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Industrial use of pepper *(Capsicum annum* L.) derived products: technological benefits and biological advantages

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SUMMARY

In pursuit of new bioactive compounds and natural ingredients for agro-food, cosmetic and pharma industrial uses, as replacements for synthetic compounds and also for the valorisation of crop plant's by-products, the recovery of pepper (*Capsicum annum*, L.) bioactive compounds represent an interesting strategy to develop new products for the industry. Besides, being used as a condiment, providing characteristic of pungency, colour and flavour, the new pepper-derived ingredients may be used in preservation and extension of lifespan of industrial products, as well as additives or technological ingredients with antioxidant and antimicrobial activities. Moreover, the applicability of the new products in pharmaceutical formulas for treating certain inflammatory and pain-related conditions is also a possibility, since pepper fruits mainly contain capsaicinoids, carotenoids, phenolic compounds, vitamin C and A, and minerals, such as iron and calcium, with health-promoting potential. Further studies on appropriate extraction protocols, stability, safety and bioactivity are key to provide with novel and promising pepper ingredients for foods, cosmetics, and pharmaceutical applications.

KEYWORDS: paprika, oleoresin, capsaicin, bioactive compounds, natural products, valorisation, agrowaste

CONTENTS

1. Introduction: Exploration and valorisation of bioactive products

Over the last years, the interest in the discovery of natural compounds, the awareness of the benefits of healthy foods, and the advances on analytical instrumentation, have allowed to establish chemical and functional properties of the bioactive compounds present in natural matrices. Thus, continuing quest of new phytotherapeutics and improved technological applications, explain the attention given to pepper fruits and their by-products as source of bioactive compounds. Indeed, developing scientific projects, to exploit plant products and by-products, is one of the main topics of research and innovation funded by the European Union under the Horizon 2020 framework program. Being the objective of these projects providing extracts, enriched fractions and isolated compounds of high purity, assessed for their safety and pharmacological effects, by cell-based and *in vivo* assays, in order to be integrated in formulations and products in the area of the food and pharma industries.

Pepper (*Capsicum annuum* L.) is an annual herbaceous plant belonging to the *Solanaceae* family, which is cultivated in warm climate regions worldwide (Thampi 2003). Generally, peppers are consumed raw (bell pepper) or in powdered form as a spice (chili pepper) or as a colorant (paprika), being their production grown in recent years in a wide number of varieties, as it is one of the most economical and agriculturally important vegetable crops all over the world (246,000 tons) (FAOSTAT 2016).

Pepper fruits range from sweet, large and thick, like green bell peppers, to thin and hot varieties, like cayenne. The fruits can be of different colours, from green, yellow, orange and, corresponding to distinct stages of maturation and capacities of synthetizing carotenoids or chlorophylls. Regarding flavour, these vegetables range from the sweet (non-pungent) varieties, such as paprika, to the hot species, such as chilies or cayenne (Buckenhüskes 2003).

In addition to the sensory features and used as condiments, due to its characteristic pungency, aroma and colour, pepper is an important source of bioactive compounds that offers health benefits, including vitamins C and E, provitamin A, carotenoids and phenolic compounds. Metabolic and chemical processes, such as ripening, never stop in samples unless these are subjected to deep-freezing in liquid nitrogen. Therefore, the storage period after sampling must be minimized, and conditions should be controlled in order to produce a high quality plant material for its characterization and further use (Padilha, Pereira et al. 2015).

Even if the majority of the peppers in international trade are fresh produce, spice or colorants, an important 4 - 5% of the fruits are discarded as non-marketable products or by-products. However, these by-products can be sources of nutrients, secondary metabolites and materials with applications in agro-food, pharma or cosmetics industries, in a growing global market of value-added products, nutraceuticals, functional foods, and personalised nutrition driven by industries and consumers.

2. Pepper as a source of bioactive compounds and nutrients

The content of bioactive compounds differs depending on the fruit part (placenta, pericarp, and seeds), the cultivar or variety, the ripening stage, the climatic and storage conditions as well as the processing practices.

Capsaicinoids and carotenoids are generally the major phytochemicals found in pepper varieties, which add high commercial value to these fruits in terms of flavour characteristics, colour and antioxidant properties, among other bioactivities. Peppers are also rich in (poly)phenolic compounds, mainly flavonoids and phenolic acid derivatives, and nutrients such as vitamins A and C, and minerals, including iron, calcium and manganese, contributing greatly to the human diet (Liu 2013). Due to this, special attention is needed in the characterization and exploitation of these plant products with multiple uses understudied at the present time.

2.1. Phenolic compounds

Phenolic acid derivatives and flavonoids represent the major groups of phenolic compounds in pepper varieties (Jayaprakasha, Bae et al. 2012). They contribute to the taste, colour and flavour of the fruits and also show health-promoting effects based on the protection of the organism from the damage produced by oxidative agents, being a good indication of the antioxidant capacity of peppers (Scalbert, Manach et al. 2005, Padilha, Pereira et al. 2015). Nonetheless, the total radical-scavenging activity of pepper is also influenced by the synergism between the total antioxidants in the sample, such as vitamins and carotenoids (Conforti, Statti et al. 2007).

Numerous epidemiological studies indicate a possible association between the uptake of phenolic acids and flavonoids and the reduction of the risk of coronary disorders, diabetes, cancer, osteoporosis, and neurodegenerative diseases (Pandey and Rizvi 2009). Among the flavonoids, the flavonol glycosides (e.g. quercetin-*O*-glycosides) are mainly found in fruits, including quercetin 3-*O*-rhamnoside, quercetin 3-*O*-rhamnoside-7-*O*-glucoside, quercetin 3-*O*-glucoside-7-*O*-rhamnoside, and quercetin glycosylated with rhamnoside-glucoside attached either at the C-3 or C-7 position. Also some glycosides and aglycones of luteolin, myricetin, kaempferol and apigenin derivatives are present in these fruits, for instance, two luteolin *O*-glycosides [luteolin (apiosyl-acetyl)-glucoside and luteolin 7-*O*-(2-apiosyl)-glucoside], five luteolin C-glycosides [luteolin 6-C-glucoside, luteolin 8-C-glucoside, luteolin 6-C-arabinoside-8-C-glucoside, luteolin 6-C-glucoside-8-C-arabinoside and luteolin 6,8 -di-C-glucoside] and two apigenin C-glycosides [apigenin 6-C-arabinoside-8-C-glucoside and apigenin 6,8-di-C-glucoside], have been found in the pericarps of bell sweet pepper varieties (Jayaprakasha, Bae et al. 2012, Asnin and Park 2015). These compounds have been identified by HPLC-MS/MS and NMR analysis and spectral data, ranging their content in pepper varieties from 5 to 20 mg 100 g^{-1} fresh weight (F.W.) (Asnin and Park 2015). Generally, flavonols have been cited as having high antibacterial, antifungal, antioxidant, and anticancer effects, related to the presence and number of hydroxyl groups at certain positions and the double bond at the C2-C3 position (Rice-Evans, Miller et al. 1996), as in quercetin 3-O-α-l-rhamnopyranoside in peppers (Materska and Perucka 2005).

On the other hand, *p*-coumaric, caffeic and 3,4-dimethoxy-cinnamic acid glycosides, are characteristic phenolic acids in pepper fruits. These hydroxycinnamic acids are found as major components in the pericarps and placenta, ranging their total contents from 50 to 500 mg 100 g^{-1} F.W., depending on variety, maturity stage, and growing conditions (Sakakibara, Honda et al. 2003). The phenolic acids from *Capsicum annum* genotypes have been also shown as antimicrobial and antioxidants (Nazzaro, Caliendo et al. 2009).

Changes in the chemical composition during maturation of fruits is not well studied, and some authors found a decrease of total phenolics content during ripening (Marin, Ferreres et al. 2004, Conforti, Statti et al. 2007), being immature sweet green peppers richer in flavonols than green, immature red, or red ripe sweet peppers (by ~4.5-fold reduction); however, differences are not dramatic and for example, the glycosides of ferulic and sinapic acid increased when fruits pass from the green to the red stage, probably because of the sink characteristics of the fruit during ripening (Howard, Talcott et al. 2000, Marin, Ferreres et al. 2004).

Anthocyanins are also present in some species of red and purple peppers and are characterized by the basic core, the flavylium cation. Results of total anthocyanins ranged from ~0.5 mg 100 g^{-1} F.W. in ripe yellow fruits to ~28 mg 100 g^{-1} F.W. in ripe red fruits, according to different works, being delphinidin-3-trans-coumaroylrutinoside-5-glucoside, the major anthocyanin present in these fruits (Padilha, Pereira et al. 2015).

A relevant subject of current research for the demonstration of health-promoting activity of the phenolic compounds is the establishment of their bioavailability. The phenolic compounds are metabolised in the enterocytes and the hepatic cells by methylation, sulphatation and glucuronidation, being then absorbed into the circulation system and distributed through the different organs of the body (Tomás-Barberán, Gil-Izquierdo et al. 2009). Their bioavailability depends on several factors, such as the permeation and transport mechanisms in the intestinal epithelium, the gastrointestinal stability of phenolic fractions and the role of the gut microbiota in the biotransformation of these compounds in their inter-individual differences, among others (Minatel, Borges et al. 2017). The use of nanoformulations enriched in phenolic compounds either in topical or oral administration formulas may increase their absorption and synergistic effects or combine their use with certain drugs (Munin and Edwards-Lévy 2011), and that would also represent new lines of research, development and innovation in the formulation of pepper-derived products.

2.2. Carotenoids

Carotenoids are lipid soluble compounds derived from the isoprenoid pathway and stored in the chromoplasts in pepper fruits. These terpenoids share a 40-carbon isoprene backbone with a variety of ring structures at one or both ends. The carbon skeleton is derived from five-carbon isoprenoid groups and contains alternating conjugated double bonds (Guzman, Bosland et al. 2011).

Raw peppers are good sources of carotenoids that may vary in composition and content due to genetic differences and degree of maturation, also influenced by production practices as well as the processing conditions. In mature pepper fruits, the total carotenoid contents showed great variability ranging from 0.69 to 30 mg g^{-1} dry weight or 15 to 148 mg $100g^{-1}$ fresh weight (Arimboor, Natarajan et al. 2015, Padilha, Pereira et al. 2015), showing the pericarp and placenta similar values of total carotenoids (~ 0.4 %), while these compounds are not found in seeds (Simonovska, Rafajlovska et al. 2014). There are at least 34 metabolic related carotenoids in *Capsicum* peppers. For instance, the red pigments capsanthin and capsorubin (unique to the *Capsicum* genus) are produced at the end of the biosynthetic pathway, being therefore, only accumulated in red peppers. Capsanthin, being mainly responsible of the red colour, usually represents a 40-60% of the total carotenoids in different varieties. Other carotenoids are also accumulated during fruit ripening, such as capsorubin and capsanthin 5,6-epoxide, β-carotene, β-cryptoxanthin and violaxanthin (Ha, Kim et al. 2007). As a result of carotenoid metabolism and accumulation in the chromoplasts of the pericarp, the green colour of the fruit, which is principally due to the presence of chlorophyll, changes to yellow-orange, having these varieties as major carotenoids, violaxanthin (37% to 68% of total carotenoids), and lutein and β-carotene (5% to 14%) (Delgado-Vargas, Jiménez et al. 2000, de Azevedo-Meleiro and Rodriguez-Amaya 2009).

Regarding the carotenoid chemical structures and potential bioactivities, these compounds have excellent antioxidant properties due to the presence of a conjugated double bond-system, which gives them the ability to protect cells against free radicals by scavenging reactive oxygen species (ROS), associated with reduced risk of developing degenerative diseases, such as cancer, cardiovascular diseases, cataract, and macular degeneration (Fiedor and Burda 2014). Capsanthin contains 11 conjugated double bonds in its structure, a conjugated keto group and a cyclopentane ring, being a powerful antioxidant (good free-radical quenching capacity). On the other hand, β-carotene and β-cryptoxanthin possess lower antioxidant abilities, even though these compounds have the same number of double bonds than capsanthin. Thus, the keto groups and cyclopentane rings, besides the number of double bonds, are enhancers of the antioxidant activity on these compounds (Kim and Oh 2009).

Pepper carotenoids are also predominantly precursors of vitamin A (α-and β-carotene and β-cryptoxanthin), the ability to yield vitamin A (retinol), being only two dietary carotenoids, lutein and zeaxanthin, able to reach the human retina, important for the prevention of age-related macular degeneration and other ocular diseases such as cataracts, since the human body is not able to synthetize them (Bernstein, Li et al. 2016).

With reference to carotenoids bioavailability, the transport of these bioactive pigments from the gut occurs on uptake with lipoproteins (chylomicrons) into the lymph, followed by circulating in the blood, and being distributed into various tissues with large differences between organs. Different factors affect their absorption and bioavailability, such as food matrix, solubilisation in mixed micelles and host-related factors (overweight, disease state, microbiota etc.) (Bohn, Desmarchelier et al. 2017).

2.3. Capsaicinoids

Chemically, these compounds are acid amines of vanillylamine and branch fatty acids containing 8 to 13 carbons (Kobata, 1999). The main capsaicinoids present in peppers are capsaicin (vanylamide of 8-methylnontrans-6-enoic acid) and dihydrocapsaicin (vanylamide of 8-methylnonanoic acid). Together, they are often present in amounts larger than 80% of total capsaicinoids, while the other derivatives occur in much smaller quantities (Thomas, Schreiber et al. 1998, Perucka and Materska 2001). Besides these two major capsaicinoids, other isolated capsaicinoids from hot peppers are nordihydrocapsaicin, norcapsaicin, homocapsaicin, homodihydrocapsaicin, nornorcapsaicin, nornornorcapsaicin, nonivamide, and some others (Barbero, Palma et al. 2006). Pungency of each capsaicinoid depends on its chemical structure that requires presence of an amide bond attached to a vanyllyl ring and an acyl chain (Szolcsanyi 2004). The most pungent capsaicinoids are capsaicin and dihydrocapsaicin having value of ~16.1 x 10^6 Scoville Heat Unit (SHU), a simple organoleptic test to determine pepper pungency (Dang, Hong et al. 2017). These compounds are synthesised in the cinnamic acid pathway in glands of the pepper's placenta and the white rib which makes these parts of fruits the hottest parts of the pepper (Topuz and Ozdemir 2007). In general, capsaicinoids contents vary with genotype and maturity stage. For example, Deepa et al., found drastic differences in capsaicin levels between genotypes, being the changes of these compounds not so pronounced by maturity states, even though a little decrease in capsaicin levels was found in some varieties (Deepa et al., 2007). These differences could be ascribed to different levels of peroxidase enzymes in different genotypes and maturity stages (Estrada et al., 2000). In hot pepper varieties, the concentration of capsaicinoids varies from 0.003 to 0.01% while in mild chillies it is from 0.3 to 0.5%. In strong chillies the concentration goes to 1% (Perucka and Materska 2001, Topuz, Dincer et al. 2011) and up to 2% in some Mexican varieties (Orellana-Escobedo, Garcia-Amezquita et al. 2013).

Capsaicin and other capsaicinoids have a rather strong biological activity and, therefore, a possible pharmacological and clinical application for the treatment of neurological and musculoskeletal pain, and inflammatory and oxidative disease states (Hayman and Kam 2008), as it would be comment below.

2.4. Capsinoids

Capsinoids are non-pungent compounds only found in few varieties of peppers with similar structure to the capsaicinoids, such as capsiate (4-hydroxy-3-methoxybenzyl (E)-8-methyl-6-nonenoate) ant its derivatives dihydro-capsiate and nordihydrocapsiate, which could be found in non-pungent red peppers, such as sweet chili pepper *Capsicum anuum* L. var. (CH-19). The fundamental structure of capsinoids is a fatty acid ester with vanillyl alcohol (Kobata, Sugawara et al. 2013). These compounds have recently emerged and their mechanisms of action are poorly understood so far, however, they have shown interesting antimicrobial activity (Bacon, Boyer et al. 2017), enhanced energy metabolism via activation of the sympathetic nervous system in mice (Ohnuki, Haramizu et al. 2001) and reported brown fat thermogenesis and reducing body fat activities in humans (Saito and Yoneshiro 2013). Nevertheless, these compounds have been presented as a promising alternative for those who abstain from capsaicin-containing foods due to the pungency (Ludy, Moore et al. 2012).

2.5. Vitamins

Peppers are good sources of vitamins, having high levels of vitamin C, E and provitamin A. For instance, one medium sized green bell pepper fruit contains 180% of recommended daily allowance (RDA) for vitamin C and 8% for vitamin A (Geleta and Labuschagne 2006). Therefore, relatively modest amount of pepper fruit ensures adult RDA for vitamin C. These vitamins are also known as strong antioxidant compounds that have positive impact on human health. Among them, vitamin C has a particular high antioxidant activity, reducing the levels of free radicals and quelling peroxidation reactions in the human body, and, therefore, reducing the risk of cardiovascular diseases and some types of cancer (Navarro, Flores et al. 2006). Levels of vitamin C present in pepper fruits depend on several factors as genotype (variety), maturity stage, and harvesting time, postharvest handling and processing and storage conditions. In general, the experiments measuring vitamin C levels during ripening show an increase in vitamin C with pepper maturity (Lee and Kader 2000, Marin, Ferreres et al. 2004). Postharvest handling and storage are mainly affected by temperature and processing, having a bigger loss of vitamin C with higher temperature and processing (like drying and grinding) (Howard and Wildman 2007).

2.6. Minerals

The most common essential minerals found in peppers are potassium (K), Magnesium (Mg), Phosphorus (P), Calcium (Ca), Iron (Fe), Copper (Cu), Zinc (Zn), Manganese (Mn), and Boron (B). Amounts of minerals vary and depend on variety, maturity stage and environment where it is grown. For example, some authors found that red peppers had higher levels of K, Mg, P, Fe, Cu, Zn, Mn, and B than green peppers (Rubio et al., 2002) while some other researchers found significantly lower levels of Fe, Cu, Zn, K, Ca and Mg in red peppers compared to green ones (Perez-Lopez et al., 2007). Additionally, some other groups studied mineral content among different pepper varieties and found a significant variability among tested cultivars (Guil-Guerrrero et al., 2006; Jadczak et al., 2010). Martinez et al. (2007) have found in green and red peppers K to have the highest concentration while green peppers from the supermarket had higher amounts of Ca and Na compared to freshly picked peppers. Other minerals scarcely changed between samplings such as Zn, Mn, and Cu. The agricultural practices (organic *vs.* conventional farming) may influence the mineral contents of plant-derived foods, including peppers, which in general, had higher mineral contents when produced organically (Pérez-López, López-Nicolas et al. 2007).

2. Specific extraction methods, extracts, enriched fractions and isolated compounds

Compounds present in peppers are subjected to different extraction methods to be isolated, characterized and finally applied to industry. These methods could be divided into two groups: classical methods such as Soxhlet extraction, maceration and magnetic stirring, and modern methods like supercritical fluid extraction, ultrasound assisted extraction, enzymatic extraction, microwave assisted extraction, and pressurized liquid extraction (Barbero, Liazid et al. 2008). Most of the classical methods require high amount of solvents and long times of extraction, as in the case of the Soxhlet extraction method (Luque de Castro and García-Ayuso 1998). On the contrary, more modern methods have reduced the extraction times and quantities of solvents, achieving a lower impact on the environment. Among these methods, supercritical fluid extractions and the use of ultrasounds or the microwave in the extractions are the most used, which basic parameters are stablished in preliminary work in order to optimize the extractions. The parameters selected to be optimized are commonly the appropriate solvent and its volume, the temperature and the time, and the quantity of the sample (Barbero, Palma et al. 2006). The selection of these criteria depends on the polarity of the specific compounds subject of the extraction, their stability, the amount of the analytes and the type of the container matrix. The most extracted compounds in pepper matrices are capsaicinoids and carotenoids, being carotenoids mainly extracted as paprika oleoresin, which is use as natural food colorant (Uquiche, Valle et al. 2004).

Capsicum oleoresin is an important product of pepper processing with application in the food and pharmaceutical industry. Oleoresin is made of lipid components (fatty acids and triglycerides), pigments (capsaicinoids and carotenoids) and some other compounds at low concentrations (Fernández-Ronco, Ortega-Noblejas et al. 2010). Different methods have been employed to extract and use these compounds for health (capsaicinoids) or food colouring (carotenoids) applications. Conventionally, oleoresin has been produced by extraction using organic solvents according to the European Medicine Agency, such as ethanol or propanol (Agency 2015) or using hexane (authorized by the FDA from the US), which is a rather complex and energy requiring process. To overcome these problems, extractions by green technologies, such as the use of supercritical CO2 methods, are being employed currently to extract oleoresin and to separate it into enriched fractions of bioactive compounds, such as capsaicinoids and carotenoids, obtained from fresh, ripe or dried fruits (de Aguiar, Sales et al. 2013, Fernández-Ronco, de Lucas et al. 2013).

Regarding modern extraction methods, the use of ultrasound assisted extraction is relatively simple and inexpensive in equipment. Different solvents, temperatures, times of extraction, solvent volumes and quantities of sample have been selected to optimized the ultrasound energy, being the optimum extraction the use of methanol 100%, extraction temperature at 50 °C and extraction time 10 minutes for 1 g of sample (Barbero, Liazid et al. 2008).

Microwave assisted extraction has been also employed to extract capsaicinoids from peppers (Barbero, Palma et al. 2006). This methodology applies the energy obtained by microwave radiation to extract the compounds of interest. In this study, authors studied five solvents (methanol, ethanol, ethyl acetate, acetone and water), different temperatures (50-200 °C), extraction times (5-20 min), solvent volumes (15-50 ml) and sample quantities (0.1-1 g) as basic parameters. The best results were obtained under optimal conditions by using 25 mL of ethanol 100 % as a solvent, at 125 °C, for 5 min with 0.5 g of pepper.

In a similar manner, Perva-Uzunalic et al., (2003) tested different pressures and temperatures for the optimization of the supercritical CO_2 extractions, obtaining the highest yield of capsaicinoids and colouring compounds from chilli pepper at the pressure of 400 bar and temperature of 40 °C, with the 96 % of capsaicinoids and 80% of carotenoids extracted from the raw material (Perva-Uzunalić, Škerget et al. 2004). According to these results, Daood et al., (2002) concluded a 5-fold increase in the extraction yield of carotenoids increasing pressure from 100 to 400 bar (Daood, Illés et al. 2002). The most important advantage of the supercritical CO_2 extraction is the collection of an extract free of residues of organic solvents when compared to the other extraction methods. Also a separation of enriched fractions of *Capsicum* oleoresin compounds could be produced using supercritical CO_2 counter current extraction methods, obtaining one fraction enriched in capsaicinoids and a refined fraction enriched in carotenoids, being the economic feasibility of the separation process evaluated in terms of costs and benefits (Fernández-Ronco, Gracia et al. 2011).

4. Agro-food industrial applications

Among the different pepper derived products used in the industry, one of the most important is the powder, called paprika, being the 70% of its production used as spice in meat products, soups, sauces and snacks. The total world supply of paprika powder is approximately 60,000 tons per annum, in contrast to the 1,400 tons of paprika oleoresin produced (Buckenhüskes 2003). Currently, additionally to the traditional pungency, colour and taste attributes, other important characteristics are considered in the food processing industries, such as the antimicrobial or antioxidant activities, as well as other multiple uses of *Capsicum* derived ingredients in the agro-food industry as exemplified in Table 1.

4.1. Antimicrobial activity

Although *Capsicum annuum* is known in Mesoamerican ethno pharmacology as a component of herbal remedies for different illnesses of microbial origin (Cichewicz and Thorpe 1996), and several scientific evidences have shown antimicrobial activities against gram positive and gram negative bacteria, the information about the responsible compounds of these effects is relatively scarce. Dorantes *et al*., (2000) reported a high inhibition activity of *C. annuum* extracts (habanero, serrano and morrón varieties) against *Listeria monocytogenes*, followed by *Bacillus cereus*, *Staphylococcus aureus* and *Salmonella enterica Typhimurium*, all of them cause of foodborne illnesses. In that work, *m*-coumaric and cinnamic acids were responsible of the inhibitory activities, while capsaicin and dihydrocapsaicin did not show these effects (Dorantes et al., 2000). Recently, Bacon *et al.,* (2017) reported the most antimicrobial activity, especially against *L. monocytogenes*, from a *Capsicum annuum* “Jalapeño” extract fraction rich in cinnamic acids (~ 5 ppm). These authors also reported a specific antimicrobial activity of capsinosides, the analogues compounds of capsicinoids, against gram positive bacteria, by disrupting biofilm formation and preventing biofilm-related infections due to their capacity of chelating calcium. In accordance to these results, Careaga *et al*., (2003) reported a minimum inhibitory concentration of a *Capsicum annuum* bell pepper extract of 1.5mL/100 g in minced beef meat preventing the growth of *S. typhimurium* (Careaga, Fernandez et al. 2003). On the other hand, *C. annuum* extracts exhibited also inhibitory activity against few different fungi, including *Penicillium expansum* (producer of mycotoxin patulin) and *Debaryomyces hansenii* (opportunistic pathogen) (Nazzaro, Caliendo et al. 2009). Also cayenne and green pepper ethanol extracts applicated to Egyptian Kareish cheese during manufacture showed antimicrobial activity against natural microflora, coliforms, molds, and *Staphylococcus aureus*, being strongly acceptable to the consumers in the concentrations of 1% for cayenne pepper and 3-6 % for green pepper (Wahba, Ahmed et al. 2010). Therefore, pepper-derived products may contribute to the development of new and safe ingredients, which could be used as antimicrobial agents for food preservation, to control foodborne pathogens in foods and/or spoilage of contaminated products, avoiding the use of other synthetic preservatives, such as nitrite, sodium benzoate or sodium metabisulfite, which have been occasionally related to allergic reactions and potential formation of nitrosamines (Roller 2003).

4.2. Antioxidant capacity

Several studies have shown that the antioxidant capacity of pepper samples increases with ripening and it is mainly attributable to the increased content of bioactive compounds including carotenoids and polyphenols as well as nutrients such as vitamins (Howard, Talcott et al. 2000, Marin, Ferreres et al. 2004, Deepa, Kaur et al. 2007). Regarding vitamin C, some studies found a decrease during maturation (Deepa, Kaur et al. 2007), while others found the opposite (Marín et al., 2004). Regarding phenolics Marín et al. (2004), also showed the highest content in immature (green) peppers, and Deepa et al. (2007) did not find a decrease of these compounds with ripening. Red ripe peppers shown higher contents of capsaicinoids than green peppers, which may also contribute to their antioxidant capacity (Materska and Perucka 2005). Therefore, these differences during maturation from pepper samples should be carefully studied and interpreted in order to understand the complex interactions occurring among different bioactive compounds and other reducing compounds in the extracts in terms of their reported bioactivity (Howard, Talcott et al. 2000). Most of these phytochemicals (e.g., carotenoids and flavonoids) with reported antioxidant capacity also influence the colour of the fruits (Ghasemnezhad, Sherafati et al. 2011, del Rocío Gómez-García and Ochoa-Alejo 2013), and *vice versa*, higher *in vitro* antioxidant activity from red and orange pepper varieties compared with the green, yellow or white fruits, is also possible (Guil-Guerrero, Martínez-Guirado et al. 2006, Matsufuji, Ishikawa et al. 2007, Sun, Xu et al. 2007). In this sense, using red sweet bell pepper as ingredient in foods could significantly reduce the cholesterol decomposition and the docosahexanoic (DHA) acid degradation during cooking, which produce toxic oxidation products which may generate off-flavours and deterioration of food quality, as well as could increase the risk for coronary heart diseases and cancer (Sun, Xu et al. 2007). Commercially available red bell pepper powders can be obtained in different formats: diced or granulated (e.g. Jinhua Huayang Co., Ltd.; URL: http://www.sinospice.com/proinfo.asp?id=256).

Even though most studies dealing with antioxidant activity of *C. annuum* have been focused on lipophilic components, such as carotenoids, the hydrophilic extracts, containing mainly phenolic acids and flavonoids, have been also highly effective as antioxidants, specially preventing deoxyribose and DNA degradation *in vitro*, therefore having potential interest for human health (Bae, Jayaprakasha et al. 2012, Materska 2014).

During industrial processing of pepper, the seeds are usually discarded as waste, and their composition is also very interesting and rich in bioactives with antioxidant capacity, such as phenolic acids, flavonols and ascorbic acid (Sandoval-Castro, Valdez-Morales et al.

2017), with a physiological role in the protection of the lipids stored in the seeds against oxidation during the germination processes (Sim and Sil 2008, Silva, Azevedo et al. 2013). Dry red bell pepper seeds could be also found in the markets (e.g. Jinhua Huayang Co., Ltd.; URL: http://www.sinospice.com/proinfo.asp?id=259).

As a concluding remark, pepper extracts and seeds (by-products) possess significant antioxidant potential that enables their application as natural antioxidants in dietary supplements or technical natural additives or ingredients, substitutes of artificial additives, as well as promising ingredients for "clean label" products.

4.3. Enhancer of sensory properties

As mentioned earlier, paprika is a worldwide well known spice (Halikowski Smith 2015), used to improve colour, flavour and to add pungency to many foods and dishes. Paprika extract (E 160c) is classified as a food additive (natural dye) in EU (EFSA, 2015). Paprika oleoresin could completely substitute ground paprika in food products due to its concentrated colour, taste and flavour (Tepic, Dimic et al. 2008), however, paprika extract as additive includes an additional purification in the manufacturing process.

The main quality attribute of paprika is the intensity of its red colour, because this influences both consumer acceptance and commercial value (Belović, Mastilović et al. 2014). More than 20 different pigments from paprika fruits have been identified, including green chlorophyll, yellow-orange pigments lutein, zeaxanthin, violaxanthin, antheraxanthin and β-carotene, as well as red pigments capsanthin and capsorubin, considered as exclusive to *Capsicum* genus and representing the main pigments that determine the colour of red pepper (Matsufuji, Ishikawa et al. 2007, Tepic, Dimic et al. 2008). There are several methods for paprika colour evaluation, based on the measurement of surface colour, extraction of pigments, and profiling of carotenoids

(Minguez-Mosquera and Hornero-Mendez 1994, Deli, Matus et al. 1996, Kevresan, Mastilovic et al. 2013). In the international trade, paprika is classified into different quality classes by the number of ASTA units per paprika dry weight, which is determined by the official analytical method of ASTA (American Spice Trade Association) (ASTA Analytical Method 20.1, 1986) (Kim, Youl Ha et al. 2008). The colour additives, such as β-carotene or paprika oleoresins, must be considered as additives and not as GRAS substances, thus the regulations for colour additives are stronger than for other additives. In order to optimize the colour stability in the processing and storage of products, special attention has to be paid to the bioactive compounds content (esterified or free pigments), drying process, temperature of storage and oxidative degradation (Biacs, Daood et al. 1989, Pruthi 2003).

The use of pepper derivatives as colouring enhancers is much extended and many products are available elsewhere: paprika powders from Perú (Inca Health Co.; URL: http://www.incahealth.com/paprika.html), Netherlands (Nedspice Holding BV; URL: http://www.nedspice.com/), or Spain (Juan Navarro Garcia, S.A.; URL: http://www.juannavarro.com/en/sweet-paprika-powder); green dehydrated pepper from Asia (http://www.orc.com.hk); jalapeño granular dehydrated pepper from US (Mincing Spices; URL: http://www.mincing.com/portfolio-items/pepper-jalapeno/); and many more.

Pungency is another important quality parameter for the use of pepper derivatives as ingredients. Even though pungency is considered a subjective variable, and this parameter has been evaluated by simple organoleptic tests such as the Scoville Heat Units (SHU), recently, the American Spice Trade Association has established a universal scale based on the concentration of capsaicionids in parts per million (ppm) in a given sample (ASTA, 2018; URL: http://www.astaspice.org/food-safety/astas-analytical-methods-manual/).

The taste of sweet peppers is determined by the sugar and organic acid contents (Selahle, Sivakumar et al. 2015). When evaluating processed foods, a soup with added cayenne pepper was perceived significantly more spicy but was equally liked as a soup without it, resulting in higher satiation at the end of the meal (Andersen, Byrne et al. 2017). During the intake of the soup with added cayenne pepper, the desire for salty and spicy foods was significantly decreased and the desire for sweet and fatty foods was significantly increased. The characteristics of the pepper flavour is a complex trait, influenced by environmental factors during growth and postharvest processing (Eggink, Maliepaard et al. 2012). More than 125 volatile compounds have been identified in fresh and processed *Capsicum* fruits (Luning, de Rijk et al. 1994). Studies on pepper flavour have been mainly focused on characterization of volatile and/or non-volatile components in *Capsicum* species, and correlations between chemical composition and sensory attributes determined by panels are usually omitted (Pestorić, Belović et al. 2015).

Ground pepper (paprika) is usually added to meat products in order to improve their colour and flavour. Fernández-López et al. (2002), showed that in batters for dry-cured sausages, lightness depends exclusively on the paprika, while paprika reflectance spectra interfered with meat reflectance spectra, mainly in the range from 500 to 580 nm. Therefore, they concluded that any colour modification observed in dry cured meat products produced with paprika are due principally to paprika colour changes more than meat colour changes (Fernández-López, Pérez-Alvarez et al. 2002).

Paprika powder could, also, be used in order to reduce the nitrite content in meat batters, improving their colour and lowering oxidative rancidity (Bazan-Lugo, Garcia-Martinez et al. 2012). Martínez et al. (2006), studied the use of pepper powder to inhibit oxidative reactions and extend the shelf life of fresh pork sausages packaged in a modified atmosphere. Their results demonstrated that sweet red and hot cayenne pepper powders enhanced red colour but failed to prevent discoloration. The highest concentration of paprika powder (2%) used in their research was very effective in inhibiting lipid oxidation and microbial growth, which resulted in a delay of off-odour formation (Martínez, Cilla et al. 2006).

Nanoparticles of paprika oleoresin and carrier systems (water/milk) were also investigated as a tool to improve physical and sensory properties of cooked marinated chicken (Yusop, O'Sullivan et al. 2012). Results showed that the incorporation of nanoparticles of paprika oleoresin to the meat using water-based carrier systems, produced the furthest colour penetration.

4.4. Health-promoting ingredients

Many of the health-promoting compounds from pepper fruits are antioxidants, such as vitamin C, capsicinoids, polyphenols and carotenoids, that exert their biological effects through free-radical scavenging, protein binding and interaction with human signal transduction pathways (Wahyuni, Ballester et al. 2011). Several studies have reported antioxidant activity *in vivo*, such as pepper polyphenols against lipid peroxidation in the rat brain and the liver, by their action as $OH^{\cdot}$ and $NO^{\cdot}$ radicals scavengers and the inhibition of overstimulation of NMDA (N-methyl-D-aspartate) receptors, the main mechanism of neurodegeneration and cognitive deterioration (Oboh and Rocha 2007, Oboh and Rocha 2008). Also a single oral dose of capsaicin diminished the oxidative stress in rat livers, suggesting an effective therapeutic formulation in preventing oxidative damage *in vivo* (Giri, Pramanik et al. 2017).

Regarding antiproliferative activities of *Capsicum annum* ingredients, extracts rich in capsaicin as well as pepper seeds extracts, have shown high *in vitro* antiproliferative activities against lung, breast, gastric and prostate human cancer cell lines, among others

(Kundu and Surh 2009, Jeon, Choi et al. 2012); however, there are few studies showing *in vivo* evidences. In this sense, capsaicin given orally to mice, markedly suppressed the growth of AsPC-1 pancreatic tumour xenografts (human tumour transplanted cells), without side effects (Zhang, Humphreys et al. 2008). On the other hand, a recent preclinical study of prostate cancer using a LNCaP xenograft model in mice, showed that capsaicin may act as radio-sensitizing agent sensitize tumor cells to the lethal effects of radiotherapy, by altering NFκB signalling pathway, and then allowing the use of lower doses of radiation to achieve equivalent cancer control results (Venier, Colquhoun et al. 2015).

However, the bioavailability of these antioxidant and antiproliferative compounds is definitely more important for exerting the *in vivo* effect than their concentration in the consumed food. Hervert-Hernández et al. (2010) investigated the intestinal bio accessibility *in vitro* of the main carotenoids and polyphenols important for human health from red hot peppers. The amount of antioxidants released from the food matrix by the action of digestive enzymes was about 75% for total polyphenols, up to 49% for both β-carotene and zeaxanthin, and up to 41% for β-cryptoxanthin. These results suggest that from 50 to 80% of these compounds could reach the colon to be potentially fermented or could remain unavailable (Hervert-Hernandez, Sayago-Ayerdi et al. 2010). Regarding capsaicin and dehydrocapsaicin, their absorbance rate was 50% in the stomach, 80% in the jejunum and 70% in the ileum (Rollyson, Stover et al. 2014).

Capsaicin has also been widely investigated and used clinically to treat neurological pain and musculoskeletal pain disorders by blocking inflammatory hyperalgesia and neurogenic inflammation (Hayman and Kam 2008), as it would be comment below regarding its pharmacological effect. Besides, Andersen et al. (2017) studied that the consumption of food with added capsaicin, such as a soup with addition of pungent pepper, may alter appetite sensations and sensory specific desires, resulted in significant higher satiation at the end of the meal and one hour post intake and, therefore, influencing eating behaviour (Andersen, Byrne et al. 2017). Several hot pepper sauces, extracts and purees rich in capsaicin could be found in the markets (e.g. Ashley Food Company products; URL: https://www.ashleyfoodcompany.com/).

Also *Capsicum annum* ingredients have high content of vitamins, mostly vitamin C and A, being both recommended by the World Health Organization on a daily basis to avoid oxidative stress, mainly for pregnant women and children, and to prevent blindness and severe infections in children, respectively (http://www.who.int/nutrition/topics/vad/en/).

Inhibitory effects of pepper extracts against enzymes such as α-amylase and α-glucosidase, are of interest for the therapeutic potential of decreasing postprandial hyperglycemia by delaying the production or absorption of glucose. Different authors have shown α-glucosidase and α-amylase inhibition activities from aqueous pepper extracts, which have been correlated to the DPPH radical scavenging antioxidant activity and the phenolic content. Also these studies showed an *in vitro* anti-hypertensive bioactivity by high acetylcholinesterase (ACE) inhibitory activity (Kwon, Apostolidis et al. 2007, Ranilla, Kwon et al. 2010).

In regards of the anti-inflammatory activity of *Capsicum annum* ingredients, chilli pepper showed a reduction of pro-inflammatory interleukin (IL)-6 and tumour necrosis factor (TNF)-alpha production both *in vitro* e *in vivo*, may be attributed to capsaicin, which has shown to modulate NFκB and IL-8 pathways(Mueller, Hobiger et al. 2010, Allemand, Leonardi et al. 2016), but also because of the presence of other bioactive compounds, such as carotenoids, which application reduced the levels of ACE activity and concentration of seromucoids in serum of rats with adjuvant-induced inflammation (Boiko, Kravchenko et al. 2017).

Therefore, including *Capsicum* derived products as ingredients in the diet could help to prevent inflammation and oxidative stress in the human body, which play an important role in the development of chronic and neurodegenerative diseases.

5. Cosmetic and pharma industrial applications

Due to the current eco-friendly behaviour of consumers and industries, there is a great interest on searching for bioactive compounds, raw plant materials or plant extracts as natural ingredients (or excipients), for the cosmetic and pharmaceutical industry. In this sense, some important properties that can influence the final product performance, should be studied and accepted by the corresponding competent authority. These characteristics are based on physical properties (such as colour, flavour, texture or permeation) and bioactivities (such as antimicrobial and antioxidant) (Agency 2007). The use of natural ingredients instead of synthetic preservatives could enhance the health properties of the cosmetic and pharmaceutical products, avoiding the contact allergies caused as side effects. These uses are regulated according the global quality standards for medicines, being the most relevant groups of experts those belonging to the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) (Eur. 2010). The Food and Drug Administration (FDA) published in 2002 a list of the scope and extent of use of *Capsicum* ingredients in cosmetics, finding a wide variety of products, such as tonics, dressings and shampoos containing *Capsicum* oleoresins (FDA 2002).

Nowadays, in the cosmetic industry, the major claims are the antiaging effect and the reduction of wrinkles by fighting against free radicals and solar radiation. Recently, Anunciato *et al.*, (2012), reviewed information about the novel term “cosmeceuticals”, as the result of the fusion between cosmetic and pharmaceutical products, which, as well as the term “nutraceutical”, could act as adjuvants in conventional drug treatment but for pathologies or skin conditions. On the other hand, the new term “nutricosmetics” can be defined as a result of the intersection of cosmeceuticals and nutraceutical, characterized as oral supplementation of nutrients formulated and marketed specifically for beauty purposes (Anunciato and da Rocha Filho 2012). Some examples of the use of *Capsicum* derived ingredients in the pharma and cosmetic industries are reported in Table 1.

5.1. Enhancer of physical properties

As it said before, paprika powder and oleoresins are rich in carotenoids and capsaicinoids,, being these bioactive compounds an excellent source of colours as ingredients in the cosmetic and pharmaceutical industry. According to the EFSA and FDA (2017), these natural ingredients not require a specific approval by these organizations; however, they must be safe for consumers under labelled or customary conditions of use, having the manufacturers and companies the legal responsibility for the safety of their products and ingredients. In this sense, paprika is commonly used as spice, and there is no reason to expect undesirable side effects from its use as a cosmetic colour, as it is accepted as a food additive (EFSA 2015). Some examples of paprika oleoresin used as cosmetic colourants in bath oils are available (Lusch Handmade Cosmetics, S.L. URL: https://de.lush.com/search/site/paprika), as well as in shampoo, soaps, shower gels, and and many beauty products including eye make-up and lipsticks (e.g. Color Marker Inc.; URL: http://www.colormaker.com/natural-ingredients_paprika). The bioactive compounds derived from pepper byproducts can be also used as flavouring or fragrance agents in cosmetic products, which may be extracted using hexane, ethanol, or vegetable oil, and could be incorporated in high concentrations (as high as 5%) without any toxic effect (Johnson 2007). Pepper oleoresin provides manufacturers an important advantage with respect to the use of essential oils, this property is called lipophilicity, allowing this product to be dissolved in fats, oils and lipids, whereas essential oils do not. Other pigments such as chlorophylls and polyphenols, mainly anthocyanins, are also present in some pepper varieties, such as black or violet peppers, where the anthocyanin delphinidin, as both an aglycone and a glycosylated compound, is accumulated. These water-soluble pigments could be used as colourants and also as therapeutic compounds (UV protectors and antioxidants) in pharmacy and cosmetic products (Zillich, Schweiggert-Weisz et al. 2015). On this wise, an acetone–water extraction of red pepper by-products was study as natural dye to be applied on woollen fabrics to produce coloured clothing and textiles with acceptable antimicrobial properties (Ksibi, Slama et al. 2015). The extended use of *Capsicum* ingredients in the market request the standardizing of the properties of the extracts, powders and oleoresins, such as the capsaicin content and flavour and colour intensity for cosmetic applications and health-promoting products.

5.2. Product stability and preservation

Capsicum compounds can be used, due to their antioxidant properties, to reduce the oxidation of active substances and excipients in the medicinal products. Their activity depends on its nature, the stage at which it is incorporated into the pharmaceutical product, the nature of the container and the formulation. Also there can be three modes of action of the antioxidants, some of them block chain reactions by reacting with free radicals, other are reducing agents, such as ascorbic acid, which have a lower redox potential than the excipients, protecting them, and, finally, there are antioxidants which act as synergists, enhancing the effects of others present in the product. This free radical scavenging activity improve the stability of the final product by delaying the oxidation of active substances, and also contribute to its beneficial effect on health, for instance, through healing skin diseases and cosmetics treatments (Pieroni, Quave et al. 2004). Dehydrated green pepper containing high amounts of vitamin C could be used as preservative antioxidant in the cosmetic industry (De 2004). Also *Capsicum* extracts containing carotenoids, mainly with the presence of functional groups in terminal rings, such as capsanthin, lutein and zeaxanthin, could be extracted by an oil-soluble solvent and, the obtained extract, can be used as active ingredient for skin care cosmetics, being better active and protected when they are incorporated to lipoproteins or membranes (Arimboor, Natarajan et al. 2015).

Antimicrobial preservatives are used to prevent or inhibit the growth of bacteria, fungal and moulds, which could present a risk of infection or degradation of the medicinal or personal care products, as these usually have more than 3 years of shelf-life (Dayan and Kromidas 2011). Cinnamic acid and *p*-coumaric acid showed strong antibacterial properties against *Listeria monocytogenes, Staphylococcus aureus, Salmonella typhimurium* and *Bacillus cereus,* among other bioactives present in *Capsicum* extracts, being able to inactivate or inhibit the growth of spoilage and pathogenic microorganisms in the industrial products. Even though there is a great potential for using *Capsicum* derivatives as preservatives, commercial examples are scarcely available.

5.3. Cosmetic and pharma applications for beauty and health

Pepper derived ingredients are currently used as part of nutricosmetics or cosmeceuticals, mainly as antioxidant and analgesic treatments, in oral supplementations or topical applications. Regarding prevention and treatment of skin diseases, new therapeutic options are always in demand. The topical application of the therapeutic agent is the most common, being used in low dosages several times daily, depending on the skin status. The efficacy of a topical therapeutic agent can influenced by different factors, such as active ingredients, excipients, possible interactions of the ingredients, galenic properties, preparation, region affected, and condition of skin or mucosa (Tiwari, Tiwari et al. 2012). Capsaicin has been approved by the EU and FDA as a drug for the topical treatment of neuropathic pain, being their analgesic action as dose dependent. Although the precise mechanism of action is not fully understood, evidences suggest that capsaicin, through continuous application (4 to 6 times daily for 4-8 weeks), acts as selective agonist of the receptor 'transient-receptor-potential-vanilloid-1' (TRPV1) of the sensory nerve fibres, preventing the triggering of an action potential by depletion of neuropeptides and transmission of pain and itching, desensitizing these nerve fibres, whereas tactile sensations remain unaffected (Ständer, Luger et al. 2001, Lysy, Sistiery-Ittah et al. 2003). According to this pharmacological effect, capsaicin is used for the treatment of painful conditions and disorders such as chronic rheumatic pain, post-herpetic neuralgia, painful diabetic neuropathy and osteoarthritis. Also, this compound can be used in patients with bladder hyperactivity to improve the bladder capacity and reduce incontinence. It also protects the stomach against gastritis induced by non-steroidal anti-inflammatory drugs; can reduce post-operative nausea, vomiting and sore throat; and can help in patients with pruritus associated with renal failure and in patients with myocardial ischemia (Hayman and Kam 2008).

Low concentrations of capsaicin are included in over-the-counter analgesic creams. High concentrations of capsaicin have been explored as treatment for neuropathic pain (e.g., Qutenza/NGX-4010), postoperative pain (e.g. Adlea; Anesiva Inc.) and cluster headaches (e.g., Civamide; Winston Laboratories).

As examples of specific researches, lipid-replenishing capsaicin cream (0.012 - 0.006 %) has been studied against chronic pruritus and cutaneous hypersensitivity (Lysy, Sistiery-Ittah et al. 2003), being the daily capsaicin applications adaptable to patient needs and possible side effects, like irritation or burning sensation. In order to avoid these side effects, *in vivo* studies have shown that capsaicin could be encased in nano-lipoidal carriers, improving skin permeation and retention and analgesic effects, minimizing its effects on skin-irritation compared with the conventional cream (Raza, Shareef et al. 2014). However, a balanced combination of lipids, water and humectants is essential in a suitable therapy, thus, water-rich topical therapy with a hydrophilic cream containing capsaicinoids (0.025 - 0.1 %) should be preferred during the acute phase of inflammation (Staubach and Metz 2013). In terms of costly and time-effective capsaicin extraction process, Thapa *et al.*, (2013) reported a straight-forward formulation development with vesicular formulations for capsaicin from a crude *Capsicum* powder, destined for localized pain relieve (Thapa, Pepic et al. 2013), which can be used in pain-balms, chest rubs or liniments.

In this sense, the Committee on Herbal Medicinal Products (HMPC) from the European Medicine Agency concluded that, on the basis of its well-established use (10 years of scientific evidence of their effectiveness and safety in the EU), capsicum can be used for the relief of muscle pain, such as low back pain (Agency 2015), which are usually available in a medicated plaster or in semi-solid forms to be applied to the skin (such as creams) according to the European Pharmacopoeia (DRS 2016). This organism has approved the use of different standardized products from cayenne pepper (*Capsicum annuum* cv. Cayenne), which have been published in the monographs: Capsicum (fruit) #1859; Capsicum oleoresin, #2336; Capsicum soft extract, #2529; and Capsicum tincture, #2337. All of them, containing from 30,000 to 50,000 Scoville Heat Unit (SHU). As an example of its application, Qutenza® is a topical patch containing 8 % of capsaicin, approved by the EU and the US-FDA (2009) and indicated for the management of neuropathic pain associated with postherpetic neuralgia.

Regarding bioavailability, capsaicin is absorbed percutaneously, and animal data suggest a systemic bioavailability of topically applied capsaicin ranging from 27 to 34%. The absorbed capsaicin is metabolised mainly in the liver and eliminated in the form of metabolites in the urine and faeces (Agency 2015). Nevertheless, further studies are necessary to more precisely establish the range of effective capsaicin concentration for long term treatments.

On the other hand, vitamin C is one of the most potent antioxidant compounds found in pepper and highly used in skin cosmetics, which acts as potent antioxidant for preventing skin oxidative damage, thus protecting the skin from reactive oxygen species (ROS), and being an important ingredient for treating skin pathologies, such as inflammation and cancer. Their content in the human body depends on their oral intake and topical delivery, as well as their low stability, which could be reduced by changes of temperature and pH, not obtaining the desirable efficacy (Telang 2013). The use is safe on a daily basis for long durations and their effects could be enhanced by topical application of ascorbic acid (the chemically active form of vitamin C), in liposomal formulations, enhancing absorption of this compound to the epidermis, and, therefore, diminishing significantly UVA-mediated damage to the skin by a reduction of nuclear factor kappa beta activity and pro-inflammatory cytokines (TNFα, IL-1, IL-6, etc.) (Serrano, Almudéver et al. 2015). Furthermore, bioavailability of vitamin C in the skin is inadequate when it is administered orally, therefore, the use of topical ascorbic acid favoured in the practice of dermatology, as well as in combination of other compounds such as tyrosine and zinc, increasing the bioavailability of vitamin C (Telang 2013).

Also paprika extracts rich in carotenoids, such as zeaxanthin and lutein, has been used with complementary ingredients in commercially available products, as facial serum and daily nutritional supplement for the skin oxidative health (by Zea Skin Solutions ZSS™; URL: https://zss-skincare.com). In this sense, a previous work demonstrated that a combined treatment with zeaxanthin and lutein showed an enhancement of elasticity of skin, with a cutaneous hydration more pronounced, compared to the isolated compounds treatments (Palombo, Fabrizi et al. 2007). As examples of clinical studies of dietary supplementation with carotenoids, treatments with carotenoids with iron and zinc supplementation following a vitamin A deficient diet, improved retinol and levels of carotenoids in plasma, respectively (Kana-Sop, Gouado et al. 2015); on the other hand, a treatment of ≥24 mg carotenoids/day for at least 12 weeks showed an effective protection against UV-induced erythema (Heinrich, Gärtner et al. 2003).

Regarding capsidiol, a compound isolated from a methanol extract of *C. annuum*, this compound showed a clear *in vitro* activity against *H. pylori*, showing its potential as a treatment for antibiotic-resistant strains and for patients who do not wish to take synthetic antibiotics (De Marino, Borbone et al. 2006).

Also flavonol glycosides, present in pepper extracts, such as quercetin-*O*-glycosides, could be used in the cosmetic industry, as these compounds have shown higher effective antioxidant and anti-inflammatory activities compared to other phenolic compounds, and have been related to the prevention of different health diseases, such as protecting cells from UV irradiation or supporting skin regeneration in wound healing (Hatahet, Morille et al. 2016). Quercetin may be formulated using oil/water micro emulsions as excipient in order to increase its solubility and stability and, therefore, optimizing the transdermal delivery of this bioactive compound (Malaj, Martena et al. 2010). Some examples could be found in facial sunscreens and serum (Korres Store; URL: http://korres-store.de/quercetin/serum).

On the other hand, polar phenolic compounds, such as chlorogenic acid derivatives, could be used as antioxidant ingredient in cosmetics by using thermodynamically stable O/W micro emulsions as vehicles, to enhance their permeation in the skin and protecting skin against UV-induced oxidative damage (Kitagawa, Yoshii et al. 2011). For instance, ferulic acid and quercetin, among other bioactives, are applied in a cosmetic serum, counteracting free radicals and minimizing wrinkles (Dr. Dennis Cross ltd., 2018; URL: https://drdennisgross-skincare.de/collections/all).

The red phenolic pigments anthocyanins could be used not only as a colouring agent, but also as antioxidants, UV-protection, inhibition of melanin production and anti-aging compounds in cosmetics preparations. These compounds could be encapsulated in the appropriate coating to enhance their bioactivity and use in topical applications for skin care (Westfall 2015).

Regarding the use of a paprika extract as ingredient in beauty and health formulation, other cosmetics could be found as healthy against aging and oxidation, such as in organic skin care products and facial masks (Eminence Organic Skin Care, URL: https://eminenceorganics.com/ca/product/paprika-herbal-treatment).

6. Future perspectives

The growing market of functional ingredients, natural foods and pharmaceutics, emerging in response to the current health claims and social awareness, has prompted to use several bioactive compounds and natural ingredients in the new products, as enhancers of the organoleptic parameters and shelf-life, which once integrated in balanced diets, would also contribute to human wellbeing. In this sense, *Capsicum* derived products, such as oleoresin, paprika powder, purified extracts and fractions enriched in bioactive compounds, continue being investigated in terms of colour, flavour, pungency and nutritional value, as potential ingredients for foods, pharma and cosmetics industries, and also as strategy to improve health and to prevent and treat diseases due to their bioactivities (antioxidant, anti-inflammatory and antimicrobial, among others). In this sense, the standardisation of these *Capsicum* derived ingredients in terms of colour, pungency, flavour and biological activities is completely needed to expand the capabilities of these compounds in the markets.

For the dermatologic and cosmetic industry, formulations with natural bioactive compounds are the challenge to guarantee stability, safety and efficiency in organic cosmetics and new products, such transdermal patches, oral nutricosmetics and cosmeto-textiles. However, there is no harmonization of these guides, and generally, pepper oleoresin or extracts can be used after perform the biological function and toxicological assessment by the manufacturers. These results together with the already approval of the use of pepper derivatives in the food industry, may suggest a future role for these extracts as bioactive ingredients in cosmetic and pharmaceutical formulas.

On the other hand, the high demand of using natural plant compounds as alternative to synthetic preservatives and pigments in the industry needs the development of new promising "green" methodologies which could fill the requirements of the market. Therefore, further studies are required to underlying the mechanisms of action of *Capsicum* ingredients at industrial scale and in the final product, providing an interesting opportunity for the utilization of pepper byproducts as a source of bioactive compounds. Besides, systematic studies are required not only concerning its technological advantages but also to guaranty foods safety for consumers.

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Table 1. Applications of *Capsicum annum* derived products in agro-food, cosmetic and pharma industries

Type	Source	Bioactive compounds	Interesting properties and uses	Potential uses	Reference
Paprika powder	Pungent paprika	Carotenoids and capsaicinoids	Colouring and flavouring of food products and dishes	Agro-food industry	(Delgado-Vargas, Jimenez et al. 2000, Tepic, Dimic et al. 2008)
Paprika powder	Red sweet pepper	Carotenoids	Nitrite replacer, colour enhancer and lipid oxidation inhibitor in pork meat	Agro-food industry	(Martínez, Cilla et al. 2006, Bazan-Lugo, Garcia-Martinez et al. 2012)
Paprika powder	Red sweet pepper	Carotenoids and capsaicinoids	Colouring stability in meat products, soups, sauces and snacks	Agro-food industry	(Fernández-López, Pérez-Alvarez et al. 2002, Pruthi 2003)
Paprika oleoresin	Sweet paprika, pungent paprika	Carotenoids and capsaicinoids	Enhancer of sensory properties of food products	Agro-food industry	(Uquiche, Valle et al. 2004, Tepic, Dimic et al. 2008)
Pepper flour	Yellow pepper	Carotenoids	Source of antioxidants and enhancer of sensory properties in wheat bread	Agro-food industry	(Danza, Mastromatteo et al. 2014)
Nanoparticle paprika oleoresin	Sweet paprika	Carotenoids	Enhancer of physical and sensory properties of cooked marinated chicken	Agro-food industry	(Yusop, O'Sullivan et al. 2012)
Isopropanol pepper extraction	Entire chilli pepper	Capsaicinoids	Antimicrobial agent against *S. typhimurium* and *P. aeruginosa* in raw beef meat in combination with sodium chloride	Agro-food industry	(Careaga, Fernandez et al. 2003)

Enriched fractions of paprika oleoresin	*Capsicum* fruits	Carotenoids and capsaicinoids enriched fractions	Colouring and biological activities: provitamin A, antioxidant capacity, analgesic effect.	Pharmaceutical, cosmetic and agro-food industry.	(Fernández-Ronco, Gracia et al. 2011)
Encapsulation of pepper oleoresin	Chilli peppers	Capsaicinoids and carotenoids	Enhancer of sensory properties (particles, emulsions) and biological activities: antimicrobial, antioxidant and anti-inflammatory	Pharmaceutical, cosmetic and agro-food industry.	(De Aguiar, Silva et al. 2016)
Isopropanol pepper extraction	Fresh chilli peppers	Cinnamic acid, o-coumaric acid, m-coumaric acid, ferulic acid and caffeic acid	Antibacterial activity against *L. Monocytogenes, B. Cereus*, *S. Aureus, S. Typhimurium*.	Pharmaceutical, cosmetic and agro-food industry.	(Dorantes, Colmenero et al. 2000)
Methanol pepper extractions	Sweet pepper	Polyphenols and carotenoids	Antibacterial activity against *B. cereus* and *E. Coli* and antifungal activities against *P. expansum* and *D. hansenii*	Pharmaceutical, cosmetic and agro-food industry.	(Nazzaro, Caliendo et al. 2009)
Methanol pepper extractions	Sweet pepper	Capsidiol	Bacteriostatic properties *in vitro* against *Helicobacter pylori*	Pharmaceutical, cosmetic and agro-food industry.	(De Marino, Borbone et al. 2006)
Formulations ingredients for topical delivery	*Capsicum* fruits	Vitamin C and carotenoids	Antioxidant and anti- inflammatory activities preventing skin oxidative and UVA-mediated damage	Pharmaceutical and cosmetic industry	(Telang 2013)
Pepper powder and oleoresin	Chilli peppers	Capsaicin	Therapeutic agent in chronic pain syndromes and in chronic inflammatory skin diseases	Pharmaceutical industry	(Ständer, Luger et al. 2001, Lysy, Sistiery-Ittah et al. 2003, Căruntu, Negrei et al. 2015)

Pepper powder	Cayenne pepper	Capsaicinoids	Pharmacological activities: alter appetite sensations by higher satiation	Pharmaceutical industry	(Andersen, Byrne et al. 2017)

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