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

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Running title: Industrial use of pepper bioactive compounds

ABSTRACT

The recovery of pepper phytochemicals present an interesting strategy in pursuit of new bioactive compounds and natural ingredients for agro-food, cosmetic and pharma industry uses, as replacements for the synthetic compounds and also in the valorisation of plant's by-products. Besides being used as a condiment, providing characteristic pungency, colour and flavour, the new pepper-derived ingredients could be used for the preservation and extension of industrial products' lifespan, as well as additives or technological ingredients with antioxidant and antimicrobial activities. Moreover, the application of the new products in pharmaceutical formulas for the treatment of inflammatory and pain-related conditions is also a possibility, since peppers contain capsaicinoids, carotenoids, phenolic compounds, vitamin C and A, and minerals, such as iron and calcium, which have a health-promoting potential. Further studies on appropriate extraction protocols, stability, safety and bioactivity are necessary to provide novel and promising pepper ingredients for food, cosmetic, and pharmaceutical applications.

KEYWORDS: paprika**,** oleoresin**,** capsaicin**,** carotenoid, vitamin C, natural products, phenolic compounds

Chemical compounds studied in this article

Capsaicin (PubChem CID: 1548943); delphinidin (PubChem CID: 68245); dihydrocapsaicin (PubChem CID: 107982); luteolin (PubChem CID: 5280445); quercetin (PubChem CID: 5280343); vitamin C (PubChem CID: 54678501); vitamin

E (PubChem CID: 14985); α-carotene (PubChem CID: 4369188); β-carotene (PubChem CID: 5280489); β-cryptoxanthin (PubChem CID: 5281235).

1. Introduction: Exploration and valorisation of bioactive products

Over the last two decades, there has been an increased interest in the discovery of chemical and functional properties of bioactive compounds present in natural matrices. This fact along with the awareness of the benefits of healthy foods and the advances in analytical instrumentation, have promoted the study of pepper fruits and their by-products as source of bioactive compounds.

Indeed, developing scientific projects, to investigate 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. The main objective of these projects is to provide extracts, enriched fractions and isolated compounds of high purity, which should be assessed for their safety and efficacy by cell-based and *in vivo* assays, to be subsequently integrated in food and pharma formulations and products.

Pepper (*Capsicum annuum* L.) is an annual herbaceous plant belonging to the *Solanaceae* family, which is cultivated in warm climate regions worldwide, such as Asia, northern America, southern and central Europe, and tropical and subtropical Africa (Thampi, 2004). Total pepper production increased by 25 % in a decade (from 2006 to 2016, last data reported by FAOSTAT), being one of the most economical and agriculturally important vegetable crops all over the world, with a production of 34.5 million tonnes (MT) of fresh pepper and 3.9 MT of dry pepper in 2016. In this sense, China (17.5 MT), Mexico (2.7 MT), Indonesia (2.0 MT) and Spain (1.1 MT) were the largest producers of fresh pepper, while India (1.4 MT) was the highest producer of dry peppers (FAOSTAT, 2016).

Generally, peppers are consumed raw (bell pepper) or in powdered form as a spice (chili pepper) or as a colorant (paprika). 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, this vegetable ranges from the sweet (non-pungent) varieties, such as paprika, to the hot species, such as chilies or cayenne (Buckenhüskes, 2003).

In addition to their sensory features, such as pungency, aroma and colour, peppers are important sources of bioactive compounds that offer health benefits for consumers, including vitamins C and E, provitamin A, carotenoids and phenolic compounds. The content of these phytochemicals changes with the metabolic and chemical processes, therefore, sampling and storage conditions (temperature < 7.5 ^{o}C, ~70 % RH (relative humidity), oxygen deficiency and absence of light) should be controlled in order to produce a high quality plant material for its characterization and further use (Padilha, Pereira, Muñoz, Vizzotto, Valgas, & Barbieri, 2015).

Even though the majority of peppers in the international trade are fresh produce, spice or colorants, an important portion (5 – 30 %) of the total fruit production is discarded as non-marketable products or by-products, such as peels, stalks, seeds, and unused flesh that are generated by different steps of the industrial processing (Sandoval-Castro, Valdez-Morales, Oomah, Gutierrez-Dorado, Medina-Godoy, & Espinosa-Alonso, 2017). These by-products could be used as sources of nutrients and secondary metabolites for the application in the industry, being an alternative to synthetic and chemical additives, contributing to the low-waste technology in the agribusiness and providing economic benefits to producers (Viacava, Ansorena, Roura, González-Aguilar, & Ayala-Zavala, 2013).

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 (Jayaprakasha, Bae, Crosby, Jifon, & Patil, 2012). 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. Capsaicinoids are mainly found in hot peppers and are responsible for the pungency of these varieties. Peppers are also rich in 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 (Pandey & Rizvi, 2009). Table 1 shows the chemical composition of raw sweet pepper, with the differences in micronutrients and bioactive compounds depending of the maturity stage (USDA, 2018; Asnin & Park, 2015). Due to their content in bioactive compounds, special attention is needed in the characterization and exploitation of these plant products with multiple uses which are 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, et al., 2012). They contribute to the taste, colour and flavour of the fruits and show health-promoting effects based on the protection of the organism from the damage produced by oxidative agents, being a good indication forthe antioxidant capacity of peppers (Padilha, 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 C and E, and carotenoid pigments content (Conforti, Statti, & Menichini, 2007).

Numerous epidemiological studies indicate a possible association between the uptake of phenolic acids and flavonoids and the reduction in the risk for coronary disorders, diabetes, cancer, osteoporosis, and neurodegenerative diseases (Pandey & Rizvi, 2009). Among the flavonoids, the flavonol glycosides (e.g. quercetin-*O*-glycosides) are mainly found in fruits, including quercetin 3-*O*-rhamnoside and quercetin glycosylated with rhamnoside-glucoside attached either at the C-3 or C-7 position, as quercetin 3-*O*-rhamnoside-7-*O*-glucoside and quercetin 3-*O*-glucoside-7-*O*-rhamnoside. 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 (Asnin & Park, 2015; Jayaprakasha, et al. 2012). These compounds have been identified by HPLC-MS/MS and NMR analysis and spectral data, found their content in pepper varieties to be from 5 to 20 mg 100 g^{-1} fresh weight (F.W.) (Asnin & 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, as in quercetin 3-O-α-l-rhamnopyranoside in peppers (Materska & Perucka, 2005).

On the other hand, *p*-coumaric, caffeic, sinapic and ferulic glycosides, are characteristic phenolic acids' derivatives in pepper fruits, such as *trans*-*p*-feruloyl-β-D-glucopyranoside and *trans*-*p*-sinapoyl-β-D-glucopyranoside, which have shown high antioxidant capacity *in vitro* (Materska & Perucka, 2005). These hydroxycinnamic acids are found as major components in the pericarp 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, Nakagawa, Ashida, & Kanazawa, 2003).

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 (Conforti, et al. 2007; Marin, Ferreres, Tomas-Barberan, & Gil, 2004), with 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 & Wildman, 2007; Marin, 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. The levels 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 studies, withdelphinidin-3-trans-coumaroylrutinoside-5-glucoside, the major anthocyanin present in these fruits (Padilha, et al. 2015).

The assessment of bioavailability of phenolic compounds is a relevant subject for the current research due to the need to clarify their beneficial activity for human health. 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. 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, Ferreira, Gomez, Chen, & Lima, 2017). The use of nano-formulations enriched with phenolic compounds either in topical or oral administration formulas may increase their absorption and synergistic effects or combine their use with certain drugs (Munin & 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 (Arimboor, Natarajan, Menon, Chandrasekhar, & Moorkoth, 2015).

Raw peppers are a good source 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 320 mg 100 g^{-1} fresh weight (Arimboor, et al., 2015; Padilha, et al. 2015), showing the pericarp and placenta similar values of total carotenoids (~ 0.4 %), while these compounds are not found in seeds. There are at least 34 metabolic related carotenoids in *Capsicum* peppers. 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 ripe pepper fruits. In this sense, capsanthin is mainly responsible of the red colour, representing a 40-60 % of the total carotenoids in different varieties. Other carotenoids present in red and orange bell peppers are β-carotene, β-cryptoxanthin and zeaxanthin (Ha, Kim, Park, Lee, & Cho, 2007). As a result of carotenoids metabolism and their accumulation in the chromoplasts, the green colour of the fruit, due to the presence of chlorophyll, changes to yellow-orange, having these varieties violaxanthin (37% to 68% of total carotenoids), and lutein and β-carotene (5% to 14%), as major carotenoids (de Azevedo-Meleiro & Rodriguez-Amaya, 2009).

Regarding the carotenoid chemical structure and potential bioactivity, 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 & 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 & Oh, 2009).

The consumption of carotenoids has been related to improve the cognitive function and cardiovascular health, and may help to prevent some types of cancer. Among them, α- carotene, β-carotene and β-cryptoxanthin are precursors of vitamin A, which have the ability to yield retinol and retinoic acid. Other dietary carotenoids, such as lutein and zeaxanthin, are able to reach the human retina and have an important role 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 (Eggersdorfer & Wyss, 2018).

With reference to bioavailability, most of the carotenoids, such as β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin, have to be incorporated into micelles, mixed with lipoproteins and bile salts and enzymes, to be delivered to the gut enterocytes (Fiedor & Burda, 2014). This is the most crucial step influencing carotenoid bioaccessibility, being undertaken in the stomach and the small intestine. There are several factors influencing micellization, which definitely affects the absorption and bioavailability of carotenoids. Some of them have shown to reduce bioaccessibility, such as the presence of fibre as a food component or the inhibition of pancreatic lipases used to treat obesity, both reducing micellisation. On the other hand, the structure of carotenoids, such as the esterification of xanthophyll (β-cryptoxanthin, zeaxanthin, lutein and capsanthin) enhanced their solubility, and therefore, increased bioaccessibility (Fernández-García, Carvajal-Lérida, Jarén-Galán, Garrido-Fernández, Pérez-Gálvez, et al., 2012). Once circulating in the blood plasma, these compounds are distributed into various tissues with large differences between organs (Bohn, Desmarchelier, Dragsted, Nielsen, Stahl, Rühl, et al., 2017).

2.3. Capsaicinoids

Chemically, these compounds are acid amines of vanillylamine and branch fatty acids containing 8 to 13 carbons (Kobata, Sugawara, Mimura, Yazawa, & Watanabe, 2013). 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 (Perucka & Materska, 2001). Besides these two major capsaicinoids, other isolated capsaicinoids from hot peppers are nordihydrocapsaicin, norcapsaicin, homocapsaicin, homodihydrocapsaicin, nornorcapsaicin, nornornorcapsaicin and nonivamide (Barbero, Palma, & Barroso, 2006a). 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 (Figure 1) (Barbero, Liazid, Palma, & Barroso, 2008). 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, et al., 2018). These compounds are synthesized 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 & Ozdemir, 2007). In general, capsaicinoids content vary with genotype and maturity stage (0.1 - 40 mg 100 g^{-1} FW). For example, Deepa, Kaur, George, Singh, & Kapoor, (2007) found drastic differences in capsaicin levels between different genotypes of sweet pepper (0.07 - 0.1 mg 100 g^{-1} FW), with the changes of these compounds not so pronounced by different maturity stages. In hot pepper varieties concentrations of capsaicinoids are much higher than in sweet pepper (0.01 to 0.5 % FW). In strong chillies the concentration could go to 1% FW (Perucka & Materska, 2001; Topuz, Dincer, Ozdemir, Feng, & Kushad, 2011) and up to 2% FW in some Mexican varieties (Orellana-Escobedo, Garcia-Amezquita, Olivas, Ornelas-Paz, & Sepulveda, 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 & Kam, 2008), as it would be commented 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) and 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) (Table 2) (Singh, et al., 2009). The fundamental structure of capsinoids is a fatty acid ester with vanillyl alcohol (Kobata, 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, Denbow, O'Keefe, Neilson, & Williams, 2017), enhanced energy metabolism via activation of the sympathetic nervous system in mice (Ohnuki, Haramizu, Oki, Watanabe, Yazawa, & Fushiki, 2001) and reported brown fat thermogenesis and reducing body fat activities in humans (Saito & 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, & Mattes, 2012).

2.5. Vitamins

Peppers are good sources of vitamins, having high levels of vitamin C, E (alpha-tocopherol), provitamin A (expressed as mcg of retinol activity equivalents, RAE) and folate (Table 1). For instance, one medium sized green bell pepper fruit (~100 g FW) contains ~180 % of the recommended daily allowance (RDA) for vitamin C, which is 90 mg for men and 75 mg for women; and around 10 % of the RDA for provitamin A (900 and 700 mcg RAE, for men and women, respectively), vitamin E (15 mg) and folate (400 µg per day, being 600 µg for pregnant women) (NIH, 2008; Kantar et al., 2016; Guil-Guerrero, Martínez-Guirado, del Mar Rebolloso-Fuentes, & Carrique-Pérez, 2006). Vitamins C and E have 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, Garrido, & Martinez, 2006). As has been described before (section 2.2), carotenoids (mainly β-carotene and β-cryptoxanthin) are responsible for the provitamin A biological functions, being metabolized intracellularly to retinol and retinoic acid, the active forms of vitamin A, which are associated with reduced risk of lung cancer, and age-related macular degeneration (AMD) (Eggersdorfer & Wyss, 2018). Epidemiological studies have suggested an inverse association between folate status and the risk of cancer, cardiovascular diseases and cognitive function, with higher values intake optimal for proper fetal and infant brain development (Kantar et al., 2016). Levels of vitamins 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 a higher amount of vitamin C in red peppers (~30 %) compared to the green ones (Marin, et al. 2004; Martínez, Curros, Bermúdez, Carballo & Franco, et al., 2007). During postharvest handling and storage at low temperature (~ 4^{o}C) are crucial to maintain vitamin levels in pepper. Indeed, the storage of fresh red jalapeno peppers during 15 days in MAP conserved better the vitamin C levels (~80 %) than in air (~50 %) (Howard & Wildman, 2007). Processing methods also decreased vitamin C content, such as peeling, slicing, blanching, freezing, drying and grinding, as plant tissue disruption increases exposure to oxygen. However, freeze-drying did not cause significant losses, being the most appropriate method for bioactive compounds conservation in the samples (Martínez, López, González-Raurich & Bernardo-Alvarez, 2005).

2.6. Minerals

The most common essential minerals found in peppers, ordered from a higher to lower content, are potassium (K), phosphorus (P), magnesium (Mg), calcium (Ca), sodium (Na), iron (Fe), zinc (Zn), manganese (Mn), boron (B), copper (Cu) and selenium (Se), and their contents in fresh sweet peppers are shown in Table 1. Amounts of minerals vary greatly with variety, maturity stage and environmental changes during growing. Rubio, Hardisson, Martín, Báez, Martín, & Álvarez, (2002), found that red peppers had higher levels of K, Mg, P, Fe, Cu, Zn, Mn and B than green peppers, while other researchers found significantly lower levels of Fe, Cu, K and Mg in red peppers compared to green ones (Pérez-Lopez, López-Nicolas, Núñez-Delicado, Amor, & Carbonell-Barrachina, 2007; Guil-Guerrero et al., 2006). Nevertheless, mineral content generally showed a significant variability among tested cultivars regardless the ripening stage (Guil-Guerrero et al., 2006). Martínez et al. (2007) found high concentration of K in both green and red peppers (~2.5g 100g DW) compared to other minerals, and higher amounts (2-fold) of Ca (150 mg 100g DW) and Na (23 mg 100g DW) in green peppers from the supermarket compared to freshly picked green peppers. Other minerals scarcely changed between samplings such as Zn, Mn, and Cu. The agricultural practices (organic *vs.* conventional farming) may also influence the mineral contents of peppers, which in general showed higher mineral contents when they were produced organically (Pérez-López, et al., 2007).

3. 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 for the industrial use. 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 (SFE), ultrasound assisted extraction (UAE), enzymatic assisted extraction (EAE), microwave assisted extraction (MAE), and pressurized liquid extraction (PLE) (Saini & Keum, 2018; Barbero et al., 2008).

Classical methods, such as maceration and Soxhlet extraction, provide high recovery of total carotenoids, however, they require high amount of solvents and long times of extraction, thus increasing the cost of extraction and limits its application due to environmental and safety issues (Luque de Castro & García-Ayuso, 1998). On the contrary, modern methods have reduced the extraction duration with minimal use of organic co-solvent, such as ethanol, achieving a lower impact on the environment. Indeed, these methods led to higher purity extracts with the highest total yield of the target carotenoids compared to traditional methods. Among these modern methods, SFE, UAE and MAE are the most used, and some examples are shown in Table 2.

The basic parameters of these extraction methods, such as the quantity of the sample, the volume of the solvent, temperature and time, should be carefully optimized as a preliminary work for different sample matrices (Barbero, et al., 2006a). The selection of these criteria depends on the polarity of the specific compounds subject tothe extraction, their stability and concentration, and the type of the container matrix. The choice of the appropriate solvent, depending the polarity of the target carotenoids, is the most critical step for the efficient extraction (Saini & Keum, 2018).

Carbon dioxide (CO_2) is the most used supercritical fluid in SFE methods, sometimes along withco-solvents, such as ethanol. Perva-Uzunalic, Škerget, Weinreich, & Knez, (2004) 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.

The most important advantages of the supercritical CO_2 extraction (SC-CO_2) are the followings: the collection of an extract free of organic solvent residues; the possibility of extracting thermo-labile compounds; and the separation of different enriched fractions of *Capsicum* oleoresin at the same time, such as the collection of one fraction enriched in capsaicinoids and a refined fraction enriched in carotenoids (Fernández-Ronco, de Lucas, Rodríguez, García, & Gracia, 2013; de Aguiar, Sales, Coutinho, Barbero, Godoy, & Martínez, 2016; Saini & Keum, 2018).

The use of UAE is relatively simple and inexpensive in equipment. Different solvents, volumes, temperatures, duration of extraction and quantities of sample have been selected to optimize the ultrasound energy, being the optimum extraction by using small particle size, methanol 100% as a solvent, extraction temperature at 50 °C and extraction time 10 minutes for 1 g of sample (Barbero, et al., 2008).

MAE has been also employed to extract capsaicinoids from peppers (Barbero, et al., 2006a). This methodology applies the energy obtained by microwave radiation to extract the compounds of interest, being a fast and economical method, however, it could cause thermal degradation and cis-trans isomerization of carotenoids

(Hiranvarachat & Devahastin, (2014). Barbero, et al., (2006a) 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 by using 25 mL of ethanol 100 % as a solvent, at 125 °C, for 5 min with 0.5 g of pepper..

In EAE and PLE methods, green solvents in reduced quantities could be used, however, these methods have not been widely employed for *Capsicum* extracts production. In this sense, some disadvantages have been previously reported regarding these methods, such as the requirement of expensive multi-enzyme preparations with longer processing times (7 – 12 h) in EAE methods (Salgado-Roman, Botello-Alvarez, Rico-Martinez, Jimenez-Islas, Cardenas-Manriquez, & Navarrete-Bolanos, 2008) and the use of high temperatures in PLE methods, which are not suitable for thermo-labile compounds (Barbero, Palma, & Barroso, 2006b).

The most extracted compounds in pepper matrices are capsaicinoids and carotenoids, being mainly extracted as paprika oleoresin, which is mostly used as natural food colorant (Uquiche, Valle, & Ortiz, 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, et al., 2013).

Among the different methods employed to extract and use these compounds for health-promoting (capsaicinoids) or food colouring (carotenoids) applications, the use of supercritical CO_2 methods may be the most successful to extract oleoresin and to separate it into enriched fractions of bioactive compounds, such as capsaicinoids, carotenoids and vitamins (de Aguiar, et al., 2016; Fernández-Ronco, et al., 2013). In this sense, this technology is recognized as green, using small amounts of organic co-solvents, such as ethanol and hexane, that have been authorized by the European Medicine Agency (EMA, 2015) and the Food and Drug Administration of U.S. (FDA, 2017a). Indeed, the economic feasibility of supercritical processes has been evaluated in terms of costs and benefits, being a promising technology to obtain bioactive compounds from multicomponent mixtures, as the investment cost may be amortized with the product high values at the nutraceutical market (Fernández-Ronco, et al., 2013).

4. Agro-food industrial applications

Among the different pepper derived products used in the industry, such as oleoresin and other enriched extracts, one of the most important is the powder, called paprika, with 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). Additionally to the traditional uses of paprika in the industry, contributing to pungency, colour and taste attributes, other characteristics are currently considered in the food processing industries, such as the antimicrobial or antioxidant activities. Some of these multiple uses of *Capsicum* derived ingredients in the agro-food industry are exemplified in Table 3.

4.1. Antimicrobial activity

Several scientific studies have shown antimicrobial activity against gram positive and gram negative bacteria which cause foodborne illnesses, nevertheless, the information about the responsible compounds for 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*, suggesting that the phenolic acids *m*-coumaric and cinnamic acids were responsible for these inhibitory activities, unlike capsaicin and dihydrocapsaicin, that did not show these effects.

Recently, Bacon *et al.*, (2017) reported the potent 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 of capsicinoids, against gram positive bacteria, which showed disruption of biofilm formation may be due to their capacity of chelating calcium, mineral which influences biofilm architecture development. In accordance to these results, Careaga, Fernandez, Dorantes, Mota, Jaramillo, & Hernandez-Sanchez, (2003) reported a minimum inhibitory concentration of a *Capsicum annuum* bell pepper extract of 1.5 mL 100 g^{-1} in minced beef meat preventing the growth of *S. typhimurium*.

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, Arnesi, Veronesi, Sarzi, & Fratianni, 2009). Also cayenne and green pepper ethanol extracts applied in the bull milk during manufacture of Egyptian Kareish cheese showed antimicrobial activity against natural microflora, coliforms, molds and *Staphylococcus aureus*, being strongly acceptable to the consumers in the concentrations of 1% (w/v) for cayenne pepper and 3-6 % (w/v) for green pepper (Wahba, Ahmed, & Ebraheim, 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 products spoilage, 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 (Nazzaro et al., 2009).

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 (Deepa, et al., 2007; Howard & Wildman, 2007; Marin, et al. 2004). In regard to vitamin C, most of the studies have found about 30 % of increase during fruit maturation (Marin, et al. 2004; Martínez, et al., 2007). Concerning phenolic compounds, Marín et al. (2004) showed the highest content in immature (green) peppers, while Deepa et al. (2007) found very varied changes in phenolic compounds during the ripening. Red ripe peppers showed higher contents of capsaicinoids than green peppers, which may also contribute to their antioxidant capacity (Materska & Perucka, 2005). Therefore, the differences in bioactive compounds content found in pepper fruits at different ripening stages should be carefully evaluated to understand the complex interactions occurring among different bioactive phytochemicals and other reducing compounds in the extracts in terms of their reported bioactivity (Howard & Wildman, 2007).

Most of the phytochemicals with antioxidant capacity (e.g., carotenoids and flavonoids) found in pepper act also as pigments, influencing the colour of the fruits during ripening. In this sense, higher *in vitro* antioxidant activities from red and orange pepper varieties have been reported when compared to the green, yellow or white fruits (Guil-Guerrero, et al., 2006; Matsufuji, Ishikawa, Nunomura, Chino, & Takeda, 2007).

The use of red sweet bell pepper as antioxidant ingredient in foods could significantly reduce the cholesterol decomposition and the docosahexanoic (DHA) acid degradation during cooking, therefore, avoiding the production of toxic oxidation products which may generate off-flavours, deterioration of food quality, and could increase the risk for coronary heart diseases and cancer (Sun, et al., 2007). Examples of commercially available red bell pepper powders can be found in different formats, such as 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 for the preservation of human health well-being (Materska, 2014).

During industrial processing of pepper, seeds are usually discarded as waste, even if they are rich in bioactive compounds with antioxidant capacity, such as phenolic acids, flavonols and ascorbic acid (Sandoval-Castro, et al., 2017). In this respect, pepper seeds could be exploited as an antioxidant ingredient, which could be also sold at the markets (e.g. Jinhua Huayang Co., Ltd.; URL: http://www.sinospice.com/proinfo.asp?id=259).

In conclusion, pepper extracts and seeds 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 oleoresin also could be used in food products, as a substitute for ground paprika, due to its concentrated colour and flavour (Tepic, Dimic, Vujicic, Kevresan, Varga, & Sumic, 2008); however, paprika extract as a food additive requires an additional purification in the manufacturing process.

4.3.1. Colour

Paprika extract (E 160c) is classified as a food additive (natural dye) in EU (EFSA, 2015). The main quality attribute of this ingredient is the intensity of its red colour, that influences both consumer acceptance and commercial value (Belović, Mastilović, & Kevrešan, 2014). More than 20 different pigments from paprika fruits have been identified, including green chlorophyll, yellow-orange pigments, such as lutein, zeaxanthin, violaxanthin, antheraxanthin and β-carotene, and the red pigments capsanthin and capsorubin, all of them considered as exclusive to *Capsicum* genus and representing the main pigments that determine the colour of red pepper (Matsufuji, et al. 2007; Tepic, et al. 2008). There are several methods for paprika colour evaluation based on the measurement of surface colour, the extraction of pigments, and the profiling of carotenoids (Belović, et al., 2014). 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, & Park, 2008). 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 (Pruthi, 2004). The use of pepper derivatives as colouring enhancers is much extended and many products are available: 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. As example for the use of pepper derivatives in the food industry, ground pepper (paprika) is usually added to meat products in order to improve their colour and flavour. Fernández-López, Pérez-Alvarez, Sayas-Barberá, & López-Santoveña, (2002), showed that in batters for dry-cured sausages, lightness and reflectance depended exclusively on the paprika, therefore, they concluded that any colour modification observed in dry cured meat products are due principally to paprika colour changes more than meat colour changes, which could be modified and enhanced by the addition of this pepper product. Nanoparticles of paprika oleoresin (1 - 3 %, w/v) were also investigated as a tool to improve physical and sensory properties of cooked marinated chicken (Yusop, O'Sullivan, Preuß, Weber, Kerry, & Kerry, 2012). Results showed that the incorporation of nanoparticles of paprika oleoresin to the meat using water-based carrier systems, produced the furthest colour penetration and increased the colour quality of cooked marinated chicken, therefore, enhancing the marinating performance.

4.3.2. Pungency and flavour

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 characteristics of the pepper flavour is a complex trait, influenced by environmental factors during growth and postharvest processing (Eggink, et al., 2012). More than 125 volatile compounds have been identified in fresh and processed *Capsicum* fruits (Luning, de Rijk, Wichers, & Roozen, 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, et al., 2015).

Paprika powder also could be used in order to reduce the nitrite content in meat batters, improving their colour and lowering oxidative rancidity, which results in a delay of off-odour formation (Bazan-Lugo, Garcia-Martinez, Alfaro-Rodriguez, & Totosaus, 2012). Martínez, Cilla, Antonio Beltrán, & Roncalés, (2006), also studied the use of pepper powder to inhibit oxidative reactions and extend the shelf life of fresh pork sausages packaged in a modified atmosphere. The highest concentration of paprika powder (2%, w/w) used in their research was very effective in inhibiting lipid oxidation and microbial growth. Indeed, their results demonstrated that sweet red and hot cayenne pepper powders (2%, w/w) enhanced red colour and prevent discoloration during 12 days of storage at 4 ^{o}C.

When evaluating processed foods, a soup with added cayenne pepper (450 mg L^{-1}) was perceived significantly spicier but was equally liked as a soup without it, having as advantage that resulted in higher satiation at the end of the meal and one hour post intake (Andersen, Byrne, Bredie, & Møller, 2017).

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, Sudarmonowati, Bino, & Bovy, 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 & Rocha, 2007). In addition, 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, Barman, & Maity, 2017).

Regarding anti-proliferative activities of *Capsicum annum* ingredients, extracts rich in capsaicin as well as pepper seeds extracts, they have shown high *in vitro* anti-proliferative activity against lung, breast, gastric and prostate human cancer cell lines, among others (Jeon, 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, Sahu, Shi, & Srivastava, 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 that 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, et al., 2015).

However, the bioavailability of these antioxidant and anti-proliferative compounds is definitely more important for exerting the *in vivo* effect than their concentration in the consumed food. Hervert-Hernández, Sayago-Ayerdi, & Goni, (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 this 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, et al., 2010). Regarding capsaicin and dihydrocapsaicin, their absorbance rate *in vivo* was 50% in the stomach, 80% in the jejunum and 70% in the ileum (Rollyson, et al., 2014). Recently, the addition of capsaicin (0.01 - 0.02 %) in the diet of obese diabetic ob/ob mice, contributed to an improvement of glucose homeostasis and the inflammatory state, which was probably mediated by the alterations found in the gut microbiota (Song et al., 2017).

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 & Kam, 2008), as it would be commented below regarding its pharmacological effect. Besides, Andersen, et al., (2017), found 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 the eating behaviour. 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 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, which is one of the main macrovascular complications of diabetes (Ranilla, Kwon, Apostolidis, & Shetty, 2010).

In regards to 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* and *in vivo,* which could be attributed to capsaicin, which has shown to modulate NFκB and IL-8 pathways (Allemand, Leonardi, Zimmer, Moreno, Romão, & Gosmann, 2016), but also because of the presence of other bioactive compounds, such as carotenoids, whose application reduced the levels of ACE activity and the concentration of seromucoids in serum of rats with adjuvant-induced inflammation (Boiko, Kravchenko, Shandra, & Boiko, 2017).

Therefore, inclusion of *Capsicum* derived products as ingredients in the diet could help 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 in searching for bioactive compounds, raw plant materials or plant extracts as natural ingredients (or excipients), for the cosmetic and pharmaceutical applications. In this sense, some attributes that can influence the final product performance, such as physical properties (colour, flavour, texture or permeation) and bioactivities (antimicrobial and antioxidant), should be studied and accepted by the corresponding competent authority (EMA, 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 plant compounds could also contribute to the major product claims from the cosmetic industry, which are the antiaging effect and the reduction of wrinkles by fighting against free radicals and solar radiation. All these uses of bioactive compounds as nutraceuticals or cosmeceuticals have to be regulated according the global quality standards for medicines, with the most relevant groups of experts those belonging to the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) (Ph. Eur. 2010). Some examples of the use of *Capsicum* derived ingredients in the pharma and cosmetic industries are shown in Table 3.

5.1. Enhancer of physical properties

As mentioned, paprika powder and oleoresins are rich in carotenoids and capsaicinoids, and these bioactive compounds are an excellent source of colours in the cosmetic and pharmaceutical industry. According to the EFSA and FDA, these natural ingredients do not require a specific approval by these organizations; however, they must be safe for consumers under labelled or customary conditions of use, with manufacturers having the legal responsibility for the safety of their products and ingredients. In this sense, paprika is commonly used as a 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; FDA, 2017b). 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 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 by-products can be also used as flavouring or fragrance agents in cosmetic products, which may be extracted using hexane, ethanol, or vegetable oil, and it could be incorporated in high concentrations up to 5 % (w/w) without any toxic effect (Johnson, 2007). Pepper oleoresin provides manufacturers with an important advantage in 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 have that ability.

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, Eisner, & Kerscher, 2015). On this note, an acetone–water extraction of red pepper by-products was studied as a natural dye to be applied on woollen fabrics to produce coloured clothing and textiles with acceptable antimicrobial properties (Ksibi, Slama, Faidi, Ticha, & M'henni, 2015).

The extended use of *Capsicum* ingredients in the market request the standardisation 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. The antioxidant capacity of these bioactives depends on their nature, the processing steps of the pharmaceutical product, the nature of the container and on 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 compounds 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, Villanelli, Mangino, Sabbatini, Santini, et al., 2004). Dehydrated green pepper containing high amounts of vitamin C (135 - 240 mg $100g^{-1}$ DW) could be used as preservative antioxidant in the cosmetic industry (Thampi, 2004). Also *Capsicum* extracts containing carotenoids, such as capsanthin, lutein and zeaxanthin, extracted with oil-soluble solvents could be used as active ingredient for skin care cosmetics. Indeed, their bioactivity and stability could be enhanced by their incorporation to lipoproteins or membranes (Arimboor, et al. 2015).

Antimicrobial preservatives are used to prevent or inhibit the growth of bacteria, fungi 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 & 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, as the use of synthetic preservatives is more than affordable, with broad-spectrum of activity against bacteria and fungi, and their compatibility with other ingredients of a given formulation. However, the introduction of natural preservative for cosmetics industries will increase in the following years, rising consumer demand for products formulated with natural plant materials (Kerdudo et al., 2016).

5.3. Cosmetic and pharma applications for beauty and health products

Pepper derived ingredients are currently used as part of nutricosmetics or cosmeceuticals, mainly as antioxidant and analgesic treatments, in oral supplementations or topical applications (Palombo, et al., 2007; Telang, 2013). In regard to the 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, et al., 2012).

Capsaicin has been approved by the EU and FDA as a drug for the topical treatment of neuropathic pain, with its analgesic action being dose dependent. Although the precise mechanism of action is not fully understood, evidence suggests 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 (Lysy, 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 to reduce incontinence. It also protects the stomach against gastritis induced by non-steroidal anti-inflammatory drugs; it can reduce post-operative nausea, vomiting and sore throat; and it can help in patients with pruritus associated with renal failure and in patients with myocardial ischemia (Hayman & Kam, 2008).

Low concentrations of capsaicin are included in over-the-counter analgesic creams and 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 research works using capsaicin, lipid-replenishing capsaicin cream (0.012 - 0.006 %, w/w) has been studied against chronic pruritus and cutaneous hypersensitivity (Lysy, et al., 2003), it should be noted that daily capsaicin applications should be adaptable to patient needs and could have 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, Singal, Sharma, Negi, & Katare, 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 %, w/w) should be preferred during the acute phase of inflammation (Staubach & Metz, 2013). In terms of costly and time-effective capsaicin extraction process, Thapa, Pepic, Vanic, Basnet, & Skalko-Basnet, (2013) reported a straight-forward formulation development with vesicular formulations for capsaicin from a crude *Capsicum* powder, destined for localized pain, 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 (EMA, 2015), which are usually available as a medicated plaster or in semi-solid forms to be applied to the skin (such as creams) according to the European Pharmacopoeia (EDQM, 2016). This body 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 in 2009 and indicated for the management of neuropathic pain associated with post-herpetic neuralgia.

In regard to the 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 (EMA, 2015). Nevertheless, further studies are necessary to establish more precisely the range of effective capsaicin concentration for long-term treatments.

Vitamin C is one of the most potent antioxidant compounds found in pepper and highly used in skin cosmetics, which acts as potent antioxidant that prevents skin oxidative damage, thus protecting the skin from reactive oxygen species (ROS), and is also an important ingredient for treating skin pathologies, such as inflammation and cancer. The absorption of vitamin C in the human body depends on the oral intake and topical delivery, as well as its low stability, which could be reduced by changes of temperature and pH, which lowers its efficacy as therapeutic product (Telang, 2013). The use is safe on a daily basis for long durations and the effects could be enhanced by topical application of ascorbic acid (the chemically active form of vitamin C), in liposomal formulations, thus 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, 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 is favoured in the dermatological practice, 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, have 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, Palombo et al., (2007) 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). As examples of clinical studies, dietary supplementation with carotenoids, iron and zinc following a vitamin A deficient diet, one study has shown improved retinol levels and carotenoids' levels in plasma, respectively (Kana-Sop, et al. 2015); further, in another study, a treatment of ≥ 24 mg carotenoids/day for at least 12 weeks showed an effective protection against UV-induced erythema (Heinrich, et al. 2003).

Capsidiol is a phytoalexin isolated from a methanol extract of *C. annuum*, this compound showed a clear *in vitro* activity against *H. pylori* (≥ 200 µg mL^{-1}), showing its potential as a treatment for antibiotic-resistant strains and for patients who do not wish to take synthetic antibiotics (De Marino, 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 problems, such as protecting cells from UV irradiation or supporting skin regeneration in wound healing (Hatahet, Morille, Hommoss, Devoisselle, Müller, & Bégu, 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, Giovenali, & Di Martino, 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, Morita, & Teraoka, 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, the anthocyanins, could be used not only as a colouring agent, but also as antioxidants, for UV-protection, inhibition of melanin production and as anti-aging compounds in cosmetic preparations. These compounds could be encapsulated in the appropriate coating to enhance their bioactivity and use in topical applications for skin care (Westfall and Giusti, 2017).

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

6. Future perspective

The growing market of functional ingredients and natural pharmaceutics has emerged in response to the current social awareness about consuming natural ingredients instead of synthetic substitutes. These natural compounds act as enhancers of the organoleptic parameters and shelf-life of the final product, and once integrated in balanced diets, it would also contribute to the human wellbeing (Anunciato & da Rocha Filho, 2012). In this sense, *Capsicum* derived products, such as oleoresin, paprika powder, purified extracts and fractions enriched in carotenoids and/or capsaicins, continue to be investigated in terms of colour, flavour, pungency and nutritional value, as potential ingredients for foods, pharma and cosmetic industries.

Furthermore, the application of these compounds into food or pharmaceutical products could be a strategy to improve health due to their bioactivity (antioxidant, anti-inflammatory and antimicrobial, among others). To this fact, the standardisation of these *Capsicum* derived ingredients in terms of colour, pungency, flavour and biological activity is completely needed to expand the capabilities of these compounds in the markets.

For the dermatologic and cosmetic industry, the challenge about using formulations with natural bioactive compounds is to guarantee stability, safety and efficiency in new organic cosmetics and products (e.g. analgesic creams, transdermal patches, oral nutri-cosmetics and cosmeto-textiles). The main reasons for this are the absence of harmonized guidelines and manufacturers are the ones responsible to ensure the safety of these dietary supplements, while there is no a need to prove the safety and effectiveness before they are marketed. Therefore, there is a legal vacuum without specific rules in the pharmaceutical sector, which suggest a future new legislation for the use of these extracts as bioactive ingredients in cosmetic and pharmaceutical formulas.

On the other hand, the high demand for using natural plant compounds as alternative to synthetic preservatives and pigments in the food and pharmaceutical industries needs to develop new promising and effective "green" methodologies, which could fulfil the requirements of the market with minimum manufacturing costs. For instance, a reduction of the energy required for the extraction and the amount of organic solvent waste, along with the development of higher value byproducts, would provide economic benefits to producers and agribusiness.

Further studies are required to elucidate the mechanisms of action for *Capsicum* ingredients at industrial scale and in the final products. These studies could also provide an interesting opportunity for the utilization of pepper by-products 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. Finally, clinical findings and epidemiological studies are needed for the better understanding of health-promoting activities of *Capsicum* derivatives, which could scientifically substantiate a health-claim and, therefore, promote the consumption of these products.

Conflict of interest

The authors declare that there is no conflict of interest.

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FIGURE CAPTIONS

Figure 1. Chemical structure of bioactive compounds present in *Capsicum annum* varieties (S*ources: Withing, et al., 2012; Fiedor & Burda, 2014; Materska, 2014).*

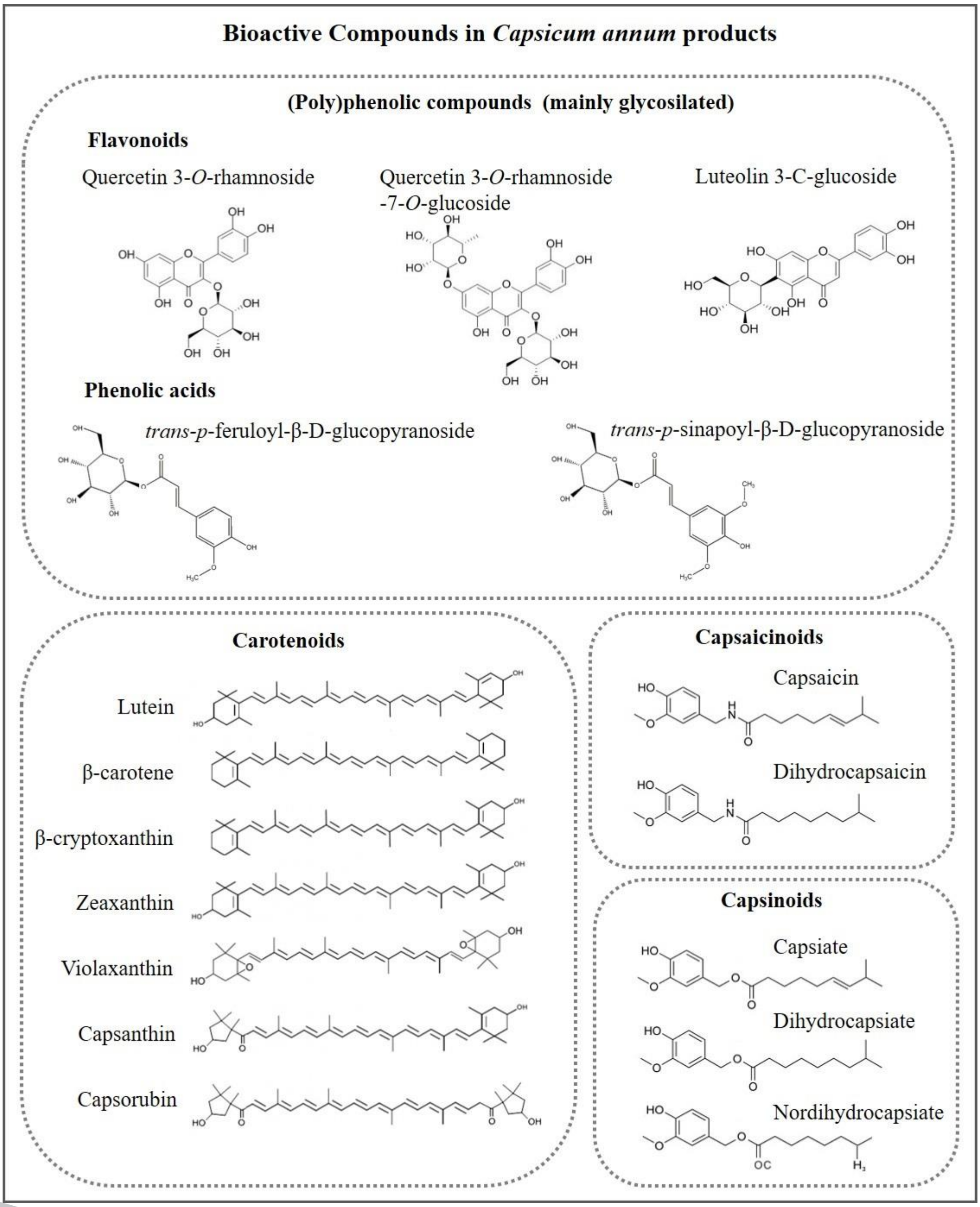
Bioactive Compounds in Capsicum annum products
(Poly)phenolic compounds (mainly glycosilated)
Flavonoids
Quercetin 3-O-rhamnoside
Quercetin 3-O-rhamnoside -7-O-glucoside
Luteolin 3-C-glucoside
Phenolic acids
trans-p-feruloyl-β-D-glucopyranoside
trans-p-sinapoyl-β-D-glucopyranoside
Carotenoids
Lutein
β-carotene
β-cryptoxanthin
Zeaxanthin
Violaxanthin
Capsanthin
Capsorubin
Capsaicinoids
Capsaicin
Dihydrocapsaicin
Capsinoids
Capsiate
Dihydrocapsiate
Nordihydrocapsiate

Table 1. Content of micronutrientes and main bioactive compounds in sweet pepper (100 g F.W.).

Micronutrients	
Minerals (mg)	
Calcium, Ca	7 - 18
Iron, Fe	0.3 - 1.2
Magnesium, Mg	12 - 25
Phosphorus, P	26 - 46
Potassium, K	211 - 340
Sodium, Na	4 - 7
Zinc, Zn	0.2 - 0.7
Copper, Cu	0.015 - 0.07
Manganese, Mn	0.05 - 0.16
Boron, B	0.05 - 0.16
Selenium, Se	0.0001 - 0.001
Vitamins (mg)	
Vitamin C (total ascorbic acid)	127 - 300
Thiamin	0.03 - 0.09
Riboflavin	0.03 - 0.09
Niacin	0.9
Pantothenic acid	0.317
Vitamin B6	0.17 - 0.29
Folate total	0.02 - 0.06
Choline	5.6
Betaine	0.1
Vitamin A	0.01 - 0.16
Vitamin E (α-tocopherol)	0.7 - 1.6
Vitamin K	0.005 - 0.014
Sources: Guil-Guerrero, et al., 2006; Kantar et al., 2016; Rubio et al., 2002; USDA, 2018.	

Bioactive compounds		
Carotenoids		
Provitamin A carotenoids (mg)		
α-carotene		0.020
β-carotene		0.5 - 1.64
β-cryptoxanthin		0.5 - 1.2
Non - provitamin A carotenoids (mg)		
Lutein + Zeaxanthin		6 - 51
	Total	15 - 320
Phenolic compounds		
Flavonols (mg)		
Luteolin		0.6
Quercetin		0.2
	Total	5 - 20
Phenolic acid derivatives (mg)		
	Total	50 - 500
Anthocyanins (mg)		
	Total	0.5 - 28
Capsaicinoids (mg)		
Capsaicin		0.07 - 0.1
Dihydrocapsaicin		0.07 - 0.1
	Total	0.1 - 0.3
Capsinoids (mg)		
	Total	3 - 50
Sources: Asnin & Park, 2015; Deepa et al., 2007; Padilha, et al. 2015; Singh, et al., 2009.		

Table 2. Examples of extraction methods for *Capsicum annum* derived products

Extract or isolated compound	Origen	Extraction method	Extraction conditions	Reference
Red pepper oleoresin and intact carotenoids	Commercial flakes of red pepper	SC-CO_2	Particle size 0.27 mm; flow rate 0.57–1.25 mm/s; 540 bar and 40 °C	Uquiche, et al., 2004.
Microencapsulation of pepper extract rich in carotenoids and vitamin E	Piquillo red pepper byproducts	SC-CO_2 + Spray dry microencapsulation	30 g of pepper; flow rate 2000 mL/h; 24 MPa and 60 °C; time 90 -120 min Spray dried Büchi B-290 and gum arabica	Romo-Hualde, et al., 2012
Encapsulation of capsaicinoids	Dry pepper	SFEE + Ultrasound emulsification	Flow rate 1.98×10^{-4} kg/s; 15 MPa and 40 °C Emulsification with Hi-Cap 100 and flow rate 0.5-1 mL/min	De Aguiar, et al., 2016
Capsaicinoids	Hot pepper	UAE	Solvent methanol 100 %; temperature 50 °C; time 10 min.	Barbero, et al., 2008
Capsaicinoids	Freshly triturated peppers	MAE	0.5 g of sample; 25 mL of 100% ethanol; time 5 min; temperature 125 °C.	Barbero, et al., 2006a
Enriched fractions of carotenoids and capsaicinoids	Chili powder	EAE	Two-stage extraction process with hexane and ethanol. Non-commercial enzymes from *R. nigricans*	Salgado-Roman, et al., 2008
Individual capsaicinoids	Hot pepper	PLE	100 atm, 200 ºC, 30 min extraction time	Barbero et al., 2006b

Abbreviations. SC-CO_2: Supercritical CO_2 extraction; SFEE: Supercritical Fluid Extraction of Emulsions; UAE: Ultrasound assisted extraction; MAE: Microwave assisted extraction; EAE: Enzyme assisted extraction; PLE: Pressurized liquid extraction.

Table 3. 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	Tepic, et al., 2008
Paprika powder	Red sweet pepper	Carotenoids	Nitrite replacer, colour enhancer and lipid oxidation inhibitor in pork meat	Agro-food industry	Bazan-Lugo, et al., 2012; Martínez, et al., 2006
Paprika powder	Red sweet pepper	Carotenoids and capsaicinoids	Colouring stability in meat products, soups, sauces and snacks	Agro-food industry	Fernández-López, et al., 2002; Pruthi, 2004
Paprika oleoresin	Sweet paprika, pungent paprika	Carotenoids and capsaicinoids	Enhancer of sensory properties of food products	Agro-food industry	Tepic, et al., 2008; Uquiche, et al., 2004
Pepper flour	Yellow pepper	Carotenoids	Source of antioxidants and enhancer of sensory properties in wheat bread	Agro-food industry	Danza, Mastromatteo, Cozzolino, Lecce, Lampignano, Laverse, et al., 2014
Nanoparticle paprika oleoresin	Sweet paprika	Carotenoids	Enhancer of physical and sensory properties of cooked marinated chicken	Agro-food industry	Yusop, 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, 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, et al., 2013
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, 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, 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, et al., 2009
Methanol pepper extractions	Sweet pepper	Capsidiol	Bacteriostatic properties *in vitro* against *Helicobacter pylori*	Pharmaceutical, cosmetic and agro-food industry.	De Marino, 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	Căruntu, Negrei, Ghiţă, Căruntu, Bădărău, Buraga, et al., 2015; Lysy, et al., 2003
Pepper powder	Cayenne pepper	Capsaicinoids	Pharmacological activities: alter appetite sensations by higher satiation	Pharmaceutical industry	Andersen, et al., 2017

3 to 5 bullet points (maximum 85 characters, including spaces)

- *Capsicum* oleoresin and purified extracts are rich in carotenoids and capsaicinoids

- Supercritical CO_2 extraction is the most useful method to enrich *Capsicum* fractions

- Pepper derivatives enhance sensory properties and shelf-life of foods

- Pepper bioactive compounds, vitamins and minerals as health-promoters