Universidade de Lisboa
Faculdade de Farmácia

Pharmaceutical Valorization of Tomato Processing Industry By-Products

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Mestrado Integrado em Ciências Farmacêuticas

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RESUMO

O potencial para a valorização dos desperdicíos decorrentes da indústria de produção e processamento do tomate é incontestável. A indústria do tomate debate-se com grandes perdas de matéria-prima. Decorridas da sobreprodução e/ou durante o processamento, estas perdas resultam em prejuízo enconómico e eventualmente em risco ambiental, caso não sejam descartadas corretamente. Atualmente, muitos destes resíduos são destruídos, em alguns casos utilizados para fortificar rações animais ou descartados no meio ambiente. Embora estes resíduos não sejam ainda considerados como uma matéria-prima, inúmeras pesquisas ilustram aplicações inovadoras e lucrativas em relação aos mesmos. Estes resíduos comummente denominados por "bagaço de tomate" (sementes, casca e tecido vascular residual) são abundantes numa variedade de compostos bioativos. O licopeno, a vitamina C, o β-caroteno, os compostos fenólicos, o tocoferol, o zinco, entre outros, são alguns dos bioativos aqui discutidos. Muitos destes compostos são antioxidantes potentes capazes de modular o sistema imunitário. Além disso, estes compostos exibem excelentes propriedades anti-inflamatórias e de eliminação de radicais livres, tendo esta temática vindo a destacar-se ao longo dos anos uma vez que o stress oxidativo parece estar no cerne do desenvolvimento da maioria das doenças e no processo de envelhecimento. Consequentemente, tem-se verificado a convergência entre a indústria alimentar e farmacêutica e, mais recentemente, com a indústria cosmética explorando-se possíveis aplicações de ingredientes naturais extraídos de produtos alimentares tal como os seus efeitos fisiológicos e farmacológicos. A aplicação dos resíduos alimentares do tomate na indústria cosmética surge assim como um conceito inovador. No passado, os cuidados/tratamentos dermatológicos estavam exclusivamente associados a formulações de aplicação tópica e só mais recentemente, vários estudos têm defendido a importância de tratar a pele de "dentro para fora". Os efeitos do processamento na qualidade dos resíduos e eventuais aplicações foram cuidadosamente analisados e descritos ao longo da presente monografia. A possível aplicação destes compostos bioactivos na suplementação e em formulações tópicas, bem como aplicações inovadoras dos resíduos do tomate foram também exploradas.

Em conclusão, as indústrias do tomate dispõem de uma grande oportunidade uma vez que produzem resíduos abundantes em princípios ativos com interesse para o desenvolvimento de formulações tópicas e orais. Assim, ao atuar em ambos os sentidos (via tópica e oral), é esperado um efeito sinérgico com resultados mais positivos para a pele e a saúde em geral.

Palavras-chave: indústria de processamento do tomate; desperdício /valorização dos resíduos do tomate; compostos bioativos; saúde e cuidados da pele

ABSTRACT

Tomato producing and processing industries present an undoubted potential for industrial waste valorization whether due to the overproduction of fresh tomatoes or to the loss during processing. These product losses may result in economic causalities and eventually constitute an environmental hazard. Most of the industrial waste is destroyed, used in animal rations, or released to the environment. Although tomato waste is not yet considered as a raw material, several studies have suggested innovative and profitable applications. It is often referred as “tomato pomace” (seeds, peel, and residual tomato tissue) quite rich in a variety of bioactive compounds. Lycopene, vitamin C, β-carotene, phenolic compounds, tocopherol, zinc, among others, are some of the bioactives here discussed. Many of these compounds are powerful antioxidants with great scavenging and anti-inflammatory properties besides modulating the immune system. In fact, the oxidative stress appears to be at the core of most illnesses and the aging process. Over the years, the tendency has been the convergence between the food and pharmaceutical industries, and more recently, the cosmetic industry. Several researchers have focused the possible application of natural ingredients, especially those extracted from foods, and their physiological and pharmacological effects. The application of tomato pomace in the cosmetic industry is a novel concept. In the past, skin care was exclusively associated with the application of topical formulations whereas recent reports have claimed the importance of skin care from an inside - out point of view. Herein, the effects of processing and further applications of the bioactive compounds present in tomato waste were carefully reviewed. Topical and oral supplementation of these active ingredients and possible innovative usage of tomato waste were explored as well.

In conclusion, there is a huge opportunity for industries to create profitable and innovative applications for tomato waste which is plentiful in active ingredients for both topical and oral formulations. A synergistic and positive outcome will certainly be obtained on health and skin care context.

Keywords: tomato; tomato processing industry; tomato waste/ pomace valorization; bioactive compounds; health and skin care

METHODS:

PubMed; ScienceDirect; Google Scholar; National Center for Biotechnology Information (NCBI); MEDLINE- National Library of Medicine® (NLM); National Institute of Health (NIH); Food and Drug Administration (FDA), Food and Agriculture Organization Corporate Database (FAOSTAT) were used to review relevant research articles.

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1. INTRODUCTION & AIMS

The tomato (*Solanum Lycopersicum*), which is commonly mislabeled as a vegetable, belongs to the nightshades family (Solanaceae), and it can be botanically categorized as a fruit.

The tomato plants tend to grow preferably at warmer temperature, and thus their blossoming starts when the weather is hotter and more sunlight is present. First, small yellow/white flowers blossom, and eventually fall to give place for the fruits to grow. The tomato fruits can vary in color (red, yellow, purple and green), shape (from oval to spherical), and size (1.5-7.5 cm).

From the historical point of view, the first wild species of tomatoes were found in South America, and only later, were domesticated and used as a food. In Europe, the tomato was introduced on the 16th century by the Spanish. Eventually, it usage spreads over the globe, in a way that today, we can contest its remarkable presence in the most different cuisines (1).

Tomatoes are rich in lycopene and other carotenoids, flavonoids, vitamin C, K1, B2 and B9, potassium, copper, iron, phosphorous, among many other active compounds. Regarding to their mineral and nutritional content, tomatoes have been considered as functional or nutraceutical foods, which means that the regular consumption of this food may prevent and/ or act on certain human diseases. Therefore, tomatoes have gained major significance over the past years in human nutrition mainly due to their phytochemical content and potential medical and pharmacological applications (2,3). Besides tomatoes, the waste from industry of processed tomato products (including peel and seeds) gives rise to other by-products with an added value. This review intends to explore the sustainable valorization of tomato processing industry by-products and its usage on both pharmaceutical and cosmetic formulations and supplements. Challenges and opportunities will be addressed as well on this context.

2. Sustainable Valorization of Tomato Processing Industry By-Products

2.1. Tomato Industry and Waste Production

The tomato industry has grown over time worldwide, achieving a total production of 182 256 458 tones in 2018. According to the latest data available (2018), China was responsible for the vast majority of the global tomato production, followed by the United States of America (USA) (4,5). In the USA, tomatoes were the most consumed "vegetable" per capita (6).

Alike most large-scale production industries, the tomato industry faces the major issue of food and by-products waste. The fact that tomatoes are especially frail to external environmental stressors, such as high temperature and humidity, adds up to this problem (7). On the other hand, the need to guarantee that enough fresh tomatoes are available for consumption or even processed in other products, leads in most cases to an overproduction, and thus, more waste. In addition, the overproduction is also a way for industry to overcome the potential tomato losses involved in the process and the high percentage of tomatoes that do not reach the market standards (8).

Food waste has been a struggle for most food-producing industries, and it has been challenging to quantify the exact extent of this problem, since there are many stages in the food supply chain in which food can go to waste. Besides being a clear economical problem for the industries involved, it also adds up to the environmental pollution and to an unbalanced relation between the scale of waste and the malnutrition crisis present on a gross part of the human population (9).

Although there are individual and organizational initiatives and programs proposed by different governmental institutions, such as EPA (United States Environmental Protection Agency), that continuously try to overcome this problem, food waste and loss are still an unsolved setback in our society (10). Developed and industrialized countries are nowadays responsible for the gross majority of the overproduction and consequent waste (11). Therefore, it becomes clear that the waste intrinsically involved in producing and processing foods should be not only diminished but also "recycled" to guarantee a sustainable valorization of processing industry by-products.

It was estimated by EPA that around 31 % of all the fresh tomatoes bought by householders were thrown away in the U.S.A. This represents approximately 21 tomatoes per person each year. This waste is estimated to cost over 2.3 billion dollars each year and it is not exclusively related to the food loss, as it equally means resource loss, like freshwater, energy, and farming fields (12).

On the other side, around 3-7% of material is lost during tomato processing. This waste is commonly named "tomato pomace" being mostly made of peels, seeds, and some residual tomato tissue. Despite these by-products being usually discarded, they are still nutrient- and vitamin-enriched sources (8,13).

Additionally, there is another waste fraction to consider: the unharvest green tomatoes, leaves, and roots. Green tomatoes that aren´t harvest and continue on the cultivar fields are rich in glycoalkaloids such as tomatine. Tomatine comprises two molecules: α-tomatine and dehydrotomatine, which accumulate in every organ of the tomato plant. In the tomato fruit, the content of these two molecules decreases with tomato ripening, being its highest when unripe (green). These fractions usually remain on the cultivar fields without further valorization. Nevertheless, many researches described the significance of tomatine for human health. Tomatine has shown to be exhibit antioxidant, anti-inflammatory, antibiotic, and anti-fungal properties. Immune-stimulating and cardiovascular effects were also demonstrated. Additionally, tomatine has demonstrated to inhibit the growth of a great range of cancer cells, like colon, breast, lung, prostate, and others. Further investigation is necessary since most of the mechanisms of action are still unknown (14–16).

2.2. Effect of Processing: Quality of the By-Products

Over the past years, the consumption of processed foods increased mainly due to population growth. Thus, the demand to convert fresh products into useful, profitable, and quality products thrived (17). Food processing has changed the way we eat and live in many ways. Nowadays, we can consume a variety of foods, all year round, most of them out of season, allowing a more diverse diet (18).

When it comes to the tomato processing industry, many advantages have been highlighted regarding the processing of fresh tomatoes (**Table 1**). Tomatoes are interestingly versatile and can be processed in many different products, such as pastes, juices, soups, jams, sauces, and others (18,19). To achieve this, the tomato processing industry resorts to different strategies and technologies, taking into account its final purpose (8). It was estimated by the Economic Research Service of the United States Department of Agriculture (USDA) that 30 % of the fresh tomatoes are processed into ketchup and juices, 35% into sauces, about 18% into tomato paste, and 17% into canned tomatoes **(Figure 1)** (20).

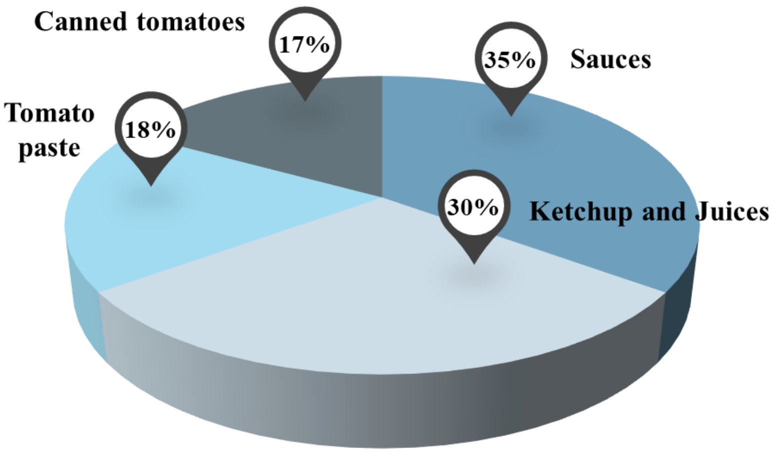

Figure 1- Graphic representation of estimated percentages of tomato processed by-products by USDA

One of the main concerns of all food processing industries is to guarantee the quality of the final processed products, and thus, it is extremely important to consider which factors affect the raw material and how they do it.

Considering that the quality of the by-products is directly connected to the processing technique and conditions employed, it is utmost importance for the tomato processors, being correctly instructed to achieve the best outcomes. The quality of tomato by-products is assessed through appearance, viscosity, taste, acidity, and nutritional content (21).

Before its final processing destination, tomatoes are harvested, precisely sorted, soaked and washed, and ultimately, trimmed as needed.

There are multiple processing strategies and most of the by-products require a long succession of different procedures to achieve its final form. As an example, tomato paste has to suffer several steps of heating, which include hot-break, drying, and others (8,22). Heat processing strategies are commonly used as they allow destroying microorganisms, enzymes, and ultimately, obtain a more efficient separation between the tomato juice and the pulp.

Therefore, the hot-breaking method is one of the most used processes of tomato pulp, juice, soup, and paste. The hot-breaking method consists of rapidly heating the tomatoes to temperatures higher than 77ºC, followed by immediate crushing or chopping. As a result, the tomato pulp obtained presents higher viscosity as desired due to the prevention of pectin (thickening agent) break-down. Pectic enzymes are inactivated by heat, and once these enzymes are destroyed pectin break-down is avoided, and thus, a more full-bodied and thicker pulp is obtained (22).

Although the hot-breaking method facilitates tomato homogenization and further handling, some studies have shown that it adversely affects mineral and vitamin content, while in other cases, it has shown to be beneficial (23,24). Several researchers have found that some bioactive molecules of tomatoes, such as lycopene and β-carotene, may benefit from heat processing and maceration since those techniques can disrupt the tomato cell-matrix and therefore, allowing these carotenoids to become more bioavailable (24).

Understanding how processing affects the natural source is extremely important since tomato consumption is encouraged for the prevention of chronic illnesses like diabetes, cardiovascular diseases, and others, specifically, due to its mineral and vitamin content. Additional further valorization is also dependent of previous processing. (8).

Table 1- Advantages and Disadvantages of processing tomatoes (18)

Advantages	Disadvantages
✓ Extended food lifespan and storage period	✓ Not fresh and with preservatives
✓ Possible consumption out of season and a varied diet with more new tastes	✓ More caloric than fresh tomatoes
✓ Facilitated food storage	✓ Decreased certain bioactive content (e.g. thermolabile molecules as vitamins) unlike others (e.g. Cis- lycopene)
✓ Higher stability	✓ More expensive to consumers
✓ Decreased tomato losses	
✓ Increased market value of tomatoes	

Effect of Processing on Vitamin C Content

Vitamin C or L-ascorbic acid is a powerful antioxidant, well known for its phytochemical properties and importance for human health. The human body is unable to produce Vitamin C, meaning that its presence in the human body relies merely on our diet (25). Fresh tomatoes are a great source of vitamin C, but processing tomatoes may negatively impact its content (26). Vitamin C content appears to increases with tomato fruit ripening, from green to red, but once tomatoes are harvest and stored, further maturation and light exposure have been related to vitamin C loss (24,27).

Vitamin C is a thermolabile and water-soluble compound, which means that, after applying the most common processing techniques as grinding, chopping, and heating, its content appears to decrease. During post-harvesting storage, light exposure seems to be the main cause of vitamin C loss, since it leads to oxidation. During cooking, Vitamin C appears to shed from the tomato matrix into the water, which can be explained by its water solubility (23,24,28).

Effect of Processing on Lycopene content

On the contrary, lycopene content has shown to increase after some processing techniques as heat processing (23,28).

Lycopene is a carotenoid responsible to give tomatoes their red pigmentation. It possesses 2 non- conjugated and 11 conjugated double-bonds, and it is due to this particular arrangement of the conjugated double bonds, that lycopene is more susceptible to degradation via enzymes, oxidation, isomerization, and others.

The main pathways of degradation of lycopene during tomato processing are oxidation and isomerization. Oxidation occurs preferably at a low pH, in the presence of light and oxygen during non-thermal processing, like cutting, grinding, and even during the storage period. Thermal processing, on the other hand, allows tomato tissue break-down, meaning that most of the bonds become disrupted (29).

Additionally, it seems that heat processing may favor isomerization. Although most identified compounds are naturally all trans-forms, cis-isomers present higher bioavailability since they are more easily absorbed in the intestine. Cis-isomers also possess improved antioxidant capacity, and thereby, heat processing and consequent isomerization are quite desirable (23,29,30).

Effect of Processing on β-carotene, Phenolic compounds, and Vitamin E Content

β- carotene is another carotenoid responsible to give fruits and vegetables, its characteristic orange color, being the second most abundant colored carotenoid in tomatoes. β- carotene is widely used in the food industry as an additive, specifically, as a food coloring agent. Its main significance on human health is related to its antioxidant capacity and to function as a precursor of vitamin A. Some studies have shown that short-term heating may decrease or, on the contrary, not affect the β- carotene content in processed tomato by-products (e.g. soups and sauces). Other investigations showed that this content may actually become more accessible. Thus, further studies are still required to become more conclusive in this matter (24,31,32).

Phenolic compounds are important phytochemicals with powerful antioxidant activities present in most fruits and vegetables. These compounds can be divided into two main categories: polyphenols and phenolic acids. Their antioxidant capacity is primarily related to free radical's scavenger properties and electronic and atomic exchanges. In tomatoes, some of the phenolic compounds are flavonoids, phenolic acids, and tannins. Phenolic content in tomatoes is significantly conditioned by farming techniques, genotype, and storage. In most fruits and vegetables, phenolic compounds have been found mostly bonded to cell walls, thus some processing strategies, especially those that help membrane rupture, increase the bioavailability of phenolic compounds. Similar to what happens to lycopene after heat treatment and homogenization, it appears that these transformations can also positively impact the phenolic content in tomatoes (24,33).

Vitamin E is a powerful liposoluble antioxidant that englobes eight molecules*:* α-, β-, γ-, and δ-tocotrienol and α-, β-, γ-, and δ-tocopherol. α-tocopherol is the compound with the major significance for human health. Tocopherols are one of the most abundant vitamins in tomatoes which intervene in photosynthesis. Vitamin E content in tomatoes is deeply dependent on environmental conditions such as heat and light. When discussing how processing variables affect the vitamin E content in tomatoes, different results have been found. Some researchers have shown that α-tocopherol content is not affected by processing since they found the same amounts in fresh tomatoes and processed tomato paste. On the other hand, γ-tocopherol has been found at a lower percentage in the final product. The same researchers reported that γ-tocopherol was mainly present in seeds and peels while α-tocopherol was present in all parts. This explains the lower levels of γ-tocopherol in the tomato paste since seeds and peel are discarded in this production process. Other studies have obtained positive results on the content of tocopherols, specifically, after boiling canned tomato paste. In regards to tomato juice production, it appears that sterilization and homogenization, decrease α-tocopherol. It seems that short-term heat processing is beneficial and can increase some tocopherols´ content, while long term heat processing results in their degradation (20,24,34).

Since processing affects the content of the various bioactive compounds differently it's important to consume fresh tomatoes to overcome any nutritional deficiencies that may occur. This is of utmost importance for thermolabile compounds such as vitamin C, which content decreases after processing.

2.3. Characteristics and Added-value of Tomato Waste

In addition to producing marketable products directly from fresh foods, industries have been equally focused on the research and development of innovative applications of tomato industrial waste and by-products (13).

By this means, it is essential to distinguish the waste that results from the overproduction of fresh tomatoes, from the waste obtained of processing. Both waste biomass is different and therefore, further applications will likewise differ. The waste that results from overproduction is mainly derived from tomatoes that do not reach market standards, whether it is in color, shape, or size. Over the years, industries have tried to develop technologies to add value to these waste fractions. The main challenge has been related to its high water content and fast rotting (8). On the other hand, waste fractions that result from tomato processing are normally depreciated and used either to feed animals, to fertilize soils, or dispose as waste. The biomass that results from tomato processing ("tomato pomace") is mainly made by seeds, peel, and some residual vascular tomato tissue (13).

It is important to note that the tomato fractions disposed of in the environment and the unharvest tomatoes that remain on the cultivar fields can lead to an environmental hazard. These fractions once discarded in the environment are further disposed of by anaerobic fermentation. As a consequence of this biochemical process, biogas composed of methane (CH_4), carbon dioxide (CO_2), nitrogen (N), and others is produced. These are considered greenhouse gases with well-known environmental side effects but also gases with possible further applications. In recent years, biomass technology specifically using waste fractions for the production of fuel has gained much interest. This besides being an alternative to the use of fossil energies, could further valorize waste fraction, not only from tomatoes but other foods also. Since methane emission from tomato decomposition is a problem, alternatively using these wastes fractions for the production of fuel, emerges as an interesting alternative, not only beneficial for the environment but also for the industries and chains that produce such waste, allowing further valorization (35,36).

2.3.1. Chemical Characterization of Tomato Pomace: Peel and Seeds

Tomato pomace is a source of protein, fat, and dietary fibers. Dry tomato pomace usually contains around 12 % fat, 20 % protein, and 30 % raw fiber (37,38).

Approximately 60% of the total tomato pomace corresponds to seed fractions. Tomato seeds have shown to be an interesting source of fat, such as palmitic and oleic acids, and protein, containing higher quantities of lysine and threonine. Tomato seeds have equally shown to be a potential source of trace elements such as Sodium (Na), Calcium (Ca), Magnesium (Mg), Potassium (K) and others. The peel is a source of other amino acids (valine, lysine, and leucine) and also trace elements (Mg, Na, K, and Ca). Additionally tomato pomace has shown to be a source of Manganese (Mn), Iron (Fe), Copper (Cu), Zinc (Zn), naringenin and chlorogenic acid (8,39).

Tomato pomace can be also a good source of dietary fiber (DF) and several studies suggested that tomato seeds and peel, have higher contents of polyphenolic compounds(37,40,41).

2.3.2. Micro-nutrients of Tomato Pomace and Biological Properties

As mentioned above, tomato by-products are a source of micro-nutrients, such as Sodium (Na), Calcium (Ca), Magnesium (Mg), and Potassium (K). These micro-nutrients are all electrically charged minerals. Electrolytes are essential for human health, as they maintain the body’s homeostasis, i.e., blood volume, fluids quantity, pH levels, and proper muscle, nerve, heart, and brain function (42). Nevertheless, the consumption of these electrolytes needs to be adjusted. Overconsumption of sodium leads to high blood pressure, while not consuming enough potassium also ads to this problem. This unbalance plays a major role in the burden of cardiovascular diseases (43). Therefore, the American Heart Association recommends a daily sodium intake not higher than 1500 mg for most people. It is important to note that the overconsumption of sodium is mostly related to the ingestion of processed foods and meals prepared in restaurant chains. While fruits, vegetables, and meats are natural sources of sodium, and other micro-nutrients, their consumption does not seem to be associated with higher sodium blood levels (44).

Some studies have found that increased consumption of potassium can be an effective way to treat and prevent hypertension and, therefore, decreasing the risk of cardiovascular disease (43). A healthy intake of potassium is encouraged not only for its vascular benefits but also for reducing water retention and bone mass loss, thus, protecting against kidney stones, strokes, and osteoporosis, respectively (43,45,46). Cardiovascular diseases, specifically strokes and ischemic heart disease, are the main cause of death worldwide according to WHO (World Health Organization) (47).

Magnesium acts as a cofactor for a large number of enzymes and a regulator of different essential functions, such as glycemia, blood pressure, muscle contraction, and neuromuscular transmission. Magnesium equally participates in energy and nuclear materials production, in active transmembrane transport and bone development (48).

Calcium is one of the most abundant minerals in the human body, being mostly distributed in the teeth and bones. Only a small part of the total calcium (around 1%) corresponds to serum calcium. This mineral is vital for bone development and health, for muscle contraction, intracellular signaling, heartbeat control, blood clotting, hormonal secretion and nerve transmission (49–51).

Oleic acid, also present in tomato seeds, is a monounsaturated fatty acid. The replacement of saturated fats with oleic acid or other monounsaturated fats appears to be beneficial for human health, including the maintenance of healthy cholesterol levels, modulation of insulin sensitivity, blood pressure, inflammatory markers, among others (52).

Palmitic acid, although being portrayed as an unhealthy saturated fat, participates in different physiological activities. It is one of the most plentiful saturated fatty acids in the human body. It is present in membrane’s phospholipids and adipose triacylglycerols.

This fatty acid acts as a surfactant in the lungs and is also essential for maintaining physical properties of membranes. Over the years, some studies have established a relationship between breast cancer and palmitic acid blood levels. Despite some researches stated the opposite, palmitic acid health benefits are still controversial (53).

Dietary fiber (DF) is usually defined as plant-derived polysaccharides that are indigestible and non-absorbed by the human gastrointestinal tract. Despite not having an actual nutritional value, DF is indispensable for human health. DF seems to act on the prevention of gastrointestinal related disorders and heart diseases. Soluble fibers appear to improve levels of LDL cholesterol, while insoluble fractions may increase bowel movements and feed healthy bacteria, acting as probiotics. Besides, DF has the ability to bond with heavy metals, aiding the natural body detoxification process (37,41).

3. Extraction of Tomato By-Products

As discussed before, tomato by-products are a great source of minerals and vitamins with a huge significance for human health. Therefore, the processing method used to obtain these by-products should ensure that their nutritional properties are maintained.

As most tomato by-products are still used as waste or in animal rations (13), industries are not targeting the nutritional content of tomato by-products yet. In fact, this should be taken into consideration for extracting bioactive compounds during tomato processing or from fresh tomatoes.

Presently, the most common used and traditional extraction techniques involve leaching processes and usage of organic solvents which may be environmental hazard and toxic besides affecting the content of bioactive molecules, thus decreasing its added value. Therefore, it has been made an effort to replace these techniques by innovative and environment friendly ones (**Figure 2**) (54).

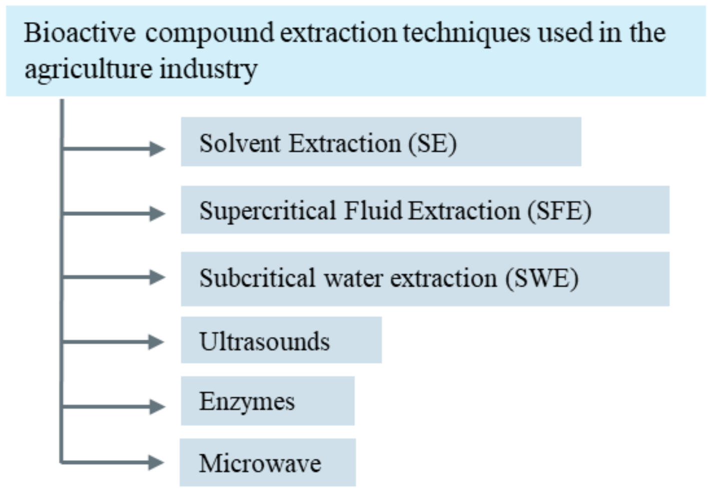

Figure 2- Common bioactive compound extraction techniques used in the agriculture industry (adapted from (54))

3.1. Solvent Extraction (SE)

The Solvent Extraction (SE) method consists of exposing suitable raw material to organic solvents. Different organic solvents will allow the separation and extraction of the soluble compounds of interest and also some natural pigments like anthocyanins.

In the SE method, samples are subjected to centrifugation and filtration to remove solid residue and isolate the extracts to be used in the manufacture of food supplements, food additives, or functional foods.

The SE method is fairly efficient to purify carotenoids, such as β-carotene and lycopene. Some studies have shown a recovery rate of carotenoids, between 50-96%, when using the SE method. To accomplish a maximum recovery, the proper selection of solvent systems, the temperature, and time (duration of the process), is quite necessary.

Some of the benefits of this technique are low processing costs and simplicity to perform it. However, the main concern is the use of high amounts of toxic solvents. Additionally, since solvents reach high temperatures during the extraction, degradation of bioactive compounds might also occur. Therefore, this method has been improved or even replaced by others discussed further ahead (54,55).

3.2. Supercritical Fluid Extraction (SFE)

The Supercritical Fluid Extraction (SFE) is a solvent-free, and thus, non-explosive, non-toxic and environment-friendly method. The selection of the supercritical fluid is of utmost importance since it will determine the suitable performance of the process. The principle of this method relies on the direct correlation between solvent power and density. To perform the SFE method, the raw material is introduced into an extraction container at controlled temperature and pressure with the supercritical fluid which allows the dissolution and separation of the compounds from raw material. After separation, both dissolved compounds and fluid are collected. The fluid can be easily removed from the final product. Since the critical temperature of CO_2 is close to the ambient temperature, SC-CO_2 method is able to extract thermolabile substances (54,56). The SFE allows the extraction of different bioactive (including lipophilic) compounds, such as catechins, flavonoids, carotenoids, tocopherols, among others. In tomatoes, the SFE method is mainly used to extract lycopene, β-carotene, and phenolic compounds.

3.3. Supercritical Water Extraction (SWE)

The Supercritical Water extraction (SWE) is an emerging alternative for the extraction of phenolic compounds from food and food wastes. The term supercritical water refers to water in the liquid state at 100ºC to 374ºC and below the critical pressure (22MPa).

This method is also an environmentally friendly technology and it appears to be one of the most promising approaches to extract multiple bioactive compounds from plants while maintaining its reduced impact on the environment. Some other advantages of SWE are higher quality as well as short time extractions, and low solvent costs (54).

SWE is not commonly used in tomatoes, nevertheless it might be promising for the extraction of flavonoids and tannins, two of the main phenolic compounds present in tomatoes.

3.4. Ultrasounds: Ultrasound-assisted extraction (UAE)

The Ultrasound-assisted extraction is another effective alternative to the common solvent extraction method and very simple to perform. Ultrasound frequencies are here used to cause a mechanical impact that disrupts the plant matrix and induces the formation of cavitation bubbles containing vaporized solvent. At these conditions, it is further easy to extract bioactive compounds. Thus, the extraction yield is highly dependent on the ultrasound frequency and nature of the plant matrix. It should be noted that the production of free radicals might occur in some cases, and then, alter the final bioactive compound content.

In tomatoes, the ultrasound-assisted method is specially used to extract lycopene and β-carotene similarly to the previous processes(54,57).

3.5. Enzymes: Enzyme assisted extraction (EAE)

The enzyme assisted extraction (EAE) method also emerges as a novel approach of bioactive compounds extraction.

In this process, enzymes are used to disrupt the plant cell walls to release the intracellular content. Since the plant cell walls usually contain polysaccharides, like hemicellulose, cellulose, and pectin, it is necessary to use enzymes that target these subtracts. As an example, β-glucosidase, cellulase, and pectinase are some of the main used enzymes to disrupt the plants´ matrix and depolymerize the polysaccharides, thus allowing the extraction of several compounds of interest.

The principle of the EAE method is to catalyze the cell wall disruption in an aqueous solution in mild conditions. Nowadays, this technique is most commonly applied to extract antioxidants from food waste. Just like the techniques mentioned earlier, it is a non-toxic and environment friendly method using water as a solvent, thus being referred as a “biological-refinery”. Additionally, other advantages have been highlighted, such as lower energy consumption and solvent use besides short extraction time.

The enzymes used for extraction can be added either alone or together. Some preparations of mixed enzymes allow obtaining improved recovery rates. In fact, the proper enzyme combination will determine optimal extraction yields. Preparations composed of pectin- and cellulose-degrading enzymes have shown to be an interesting alternative for lycopene extraction in tomato skin when compared to other enzyme assisted extractions. In tomato matrix, some studies have shown efficient extractions of phenolic compounds and carotenoids when using the EAE method. Accordingly, higher recovery rate of lycopene from tomato waste (peel) or paste has been reported.

The enzyme combinations arise as more affordable and with possible industrial-scale applications (54,58).

3.6. Microwave: Microwave-assisted extraction (MAE)

The microwave-assisted extraction (MAE) is an innovative method that combines the conventional solvent extraction technology with microwaves.

The principle of the MAE method is the separation of solutes from plant matrices by inducing diploid rotation and ionic conduction and by transforming microwave energy into heat.

When selecting the solvent for this method, it is of great importance to consider the plant matrix, target compounds´ polarity and structure, toxicity, and economical cost. Some of the most commonly used solvents are water, ethanol, hexane, among others, used either alone or combined. In order to increase the extractions rates, other solvents may be also added, for example, sodium hydroxide or acid chloride.

Some of the advantages of this technique are improved extraction rates, short extraction periods, lower solvents requirements, and costs when compared to conventional methods.

The MAE can be used for the extraction of different compounds, including polysaccharides, polyphenols, etc. However, it has not been widely used for tomato extraction yet. According to few reports, the extraction of polyphenols and flavonoids from tomato peel waste using the MAE method presented an extraction recovery rate highly influenced by temperature, solvent mixture, and extraction time. To achieve optimal recovery rates, further studies are still necessary. Nevertheless, the MAE method arises as a promising alternative for the extraction of polyphenols in tomato waste, with improved and fast recovery (54,59).

In summary, **Table 2** presents an overview of all these techniques for the extraction of bioactive compounds from tomatoes.

Table 2- Summary of advantages, disadvantages and extracted compounds in tomatoes by different methods

Method	Advantages	Disadvantages	Extracted compounds
Solvent Extraction (SE)	• Low processing costs • Simple performance • High carotenoids recovery rate	• Toxic Solvent use • Environmental and health Hazard • Decreased added value of extracts	• Lycopene • Anthocyanins • β-carotene
Supercritical fluid Extraction (SFE)	• Environmentally friendly • Non explosive • Non-toxic • Inexpensive (except the equipment) • Increased nutrient retention • Extraction of lipophilic compounds	• Selection of the proper super critical fluid for optimal extraction	• Lycopene • β-carotene • Phenolic compounds • Tocopherols
Supercritical water extraction (SWE)	• Environmentally friendly • Non-toxic • Low costs • Short extraction times	• No studies available yet for the extraction in tomatoes	• Phenolic compounds
Ultrasounds	• Simple to perform • Higher yields of recovery	• Highly dependent on the ultrasound frequency and nature of the plant matrix • Production of free radicals that can alter the bioactive compound content	• Lycopene • β-carotene
Enzyme	• Non-toxic • "Bio-refinery" • Increased extraction rates • Lower energy consumption • Less solvent consumption • Faster extractions • Affordability • Possible industrial scale application	• Proper enzyme combinations	• Phenolic compounds • Carotenoids
Microwave	• Improved extraction rates • Short extraction period • Lower solvents requirements • Lower costs	• Toxicity • Highly influenced by temperature, solvent and duration of the process • Few studies available to this date	• Polysaccharides • Polyphenols

While the majority of these techniques can be used to successfully extract lipophilic compounds, not all are suited for the extraction of hydrophilic compounds like vitamin C. The solvent extraction method (SE) can be used for the extraction of any compound, as long it is soluble in the solvent used for the extraction. Techniques like Supercritical water extraction (SWE) could also be an interesting alternative for the extraction of hydrophilic compounds. Pressurized liquid extraction (PLE) although not here explored is equally an alternative technique for the extraction of vitamin C from foods. Since there are not studies available studying such extraction in tomato wastes, further research is necessary.

Since microwave and ultra-sound assisted extractions also use solvents during their extraction procedures, eventually the extraction of compounds like vitamin C (as long as the right solvents are applied) would also be a possibility. Yet temperature and the formation of free radicals that interfere with these techniques respectively may result in inefficient extractions (54,60).

When talking about the extraction of bioactive compounds from food waste there are additional challenges to consider. While the extraction of bioactive compounds from whole foods is already challenging especially due to instability (once removed from its original matrix) when extracting target compounds from food waste the low concentrations that can be extracted are one of the main challenges (54,61).

Nevertheless, once extracted purity and content should be readily accessed through chromatographic methods as High-Performance Liquid Chromatography (HPLC), spectrophotometric or others according to the bioactive of interest (62–64).

4. Tomato extracts in human health and dietary supplements

Nowadays, the majority of the population takes dietary supplementation. In America alone, around 70 % consumers take supplements daily. Although most dietary supplements are safe, there is a risk of overtaking some vitamins and minerals, which is why consumers should always seek advice from trained health-care providers (65).

As the consumption of supplements increased, the requirements towards these products also changed. There is a greater demand for safe and natural products. Labels have changed, and “organic”, “eco-friendly”, “vegan”, “gluten-free”, among other tags gained notorious appeal. Much more people are seeking for natural ingredients whether they are present in oral supplementation or in skin-care products. This is where nutraceuticals and cosmeceuticals make their debut (66–68).

The original definition of nutraceuticals was first proposed by De Felice as the portions of foods that could supply the human body with health or medical benefits. These portions are considered as “active ingredients” essential for the prevention and protection against illness and aging. On the other hand, the cosmeceuticals were first introduced by Raymond Reed who associated the use of certain molecules in topical cosmetics to enhance skin appearance and function. The main difference between cosmeceuticals and simple cosmetics is that the first ones exhibit similar features to pharmaceuticals. Cosmeceuticals can induce long-lasting pharmacological and/or physiological effects (66).

Over the years, the knowledge of how diseases and aging can develop has significantly increased. Although there are not definitive answers yet and there is still a long way to go, some processes have been associated with the aging process and the appearance of certain illnesses. In fact, the inflammatory process and oxidative stress appear to play major roles in this matter.

There is a wide range of known active ingredients that has shown to modulate certain diseases mostly in animal studies (69,70). In particular, tomatoes and their by-products present a wide range of active ingredients as discussed below.

4.1. Effects of Oral Supplementation and/or Topical Application of Vitamin C, Lycopene, β-Carotene, Palmitic acid, and Zinc

The concept of ingesting bioactive compounds to improve skin outlook and overall health is becoming even more significant. In fact, the human skin is continuously exposed to external aggressors, such as solar UV radiation, pollution, smoke, among others which are related with the formation of free radicals or reactive oxygen species (ROS). ROS are highly unstable and toxic molecules that can damage the cell membranes, proteins, and even DNA (66,71).While the application of topical formulations to neutralize such compounds appears, at first hand to be enough, some researches show that enriching the skin from within is also important to reduce the impact of those external stressors. Although there are not available oral and/ or topical treatments yet for a huge variety of skin disorders, there is a consensus regarding the importance of maintaining a healthy state including a well-hydrated skin, the right balance of the microbiome film, and the essential skin nutrients in order to retain its barrier integrity and properties (66,71–73).

Vitamin C is an anti-inflammatory agent due to the transcription factor (NF-kb) modulation and a powerful antioxidant able to neutralize the ROS and regenerate vitamin E. It is also essential for different physiological processes such as collagen biosynthesis, protein metabolism, etc. The presence of this vitamin in the human body relies solely on diet and/or oral supplementation to reach the standardized daily values. It is important to note that even when supplementing high doses of vitamin C, only a small fraction is actively bioavailable on the skin. Thus, the association of oral supplementation with topical vitamin C may be a good start point of research to evaluate the real benefits and additive outcomes (66,71,74). Most studies suggested that improved nutritional vitamin C intake is more associated with skin benefits compared to topical formulations (mostly anti-aging and anti-pigmentation creams) (71,73).

Additionally, it has been suggested that vitamin C can play a major role in the prevention and modulation of other diseases, such as cancers, cardiovascular disorders, age-related macular degeneration, and cataracts, in which oxidative stress plays an important role (74).

β-carotene is a precursor of vitamin A that exhibits free radicals scavenging properties, and therefore, protection against UV- induced photodamage (66,75). When it comes to oral β-carotene supplementation, studies suggest that it can improve the skin outlook and protect it against sunburn reactions (66,76). Other health benefits have been associated with β-carotene supplementation, especially when combined with other antioxidants (e.g. vitamins C or E). Additionally, diets with a higher content of β- carotene and α-carotene have also been associated with reduced incidence of type 2 diabetes (77). Nevertheless, it is important to note that a continuous β-carotene supplementation, specifically at high cumulative level (above physiological levels), might be associated with negative side effects. In particular, some concerns were raised in populations with respiratory conditions (76).

Other carotenoids from tomatoes, such as lycopene, have also been shown to improve the skin´s tolerance to UV radiation. Studies demonstrated that the consumption of tomato-based products, that nourished the body with around 16 mg of lycopene, reduced the sun- induced erythema, demonstrating that lycopene exhibits photoprotective activity when ingested (66,76). Other reports showed that lycopene supplementation could improve the endothelial health in patients with cardiovascular disease (78). Additionally, one study concluded that oral lycopene supplementation in middle-age individuals allowed the lycopene skin accumulation up to levels similar to younger individuals (79). Lycopene has demonstrated to own photoprotective properties being a powerful quencher of ROS whether ingested or topically applied. As it has a lipophilic profile and reduced molecular size, enhanced skin absorption is observed when it is incorporated in topical formulations. Therefore, researchers are investigating the best topical systems that allow lycopene to retain its properties and delay its degradation taking into account the low chemical stability of this molecule (61).

Palmitic acid is the most abundant saturated fatty acid on the skin and possesses a crucial role in epidermal morphogenesis. The topical use of palmitic acid is commonly related to skin lipids replacement and skin repair whether its supplementation is used to treat and/or prevent certain skin disorders. However, high amounts of palmitic acid can lead to the inhibition of linoleic acid and thus to undesired effects (80,81).

Zinc is an essential nutrient for the proper function of the human metabolism and immune system besides playing an important role in healthy skin. Zinc is highly abundant in the skin and it is especially important for wound healing. This bioactive has shown to modulate the expression of inflammatory factors and to exhibit antioxidant properties. Some researchers have suggested that diseases with skin manifestations can be caused by mutations or dysregulations in zinc transporters that could lead to its deficiency. Zinc deficiency affects mostly the epidermis, and gastrointestinal, skeletal, nervous, reproductive, and immune systems. Additionally, if it occurs during the growth period it can lead to growth failure. Oral zinc supplementation is generally safe and beneficial and necessary for those with lower levels, but when it comes to skin manifestations, topical treatments may be enough. Formulations containing zinc have been used over years as active ingredients in antidandruff products, as soothing agents, and even in sunscreens. More recently, other applications have emerged as the treatment of pigmentary disorders (melasma), inflammatory dermatoses (rosacea and acne vulgaris), and even neoplasia (82–84).

At last, it is important to consider that while oral supplementation appears to be more efficient to lead to desired outcomes, daily values should be respected and not exceeded. Lipophilic molecules as β-carotene are not directly excreted through urine like hydrophilic compounds (Vitamin C). Some of these molecules have to first undergo metabolization processes before being excreted. Therefore, they present lower daily values to avoid accumulation and potential side-effects.

Additionally, while antioxidants have many described benefits they can work as pro-oxidants instead in certain situations. The pro-oxidant effect may occur when the antioxidants are in high concentrations or depending on matrix's nature and redox potential. Vitamin C for example although being a powerful antioxidant can work as a pro-oxidant when administered in concentrations around or higher than 1000 mg/kg of bodyweight. Vitamin C can also act as pro-oxidant in the presence of minerals such as iron and copper when participating in redox reactions. The same happens to α-tocopherol that acts as a pro-oxidant in high concentrations, to the point of working as a free radical instead. If not enough vitamin C is available to reduce these tocopherol molecules, they remain in their reactive state and lead to undesired side effects (85,86).

4.2. Approaching the tomato food producing industry to the cosmetic and pharmaceutical industry by using waste?

Taking into consideration what was previously discussed, tomato by-products present themselves as great raw materials to explore innovative applications towards cosmetics and nutraceuticals besides other health products.

Over the past years, the trend is to take care of the skin inside-out. Although new delivery systems are being developed, with the ability to target and deliver the active ingredients to the exact location, additional studies recognize the importance of nutrition (including diet and oral supplements) for guarantee the skin health and overall well- being (66,73,87).

Most tomato by-products contain active ingredients with photoprotective, antioxidant and anti-inflammatory activities, thus the further application of these compounds either in topical or oral formulations could be an interesting alternative for tomato producing industries instead of disposing these compounds as industrial waste. Incorporating lycopene, β-carotene, vitamin C, palmitic acid, and zinc sustainably obtained from tomato by-products, into supplements and topical formulations would allow building a bridge between the food industry and pharmaceutical and cosmetic industries. This bridge would allow us to further approach the concept of using natural whole foods to treat and prevent diseases from the inside-out point of view. Notwithstanding, further and rigorous studies are still necessary to become more consensual. Anyway, it becomes clear that it is no longer possible to target disorders at only one pathway. Lastly to enhance public acceptability, color, smell, and texture of these formulations, especially in cosmetics should be improved. (66,72,73).

Additional considerations:

The protein content of tomato seeds should also be considered as some studies suggest that its quality is comparable to other plant proteins and shown to have cholesterol-lowering effects. Tomato seed meals could therefore be an alternative for vegetarians and others, to ensure protein intake. Tomato seed oil extracted either through solvent or mechanic extraction for edible purposes, appears also a healthy alternative for tomato pomace use, since tomato seeds present high levels of linoleic acid an essential fatty acid for humans (39,88). Further, although studies are limited, using tomato pomace for pectin production emerges as an innovative application. Most pectin is extracted from apple pomace and citrus peels, through solvent, ultrasound, or subcritical water-assisted extraction methods and used as a food additive (thickener). Some studies also showed that pectin could inhibit tin corrosion having therefore diversified applications. Rheology proprieties need to be accessed but studies suggest that tomato waste could be a novel alternative for good pectin extraction yields (89,90).

The application of wasteful products to enrich foods in developed countries also emerges as an interesting concept that could help to increase the access to resources especially those with the necessary nutritional value (82).

5. Challenges and Opportunities

The tomato industry is a global and large-scale manufacturing industry with considerable product loss. Potential added-value by-products could be thus explored for alternative applications as shown in **Figure 2**.

The traditional tomato production and processing pathway dispose of the rotten or non-standard "fresh-tomatoes" and by-products either as environmental waste, or as non-valued materials used in the manufacture of soil fertilizer or animal rations.

The opportunity to reduce such waste and eventually find additional processing methods could be quite interesting for most tomato processing industries. The tomato industry represents one of the major vegetable production industries over the globe, thus the results of the trial and implementation of new procedures or by-products applications could be readily accessed. This large-scale dimension allows a more flexible approach, since fresh tomatoes (that do not reach market standards) or by-products are not yet considered as "raw-materials", therefore they would not face ethical issues in contrast to perfectly eatable fresh tomato fruits for the research of novel applications.

One of the main opportunities for the tomato processing industries is related to the increased industrial income and possible medical discoveries whether tomato waste becomes an added- value material or the extraction and isolation processes allow obtaining target tomato bioactive compounds. The supplementation of tomato bioactive extracts (including vitamins and minerals) has shown positive outcomes for human health in modulation and treatment of certain diseases. Nevertheless, more studies should be focused on the long-term effects of tomato bioactive on the human body.

Additionally, the opportunity to transform these industries into more environmentally friendly ones emerges as well. The initial waste can be reused to extract bioactive compounds with likewise "eco-friendly" methods.

While this matter appears as a potential income of these industries, there are still some challenges to considerate, such as: a) available and strict studies demonstrating efficient and profitable applications of tomato by-products; b) defined standard procedures or techniques for optimal extraction of bioactive compounds and moisture of fresh raw material; c) materials, equipment, and trained professionals still needed for this new purpose. In order to achieve an efficient and profitable use of the industrial waste, the companies require a paradigm shift, i.e., stop looking at tomato by-products as waste and see it as added-value material.

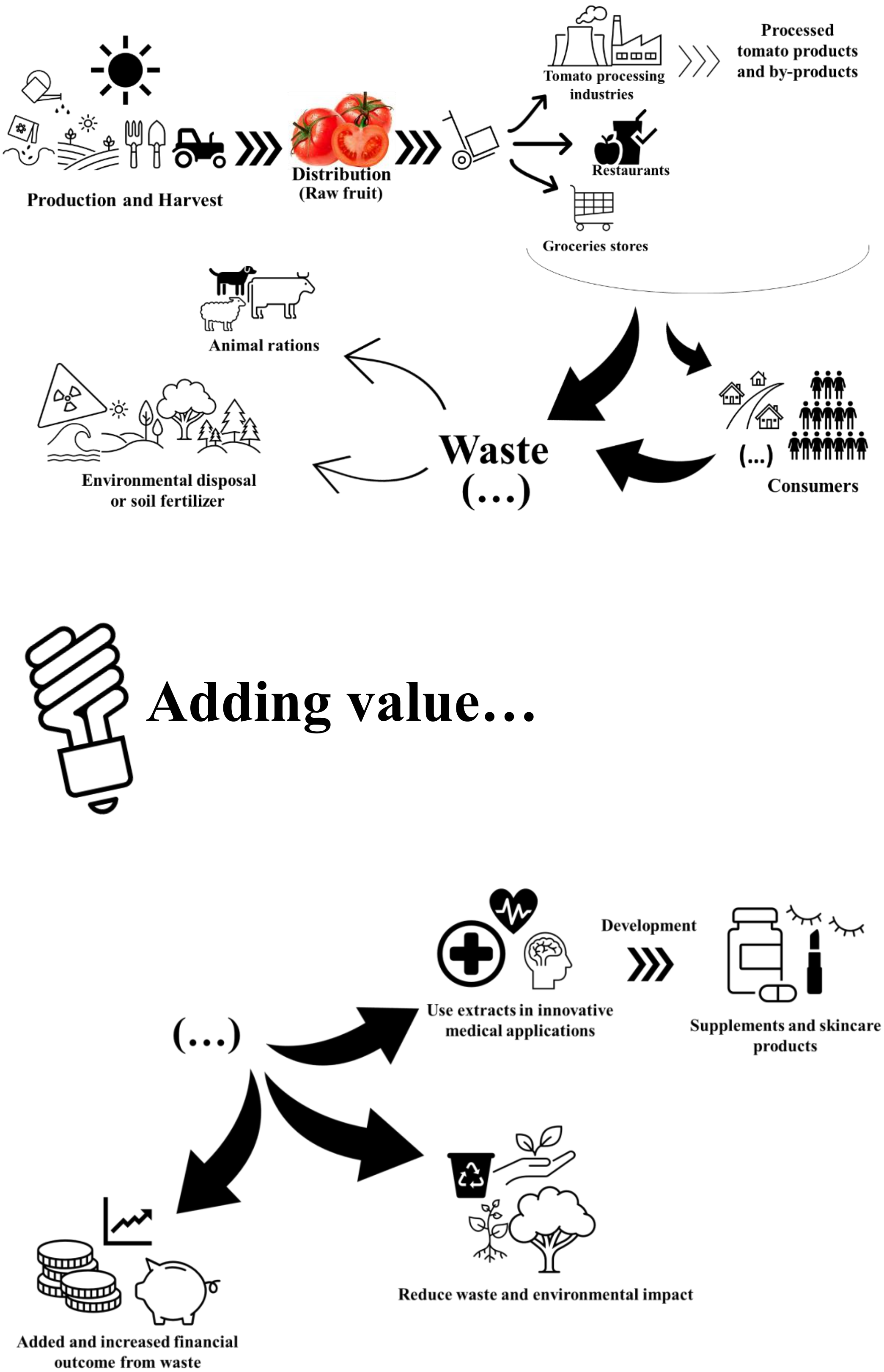

Figure 2 -Traditional tomato production and processing circuit *versus* added -value circuit. (adapted from Copyright©Depositphotos.com/Sergejs Bespalovs)

6. Conclusion

Tomato by-products do not longer need to go to waste. As here extensively discussed, there are plenty, interesting and sustainable applications for tomato by-products.

The cosmetic industry is growing more over the years, and society is searching for more natural and environmentally friendly products. The concept of treating the skin from the inside-out is getting ingrained in people’s mind and, as the gap that exists between the food and cosmetic industries is being dissolved, the near future seems to be promising towards these areas. This wills not only raise the industries profit but also create more sustainable industries.

The presence of important bioactive compounds in wasteful by-products shows that not all waste is wasteful. The fact that tomato by-products contain great levels of anti-inflammatory and antioxidant compounds, with the ability to modulate the development of certain disorders, shows that potential sources of cosmetic and medical discoveries that could be further explored on this context.

Additionally, since tomato by-products are not considered as valued raw materials yet, the possibility for the investigation and development of further applications is facilitated and could be conducted at very low costs, with great profitable outcomes. It is important to note that there are still not many studies available that prove the efficiency of these innovative applications. Pioneer industries would require multidisciplinary teams to efficiently develop such products and analyze the stability of these compounds when incorporated in different formulations. Stability is one of the main concerns when it comes to incorporating food compounds in skincare and supplements since the dissociation of the initial matrix may affect on a negative way.

In conclusion, there is still a long way to go, but the promising outcomes of these applications should not be definitely neglected.

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