free extraction.	Expensive method; Polar extracts are not soluble in the CO2 mobile phase	de Campos, Leimann, Pedrosa, & Ferreira, 2008; Oliveira et al., 2013; Manna, Bugnone, & Banchero, 2015; Herrero et al. 2015

Therefore, applying the same technology with varying temperatures, water–ethanol ratios, and extraction times can extract polyphenols and carotenes or increase the recovery rate of polyphenols, relatively to carotenes vice-versa, thus, allowing to improve the richness of BC in the final extracts. The low-temperature application helps to prevent thermal losses, and with an earlier rehydration stage, a recovery yield may be improved. Furthermore, different phases of industrial tomato processing are carried out with the pulsed electric field (PEF). PEF was used to maximise further juicing yield, presenting a 90.2 % average yield to residues from the first tomato juicing stage (seeds, peels and a fraction of tomato). This technique improved the lycopene extraction from 9.84 mg lycopene/100 g to 14.31 mg/100 g tomato residue at 1.0 kV/cm for 7.5 ms. Total phenolic compounds isolated doubled their concentration (56, 16 mg gallic acid/kg) with the treatment of 2 kV/cm (700 pulses). Targeted PEF pre-treatment in tomatoes' industrial production generally leads to lower energy requirements (Andreou, Dimopoulos, Dermesonlouoglou, & Taoukis, 2020). The impact on the recovery rate of lycopene in either acetone or ethyl lactate from industrial tomato peels was investigated by Pataro and colleagues by the effect of PEF pre-treatment with different field intensity (E = 1–5 kV/cm) and the energy input (WT = 5–10 kJ/ kg). The authors have demonstrated that with PEF treatment (5 kV/cm, 5 kJ/kg) both acetone and ethyl lactate extracts improved considerably, with lycopene (12–18 %) and antioxidant strength (18.0–18.2 %), respectively. Yet acetone yielded the most significant amount of lycopene. HPLC analyses found that lycopene's significant carotenoid derived and degradation was not evident (Pataro, Carullo, Falcone, & Ferrari, 2020).

Super-critical fluid extraction (SFE) is suitable for recovering carotenoids and polyphenols from tomato by-products, as it reduces the use of toxic solvents since it generates solvent-free extract at moderately high selectivity and yield temperatures. SFE is a non-toxic and non-inflammable method, but because of its non-polar nature, it requires a stabiliser and a cosolvent. Besides, during any extraction phase, carotenoid degradation and/or isomerisation can occur. As an alternative to supercritical carbon dioxide, the use of ethane may also result in a less costly process, faster extraction, higher recuperation of compounds due to higher polarising and low critical temperature and pressure (305.4 kg and 48.2 kg, respectively) (Arab et al., 2019; Caseiro et al., 2020).

High hydrostatic pressure (HHP) is an emerging non-thermal, non-conventional technology first studied as a technique for food preservation. It has been used to extract BC from fruit and vegetable products and contributes to the improvements in the bioaccessibility of BC (Coelho et al., 2020; Jun, 2006). It is simpler and more efficient than traditional extractions. In an effective solvent-free procedure, phylloquinone was obtained from tomato leaf waste (29.17 ± 0.96 μg^{-1}) using high-pressure CO_2 and a room temperature of 180 bar (Arab et al., 2019). The same authors also reported higher vitamin K1 recovery rates for subcritical CO_2 than conventional extraction methods. Phenolics (240 mg (GAE). g^{-1}) and flavonoids (184 mg QE g^{-1}) were also present in tomato leaf. High protein content (24.47 ± 0.38 %) is also present in tomato leaf, and the dominant free amino acids are aspartic acid, glutamic acid, and leucine (13 ± 0.1, 15:1 ± 0.2; 12.8 ± 0.1 mg g − 1 dry weight, respectively). Other authors reported that the extraction of lycopene from the tomato paste waste by HHP was promising. They improved the recovery process with different laboratory conditions for the HHP process, such as solvents (chloroform, ethanol 95 % and purified water), and ethanol levels (45–95 % v/v), pressures (100–700 MPa), durations (1–10 min) and solid/liquid ratios (1:1 to 1:8 g/mL). HHP allowed lycopene extraction from tomato waste without heating for just 1 min at room temperature. The fastest recuperation (92 %) was achieved by extracting at 500 MPa, 1 min, 75 % ethanol and 1:6 (g/ml) solid/liquid (Jun, 2006).

Microwave-assisted extraction (MAE) is a new method of extraction that combines microwave and conventional solvent extraction (Coelho et al., 2020). MAE is a quick technique to recover all-trans and total lycopene, whereas conventional extraction provides a higher percentage of cis isomers. MAE causes fast heating of the polar components, increasing the migration of carotenoids into the extraction solvent and limiting the heat exposure of non-polar components with limited treatment time (El-Malah, Hassanein, Areif, & Al-Amrousi, 2015; Ho, Ferruzzi, Liceaga, & San Martín-González, 2015).

Ultrasound-assisted extraction (UAE) has improved solvent penetration into plant cells and cell wall destruction, facilitating BC release and interaction between solvent and analyte (Amiri-Rigi, Abbasi, & Scanlon, 2016; El-Malah et al., 2015; Rahimi & Mikani, 2019). UAE was applied to tomato by-products to recover lycopene. The authors used three independent variables: ultrasonic pressure (30–70 W/m2), solid/oil (3.18–36.82 % w/v), time to remove (1.59–18.41 min) and lycopene quality samples. They verified that the UAE allowed 87.25 % of the lycopene extraction yield instead of conventional solvent recovery (63.66 mg/100 g with hexane: acetone: methanol at 2:1:1 v/v and 91.49 mg/100 g with UAE method) (Rahimi & Mikani, 2019).

5.1.3. *Extracts' purification*

The purification of the extract is essential for interferences and impurities to be eliminated, and a stable product is obtained after the extraction process. This purification involves the isolation of such compounds or fractions with high precision from complex mixtures. It encompasses techniques such as chromatography (partition, modification, adsorption, ion exchange, removal from scale or gel filtration), membrane filtration and crystallisation (M. C. Coelho et al., 2020).

5.1.4. *Extracts drying*

The drying technique is good for reducing the chance of oxidation of their BC. The widely used methods include freeze-drying, spray drier, sprinkling, and rotary drying vacuum.

6. Bioaccessibility, bioavailability and metabolism

The bioavailability of BC is the most significant element when designing functional foods. This is defined as the measure of a BC that will enter the bloodstream. When BC are administrated orally, these compounds pass through the mouth, stomach and gut to become available for bloodstream absorption (bioaccessibility) (Coelho, Oliveira, Coscueta, Fernandes, Pereira, Teixeira, Rodrigues, & Pintado, 2022). Protection against these gastrointestinal tract (GIT) conditions involves protection against digestive enzymes, pH values, and temperature. It is essential to change the constancy of BC and change their concentration by epithelium cells to change bioavailability. Thus, the term bioavailability includes the bioaccessibility of compounds. The organism's absorption, bioavailability, disintegration, distribution and storage are affected by many modulating factors (Desmarchelier & Borel, 2017; Szabo et al., 2018; Vulić et al., 2019).

Carotenoid compounds are probably digested and absorbed as hydrophobic molecules such as lipids (Fig. 2). After that, through bile salts and pancreatic lipases, they may be integrated into micelles that are assimilated into the mucosal cells by passive absorption (Nagarajan, Ramanan, Raghunandan, & Krishnamurthy, 2017). After that, carotenoids are carried from the intestine mucosa by chylomicrons. In some studies, lycopene, like other carotenoids, has been present in wet protein-carotenoid complexes and crystalline aggregates in most nutrients, resulting in some critical barriers to absorption (Shi & le Maguer, 2000). Some studies evaluated the bioaccessibility of BC from tomato by-products (Coelho et al., 2021, 2022; Dewanto, Xianzhong, Adom, & Liu, 2002). Nevertheless, there is no straightforward correlation between process-induced matrix delay and BC extractability and bioavailability.

The absorption, bioavailability, degradation, distribution and preservation of carotenoids are affected by many factors. There are not enough studies to explain all the complexity involved in the bioavailability of carotenes. The same is confirmed by the difference mentioned in the studies related to the proportion of β-carotene bioavailability, which ranges between 3.5 % and 90 % (Desmarchelier & Borel, 2017).

Carotenoid bioavailability can be reduced by the competition between carotenoids during absorption when eaten within the same meal. Dietary fibre, for example, was discovered to minimise carotenoid absorption from tomato plant sources, and bioavailability could be reduced in the location of carotenoids with chromoplasts and plant chloroplasts (Mapelli-Brahm et al., 2018; Tan & Norhaizan, 2019). The release of carotenoids from the food matrix depends heavily on their condition and interactions with other food components, including protein. In contrast with those immersed in lipid droplets, the microcrystalline type of carotenoids, for example, lycopene form in the tomatoes have lower bioavailability. Earlier data have shown that almost 5 % of carotenoids are absorbed by the gut, whereas up to 50 % are absorbed from the micellar solutions. Also, at the same meal of carotenoid ingestion (cooked vegetables or raw vegan salads), dietary intakes of fat (for example, extra virgin olive oil or whole egg) have been shown to improve the absorption of some carotenoids effectively (Tan & Norhaizan, 2019).

This result suggests the crucial importance of the physical form of carotenoids in intestinal mucous cells. Several experiments have shown that thermal mechanisms enhance carotenoid bioaccessibility and promote absorption by loosening the bond and disrupting cell walls.

Relatively to specific carotenoids, such as lycopene, little is understood considering dietary biological impact, particularly its behaviour in the human gastrointestinal tract. However, it is presumed to undergo a similar pathway as β-carotene.

6.1. *Human wellbeing benefits from the consumption of tomato by-products*

Tomato and its by-products intake are inversely proportional to coronary diseases and different kinds of cancer. The carotenoids and phenolic compounds with high antioxidant activity are responsible for these favourable properties (see Fig. 3) (Szabo et al., 2018; Viuda-Martos et al., 2014).

a) antioxidante properties

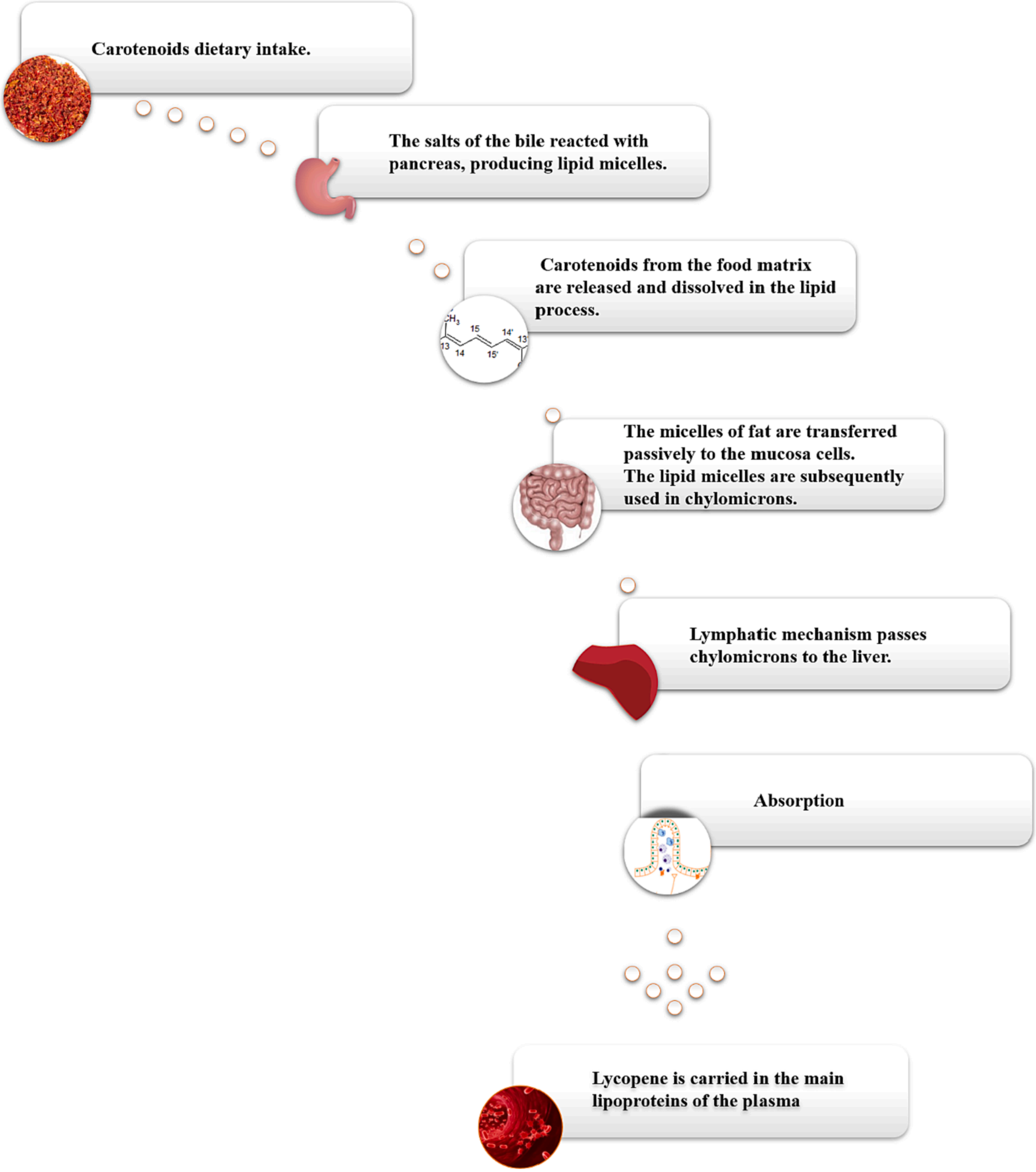


Fig. 2. The absorption process of carotenoids from dietary intake (Adapted from Caseiro et al., 2020).

In the finishing of oxidative chain reactions, antioxidants play a critical role in scavenging free radical intermediates. Antioxidants regulate autoxidation, either by disrupting the development of free radicals or by suppressing the spread of free radicals (del Carmen Robles-Ramírez, Monterrubio-López, Mora-Escobedo, & del Carmen Beltrán-Orozco, 2016; Pinela et al., 2017).

The BC in tomato by-products related to the antioxidant activity are essentially carotenoids, polyphenols, and specific vitamins. Carotenoids and other phytochemicals are recommended to shield the body from various reactive oxygen species (ROS)-mediated conditions, such as neurodegenerative diseases, cancer, eye-related and photosensitive disorders (Viuda-Martos et al., 2014).

Recent studies have shown that daily tomato intake significantly decreases DNA damage arising from Fe^{2+} and increases the defence against UV and transition metal ions. Tomato peel extract has been tested by Elbadrawy and Sello (2016) for its antioxidant and nutritional activity. The authors used petroleum ether and chloroform extracts, concluding that the peel can be used as a functional component in the foodstuff to increase the diet's antioxidant level (Elbadrawy & Sello, 2016).

It has been experimentally demonstrated that lycopene effectively scavenges free radicals, extinguishing singlet oxygen, thiol and sulfonyl radicals. Its chain structure is also significant because of its biological properties, such as its resistance to oxidative degradation.

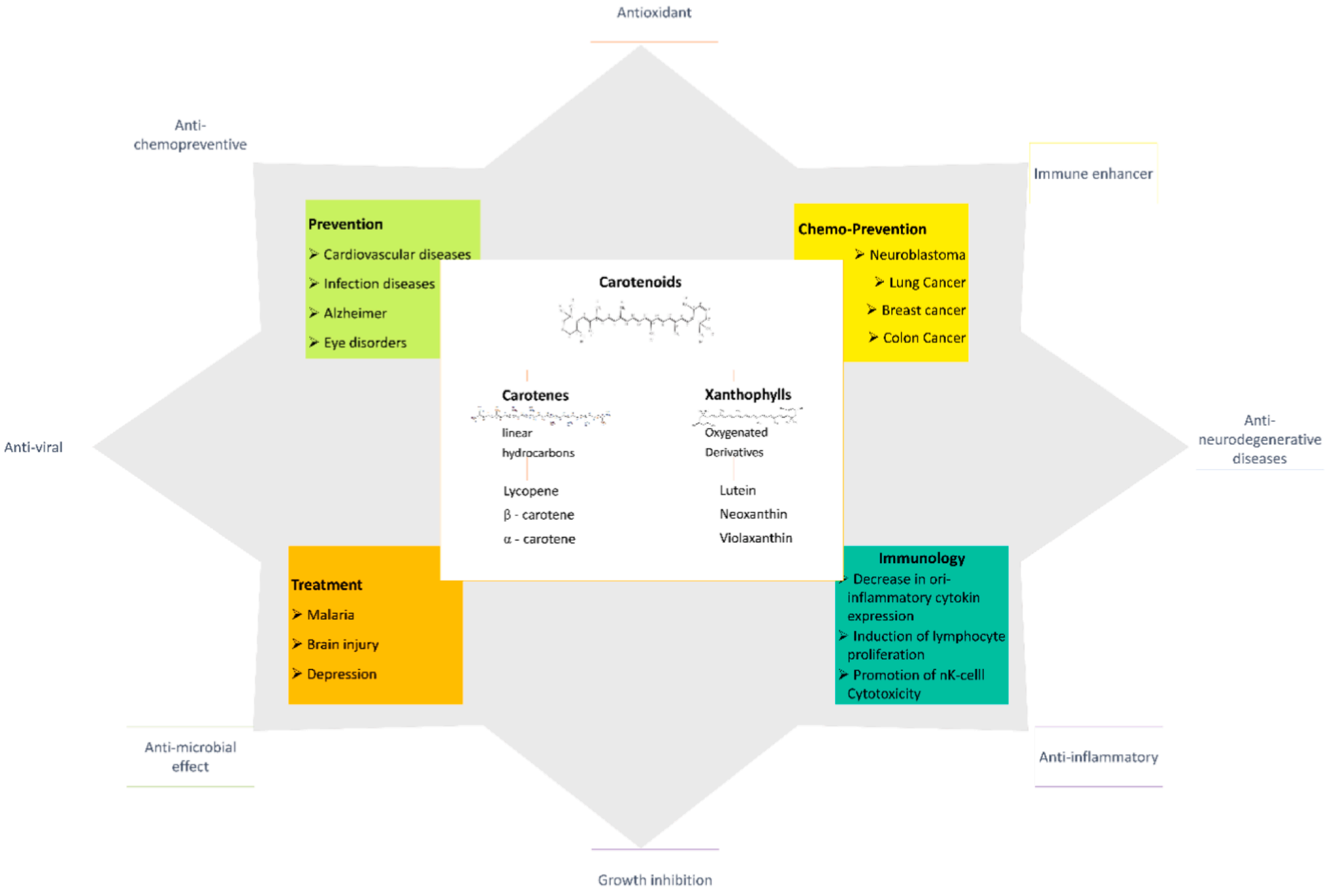


Fig. 3. Chemical scheme of carotenoids division and its biological properties used to treat various diseases (adapted from Nabi et al. 2020).

Lycopene is known amongst common carotenoids as the best antioxidant, shown by experimental *in-vitro* systems [6], [12], [50], [51].

Lycopene is stated to be the single most effective quencher in the carotenoids. The ability to quench depends primarily on the number of double conjugate bonds and, to a lesser extent, on the presence of cyclical or acyclic terminals.

A blood antioxidant status study in rats showed that lycopene and GSH, and phase II GST enzymes could induce certain antioxidant enzymes such as superoxide dismutase (SOD), glutathione reductase and glutathione peroxidase (GSHPx) (Bhatia, Singh, & Koul, 2018).

The antioxidant effects of lycopene can be enhanced by other BC, such as carotenoids and vitamins, due to synergistic antioxidant activity. This hypothesis has been the subject of numerous studies confirming the positive correlation between the antioxidant properties of lycopene and interactions with other studied BC (Viuda-Martos et al., 2014). Combined double bonds allow electrons from reactive species to be accepted and free radicals to be neutralised. A mixture of two lipophilic antioxidants (e.g., vitamins E, C, and β-carotene) has synergetic results, which can be considerably more significant than the one-effect combination of scavenging reactive nitrogen and lipid peroxidation (Milani, Basirnejad, Shahbazi, & Bolhassani, 2017).

b) Cardiovascular diseases

The most prevalent causes of mortality and incapacity in the world are cardiovascular diseases (CVDs). According to the (World Health Organization. (2019), 2019) almost 17.9 million people die from CVD, representing 31 % of deaths globally. Obesity, blood pressure, elevated cholesterol in the blood, physical inactivity and smoking are the major causes of CVDs. Coronary artery disease and stroke that gradually progresses to endothelial dysfunction, inflammation, vascular over-rehabilitation and atherosclerosis are among the most prevalent forms of these conditions (Chaudhary et al., 2018; Nagarajan et al., 2017; Szabo et al., 2018; Tan & Norhaizan, 2019).

Metabolism and lifestyle affect modifiable risk factors. The main risk factor for CVD is an increased level of low-density lipoprotein plasma (LDL). The elevated risk of atherosclerosis, a lifelong condition with a strong health impact, is expected to be linked with increased LDL oxidation causes.

Fortunately, a series of epidemiological research suggests that the consumption of bioactive nutrients, including food containing lycopene, is inversely linked to the occurrence of CVD (Arab & Steck, 2000). Studies have shown that a modest amount of dietary fats, such as olive oil or avocados, ingested as a whole food supplement of tomato soup, tomato-puree, tomato-paste or other tomato-drink lead to plasma carotenoids increase, especially lycopene.

The recommended daily intake of lycopene has been set at 35 mg, obtained by consuming two glasses of tomato juice or combining tomato products.

Although the precise mechanism(s) are still uneven, lycopene is likely to defend against atherosclerosis. It has been shown that lycopene inhibits *in vitro* ROS development and prevents LDL oxidation (Stajčić et al., 2015). The development of foam cells, atherosclerotic lesions and CVD may also include the oxidative alteration of the LDL particles (Szabo et al., 2018).

Further evoked mechanisms include endothelial injury prevention, lipid metabolism modulation by (i) cholesterol synthesis control and oxysterol toxic activities, (ii) reduction of inflammatory reactions by changes in cytokine production, (iii) inhibition of smooth-based muscular cell proliferation through regulation cell-proliferation molecular pathways (Cámara, de Cortes Sánchez-Mata, Fernández-Ruiz, Cámara, Manzoor, & Caceres, 2013; Choe, Sun, Bailoni, Chen, Li, Gao, Wang, Rao, & Yu, 2021).

Carotenoids can also stop coronary problems and suppress hyperlipidaemia, reactive protein and homocysteine in addition to their antioxidant properties. A study with 2856 adults (men and woman) showed a critical inverse relationship between LDL cholesterol and β-carotene Intake ($p < 0.05$) and lutein + zeaxanthin ($p < 0.001$) and a decrease of total homocysteine with intakes of β- carotene ($p < 0.05$), lycopene ($p < 0.05$) and total carotene ($p < 0.05$). Lutein consumption was also correlated positively with HDL cholesterol ($p < 0.01$) and β-carotene serum inverting hsCRP (P-interaction < 0.05) levels along with zeaxanthin (Wang et al., 2014).

Several *in vitro* and in vivo studies have been included in a previous study on lycopene and cardiac protection. The general finding was that the leading cause for the inflammatory mechanism could be tomatoes and tomato products' antioxidant and anti-inflammatory mechanisms. However, more studies are required to validate these results of CVD prevention.

If we understand the health implications of a dietary ingredient, the influence of one compound is difficult to distinguish from that of many compounds in whole foods and whole diets. If tomato lycopene affects wellbeing, it is an essential active ingredient or acts with other bioactive agents in tomatoes in conjunction with it (provitamin A, flavonoids, vitamin C, fibre, each other.). It has been documented that tomato flavonoids, including rutin, quercetin, naringenin, have possible health effects. The neutrophil-induced LDL oxidation of quercetin is reduced (Liu, 2003). These findings show that tomatoes and tomato derivatives can play a role in their health effects. Other experiments have demonstrated that glycoalkaloids in tomatoes have many biological effects as well. Also, recent research has shown that water-soluble tomato's extracts can minimise platelet aggregation, which is a risk factor for cardiovascular diseases (Bhatia et al., 2018; Chaudhary et al., 2018; O'Kennedy & Duttaroy, 2021). The body of evidence shows that whole food is more effective in reducing the disease risk than individual compounds.

c) Eye disorders

The second most frequent cause of blindness has been visual impairment.

The most prevalent vision loss in the elderly is diabetic retinopathy, glaucoma, cataract and age-related macular degeneration (AMD). AMD is not only triggered by age but may also raise the risk of other causes, such as dietary habits, oxidative stress and smoking (Desmarchelier & Borel, 2017). A high degree of phototoxic and oxidative stress comes from constant skin sensitivity to light and oxygen. Therefore, many studies have assessed the role of antioxidants in preventing light and oxygen damage and age-related cell and tissue damage.

β-carotene, lycopene, lutein and zeaxanthin have been the most studied carotenoids. β-carotene also offers additional advantages besides its antioxidant properties since it can be transformed into vitamin A, while lutein and blue light penetrate the eye. Such a carotenoid (β-carotene, α-carotene, β-cryptoxanthin) can be classified as provitamin A, which consists of a β-ionone ring that can be converted into retinal. The macular pigments present in human retinas are two dietary carotenoids, namely zeaxanthin and lutein. Macular pigments have antioxidants that absorb short and high wavelengths(Tuj Johra, Kumar Bepari, Tabassum Bristy, & Mahmud Reza, 2020; Wu, Cho, Willett, Sastry, & Schaumberg, 2015).

Vitamin A deficiency influences immunity and could destroy receptors that are sensitive to light (Awasthi & Awasthi, 2020). Furthermore, vitamin A deficit may also cause xerophthalmia and progress to irreversible blindness (Maurya et al., 2020) [21]. The retina, particularly in the macula lutea and the lens, possesses a possibly particular role in these two essential ocular tissues and has a unique lutein and zeaxanthin concentration [59]. Many clinical trials and epidemiological research endorse lutein and zeaxanthine's possible role in preventing and treating a wide range of eye disorders, including age-related macular degradation, cataracts and retinitis pigmentosa (Tan & Norhaizan, 2019).

Zeaxanthan/Lutein (2 mg/10 mg) reduced the risk of cataract surgery. Further, compared to persons who seldom or never eat carotenoids, AMD is inversely associated with dietary supplementation intakes in carotenoid-rich diets (5–10 mg/day). Oxidative stress also appears to be an essential element in the growth of prematurity and diabetic retinopathy.

Indeed, a randomised controlled clinical trial has demonstrated that lutein is neonatally anti-inflammatory to preterm children. In contrast, forward trials have shown that in patients with non-proliferative diabetic retinopathy, lutein and zeaxanthin serum levels are slightly lower than standard subjects. In a previous study, carotenoid supplementation, including zeaxanthin (2 mg/day per year) and lutein (10–20 mg/day per year), could increase the optical density level of the macular pigment (Chew et al., 2013). Several studies have also shown that zeaxanthin/lutein can improve its visual output (2 mg/10 mg/day/year), including regeneration of photo stress, glare resistance, and contrast. Collectively, the consumption of carotenoids may be a possible solution to oxidative stress improvement and potentially have benefits to eye protection and work.

On the other hand, more lung cancers in the β-carotene vs no β-carotene group (23 [2.0 %] vs 11 [0.9 %], minimal $P = 0.04$) were found in the broad Age-Related Eye Disease Analysis (AREDS) (Chew et al., 2013). The expectation of lutein/zeaxanthin was not a risk.

d) Neurodegenerative diseases

The gradual degradation of neural structure or activity, including neuronal killing, is neurodegeneration. As a consequence of neurodegenerative surgery, several neurodegenerative disorders — including lateral amyotrophic sclerosis, Parkinson, Alzheimer's and Huntington's — arise. Many similarities exist between neurodegenerative diseases and cell death caused, including atypical protein assemblies (Tan & Norhaizan, 2019).

The greatest risk factor for neurodegenerative diseases is ageing. Mitochondrial DNA mutations as well as oxidative aerobic stress both contribute to ageing. Many of these diseases are late-onset, meaning some element changes as a person ages for each illness. One constant factor is that neurons gradually lose function in each disease as the disease progresses with age. It has been proposed that DNA damage accumulation provides the underlying causative link between ageing and neurodegenerative illness.

Previous research shows that the accumulation of carotenoids in cognitively intact and cognitively disabled people is passively correlated with cognitive success (Tan & Norhaizan, 2019). Several reports indicate that carotenoids can reduce the neuronal harm caused by free radicals, an alterable risk factor for cognitive decline. National Health and Nutrition Survey from 2011 to 2014, including 2796 participants over age 60, showed that lutein and zeaxanthin supplementation (2.02 mg/day) would help reduce cognitive loss (Christensen, Gleason, & Mares, 2020). Carotenoids delay the development of neurodegenerative diseases by many means, such as suppressing proinflammatory cytokines, triggering the synthesis of peptides, and reducing oxidative stress. Since it has high binding energy from receptors (histone-deacetylase and P53 kinase receptors) associated with Alzheimer's, carotene is likely to become an Alzheimer's disease antagonist. The inflammatory cytokines (for example, TNF—, NF-B, IL-1) and transforming growth factor-beta (TGF-) in the brain also decrease with lycopene (1–4 mg/kg body weight/14 days) (Sachdeva & Chopra, 2015). Alzheimer's disease is decreasing in high levels of serum carotenoids such as lycopene, zeaxanthin and lutein. Carotenoids collectively play an essential role in delays in neurodegenerative disease development as an antioxidant.

e) Cchemoprevention

With almost 9.6 million deaths and 18.1 million new cases in 2018, cancer constitutes the second most frequent cause of death worldwide. Emerging literature indicates that 30–50 % of deaths can be avoided by changes in primary risk factors such as physical exercise, bodyweight conservation, alcohol reduction and tobacco avoidance (Szabo et al., 2018; Viuda-Martos et al., 2014).

In addition, oxidative stress was implicated in cancer development through increased DNA mutations or disruption to DNA, genome instability, and cell proliferation (Szabo et al., 2018). These disorders can lead to various cancers, particularly prostate, lung, and stomach, which has decreased with consuming tomato and tomato products.

The reverse relationship between this kind of diet and colorectal cancer was reported in a recent study on the key components of the Mediterranean diet (olive oil, red wine and tomatoes). Colorectal carcinoma can be prevented by tomatoes, which are considered key to the Mediterranean diet and a principal source of lycopene. Any of the most critical epidemiological data support a connection between the intake of tomatoes and a decreased occurrence of prostate cancer and benign prostatic hyperplasia (BPH). A prospective retrospective analysis of 47.365 men in 1986, 1990 and 1994 among the population obtained by the Food Frequency Question (FFQ) has been done. The study showed a relation between the consumption of tomato sauce servings each week with the reduced risk for prostate cancer (Grainger et al., 2008).

At least 12 clinical trials have been investigated with the association of tomato byproducts or lycopene with prostate cancer since 1999. Any of these experiments have measured prostate antigen in particular (PSA). Consumption of tomatoes and tomato products daily (target intake level 25 mg/day lycopene) for eight weeks reduced serum PSA levels in 34 % of the subjects.

Various carotenoids such as lutein, zeaxanthin and lycopene have been shown to reduce the development of the inflammatory mediator, such as TNF-α, IL-1β, and IL-6, by blocking the NF- B pathway (Cha, Kim, Ha, Kim, & Chang, 2017; Tan & Norhaizan, 2019).

The activation of intercellular gap interconnection communications is another important biochemical mechanism of action. β-carotene, canthaxanthin and lutein are effective inducers of intercellular gap interconnection, whereas α-carotene and lycopene are less involved. The ingestion of *cis*-lycopene has a significant cancer prevention activity (Caseiro et al., 2020; Jimenez-Lopez, Fraga-Corral, Carpena, García-Oliveira, Echave, Pereira, Lourenço-Lopes, Prieto, & Simal-Gandara, 2020; Tan & Norhaizan, 2019). Lycopene tends to have the most significant impact in delaying the growth of the disease (Caseiro et al., 2020; Jimenez-Lopez et al., 2020; Tan & Norhaizan, 2019).

A dose–response systematic study of the dietary consumption or blood concentrations of carotenoids concerning prostate cancer risk revealed the inverse association of α-carotene and lycopene, but not of β-carotene with prostate cancer risk; thus, α-carotene and lycopene did not decrease advanced prostate cancer risk. Also, *in vitro* IGF-1-induced prostate cell proliferation has been decreased by quercetin and rutin (Boileau et al., 2003; Grainger et al., 2008).

Research by Cui, Shikany, Liu, Shagufta, and Rohan (2008) and others showed that the use of lycopene is inversely linked to a positive risk of breast cancer in postmenopausal women (n = 84.805) for estrogenic and progesterone-receptors and was followed up over a 7.6-year average.

A randomised, placebo-controlled, double-blind crossover study performed by Voskuil, Vrieling, Korse, Beijnen, Bonfrer, van Doorn, Kaas, Oldenburg, Russell, Rutgers, Verhoef, van Leeuwen, and Veer (2008), found a two-month reduction in free insulin-like growth factor I (IGF-I) over two months in premenopausal women at high risk of breast cancer (n = 36). There was also a substantial decline in the chances of people who ate the highest compared to the lowest amount of nutrient lycopene from two case-control trials comparing the nutritional habit of women with and without breast cancer. The high hydrophobicity of lycopene, an obstacle to cell culture studies, is a weakness of cell culture studies. Because lycopene is water-insoluble, steps must be taken before *in vitro* studies to improve its solubility inside cell culture media/buffers.

Tomato powder and distilled lycopene supplements have demonstrated antineoplastic effects in animal studies. (Boileau et al. (2003), reported significant inhibition of *N*-methyl-*N*-nitrosourea –testosterone-induced carcinogenesis in male Wistar-Unilever rats following consumption of tomato powder (13 mg lycopene/kg diet). In contrast, no effects were observed with lycopene supplementation per se (161 mg lycopene/kg diet). This study suggests the synergistic effects of lycopene with other antioxidants in tomatoes in exerting an antineoplastic effect.

Autocrine/paracrine loops in the model of Dunning prostatic cancer interact with lycopene and vitamin. Also, lycopene can only suppress prostate cancer development at higher concentrations than tomato antioxidant supplementation, as seen by *in vitro* and animal studies. Karas et al. (2000) further documented lycopene inhibitory effects on MCF7 human mammalian cancer cell growth due to the involvement in the signalling of the IGF-1 receptor and progression of the cell cycle (Karas et al., 2000). Thus, the main pathologies in which lycopene prevents prostate and breast cancer development are seen as the involvement of androgen metabolism and inhibition of growth factors and cytokines. Additionally, also shown to avoid modification to the p53, p53 phosphorylation, and p53 target genes due to tobacco smoke exposure in the gastric mucosal of ferrets were the addition of tomato lycopene (1.1 mg/kg/day, equivalent to 15 mg lycopene intake of 70 kg individual) was tested. This result indicates more protection against gastric cancer by lycopene (Liu et al., 2006).

The antioxidant function may also be due to the protective effect of carotenoids against cancer. Indeed, carotenoids such as lycopene's anticancer abilities are modulated by various pathways, including apoptosis, arresting cell cycles, detoxifying the phase II enzymes, and signalling for the growth factor (Jimenez-Lopez et al., 2020).

f) Iimmune system regulators

Lycopene's ability to stimulate the expression of antioxidant genes and control signalling pathways likely to induce inflammatory mediators has beneficial effects on inflammation and redox imbalances. Several anti-inflammatory properties of lycopene can be summarised as follows: a) regulation of inducible nitric oxide synthase; b) modulation of cyclooxygenase and lipoxygenase expression; c) interference NFkB NFkB as well as with activator protein-1 (AP-1) and with the signalling of MAPK (Caseiro et al., 2020).

Lycopene also can activate the adaptive immune response, maintaining an adequate defence against microorganisms (Caseiro et al., 2020). Thus, it protects against bacterial infection and radiation (Ascenso et al., 2013).

An investigation with male mice found that lycopene would decrease plasma interleukin (IL)-6 and TNF-α considerably after intraperitoneal lipopolysaccharide injection, preventing inflammations of the brain tissue at six hours.

Serum lycopene is reversely correlated with plasma glucose concentrations and fasting insulin (Caseiro et al., 2020). Cross-cutting research observed that a rise of 1 mg in lycopene intake lowers the likelihood of gestational diabetes mellitus to 0,005 mmol/L, fasting blood glucose. This study promoted a decrease in blood glucose intake in dietary lycopene, which may decrease the risk of gestational diabetes mellitus (Gao et al., 2019).

7. Industrialization of alternative and innovative extraction techniques

The demand for high-purity, well-characterized and low-cost natural carotenoids, conveyingbeneficial health effects, is constantly increasing, and its market is expected to grow from 1.5 billion USD in 2019 to 2,0 billion dollars in 2026. In addition, the Food and Drug Administration only approved lycopene extracted from tomatoes as an additive and not synthesized or extracted from other natural sources. Consequently, the extraction of industrial by-products from tomatoes constitutes a very valid alternative. This may lead to a revaluation of isolated substances in line with the growing trend of using food processing by-products as a source of functional food ingredients or as a component of pharmaceuticals and cosmetics.

Given what has been described previously-one of the main opportunities for the tomato processing industries is related to increased industrial yield and discoveries in which tomato waste may become a value-added material, in which extraction and insulation processes allow the obtaining of target bioactive compounds.

The fact that it is increasingly imperative that industries use increasingly environmentally friendly processes to valorize by-products generated during tomato processing to extract BC, since this constitutes an opportunity for industry and society that is increasingly demanding.

The exploitation of agro-industrial by-products meets several sustainability criteria; using a renewable raw material, avoiding the accumulation of residues, while providing process “input-push”, through the use of an abundant and economical matrix. Although all entities are focused on establishing a circular economy in the industry with environmentally friendly technologies, they must stop looking by-products as waste and start to look at added value. So, there is still several challenges to be addressed, such as 1) the Life Cycle Assessment environment offers, in which they still demonstrate the entire process that establishes efficient methods and applications for profitable tomato by-products; 2) integration of procedures/techniques of bioactive procedures to maintain food/product safety 3) purpose, equipment and trained professionals material yet material; 4) production that took place along the chain of products/new products produced and that made the history of the long-term production chain.

Many authors have studied the scale-up of the extraction process of BC during the industrial process and have shown that although each type of manufacturing industry needs different adaptations, unconventional methodologies can generate high-energy microenvironments, fractionate biomass to generate value and obtain “zero waste” with low energy consumption and high efficiency. Examples of this are the use of ultrasound, ohmic heating, or hydrodynamic cavity Alancay, Lobo, Quinzio, & Iturriaga, 2017; Andreou et al., 2020; Dewanto et al., 2002; Fritsch et al., 2017; Kalogeropoulos et al., 2012; Poojary & Passamonti, 2015; Strati & Oreopoulou, 2014, 2016.

8. Conclusions

Biotechnology has brought a modern view of agriculture and health, which brings creativity and provides productive and economical ways of producing different products and resources. The tomato processing industry produces large quantities of waste, especially seeds and skins, which are wasted and can exacerbate the degradation of the environment. The use of green technologies, like the PEF and OH, have been applied to tomato waste with better results to recover BC than with other extraction methods. Thus, these green technologies and their combinations appear to be the best methodology for obtaining target BC with market potential, namely carotenoids, polyphenols, fibres, proteins, among others. Also, this review showed that incorporating whole tomato by-product (bagasse) can be more beneficial for preventing the risk of some chronic diseases than individual compounds. As the tomato peel is rich in BC, such as lycopene, it would be possible to apply this by-product as ingredients to the food directly and obtain lycopene enriched products.

Similarly, more studies are necessary to overview the individual compounds’ behaviour, absorption rate, metabolism, and bioavailability. It is also essential to determine the dose levels and enhance its cost-benefit efficiency for various applications, such as additives/ingredients for food and feed, cosmetics, and natural pesticides. These applications result in the acquisition of value-added products based on the circular economy, which could mitigate the adverse effects caused by tomato by-products accumulated in the landfills. Thus, the sub-products obtained were essential and must therefore be priced in line with the CBE principles.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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