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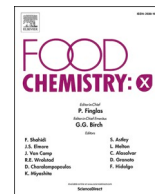
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## Supercritical fluids and fluid mixtures to obtain high-value compounds from *Capsicum* peppers

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### ABSTRACT

Peppers of the *Capsicum* genus have a rich nutritional composition and are widely consumed worldwide. Thus, they find numerous applications in the food, pharmaceutical and cosmetic industries. One commercial application is oleoresin production, a nonpolar fraction rich in bioactive compounds, including capsaicinoids and carotenoids. Among the technologies for pepper processing, special attention is given to supercritical fluid technologies, such as supercritical fluid extraction (SFE) with pure solvents and CO<sub>2</sub> plus modifiers, and SFE assisted by ultrasound. Supercritical fluid-based processes present advantages over the classical extraction techniques like using less solvents, short extraction times, specificity and scalability. In this review, we present a brief overview of the nutritional aspects of peppers, followed by studies that apply supercritical fluid technologies to produce extracts and concentrate bioactives, besides oleoresin encapsulation. Furthermore, we present related phase equilibrium, cost estimation, and the gaps and needs for the full use of peppers from a sustainable perspective.

### Introduction

In the last two decades, there has been an effort to study the chemical composition and consequently to discover new functional compounds in plant matrices. One of the plants that deserve special mention is pepper

belonging to the *Capsicum* genus and their byproducts.

*Capsicum* peppers have different classes of bioactive compounds in their composition and the profile and concentration of these compounds vary widely depending on the cultivar or variety, stage of ripeness, part of the fruit (placenta, pericarp and seeds), cultivation and climate

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conditions (Luo, Peng & Li, 2011; Reyes-Escogido, Gonzalez-Mondragon & Vazquez-Tzompantzi, 2011). The main bioactive compounds present in Capsicum peppers are carotenoids, capsaicinoids, capsinoids, phenolic compounds, vitamins and minerals (Deepa, Kaur, George, Singh & Kapoor, 2007; Materska & Perucka, 2005; Aguiar et al., 2019).

The extraction of bioactive compounds from Capsicum peppers by different techniques has three main objectives: characterization, isolation, and application. According to Baenas, Belović, Ilic, Moreno and García-Vigueira (2019), the extraction techniques can be divided into two groups: conventional or classic methods (Soxhlet, maceration, magnetic stirring and hydrodistillation) and non-conventional or modern methods (supercritical fluid extraction – SFE, ultrasound-assisted extraction – UAE, enzymatic assisted extraction – EAE, microwave-assisted extraction – MAE, and pressurized liquid extraction – PLE). The main advantages of modern methods over the conventional ones are the reduced extraction time and consumption of organic solvents, and the possibility of using green solvents such as ethanol, water and carbon dioxide (CO<sub>2</sub>) (Mustafa & Turner, 2011; Gallego, Bueno & Herrero, 2019). These combined features can result in industrial processes that provide less environmental impact, as well as being economically viable (del Valle, 2015; Aguiar et al., 2019; Aguiar, Osorio-Tobón, Viganó & Martínez, 2020). Another remarkable advantage of modern extraction techniques is the possibility of obtaining extracts with higher purity in each bioactive compound by optimizing the extraction process parameters for a specific response.

An important aspect of natural extracts, mainly extracts obtained from Capsicum peppers, is that they are rich in bioactive compounds that are prone to degradation by oxygen, light, high or low temperatures, and pH variations. Therefore, many studies have encapsulated these extracts to confer protection on the external environment, providing their application in food and pharmaceutical products (Aguiar, Paula, Mundo, Martínez & McClements, 2021). Thus, this review briefly describes some relevant results about the encapsulation of Capsicum and derivatives.

The scope of this review is to provide an updated overview of the use of supercritical fluids and fluid mixtures to obtain high-value compounds from Capsicum peppers and their byproducts. The most notable applications of supercritical fluid technology and its coupling with modern techniques are highlighted and critically discussed. Moreover, future needs and trends are also addressed.

### Capsicum peppers and its main bioactive compounds

Peppers of the genus *Capsicum* are annual herbaceous plants belonging to the *Solanaceae* family, predominantly cultivated in warm climate regions such as Asia, tropical and subtropical Africa, northern America and central and southern Europe (Thampi, 2003). Among the species of the genus *Capsicum*, five are domesticated, widely cultivated and consumed: *Capsicum annuum*, *Capsicum baccatum*, *Capsicum chinense*, *Capsicum frutescens* and *Capsicum pubescens*. In botanical terms, the fruit is defined as a berry of hollow structure and capsule-like shape. The great morphological variability presented by *Capsicum* fruits is evidenced by multiple shapes, sizes, colors (from green to red) and pungency levels (Barbero et al., 2016). This last feature, unique to the *Capsicum* genus, is attributed to a group of compounds called capsaicinoids that accumulate on the surface of the placenta (tissue located on the inner wall of the fruit) (Carvalho & Bianchetti, 2007).

Worldwide pepper production increased by 25% between 2006 and 2016 (FAOSTAT, 2016). The increase in the consumption of peppers in developed countries is related to the increased awareness of the benefits that a diet rich in vegetables promotes to health, coupled with the migration of populations, which spreads eating habits. On the other hand, in developing countries, the same increase is observed, but it is a reflection of the increasing industrialization and urbanization. Capsicum peppers are one of the most agriculturally and economically important vegetable crops all over the world, reaching a production of 34.5 and 3.9

million tons of fresh and dry pepper, respectively, in 2016 (FAOSTAT, 2016).

Capsicum peppers are rich sources of phytochemicals such as vitamins, capsaicinoids, carotenoids and polyphenols. The chemical structures of the main bioactive compounds found in *Capsicum* peppers are shown in Fig. 1. Such compounds are of great interest to human consumption, and thus for the food industry. In this section, we will briefly discuss the main characteristics of the bioactive compounds of *Capsicum* peppers. Readers can find more information on the topic in the interesting reviews published by Mendes and Gonçalves (2020) and Antonio, Wiedemann and Junior (2018).

Capsaicinoids are secondary plant non-toxic alkaloid metabolites found uniquely in peppers of the genus *Capsicum*. Capsaicinoids are vanillylamides of branched fatty acids, with 9-11 carbons, of which capsaicin (8-methyl-*N*-vanillyl-6-nonenamide: C) and dihydrocapsaicin (8-methyl-*N*-vanillylnonanamide: DHC) occur in quantities greater than 80%. The remaining derivatives, such as nordihydrocapsaicin (*n*-DHC), homocapsaicin (h-C) and homodihydrocapsaicin (h-DHC) among others, are found in small quantities (Perucka & Oleszek, 2000).

A group of capsaicinoid-like compounds called capsinoids (found in some varieties of sweet peppers) has been studied and showed physiological effects equivalent to those of capsaicinoids without, however, expressing the pungency characteristic (Hursel & Westerterp-Plantenga, 2010). Capsiate (4-hydroxy-3-methoxybenzyl (E)-8-methyl-6-nonenolate: CTE) and dihydrocapsiate (4-hydroxy-3-methoxybenzyl 8-methylnonanoate: DHCTE) were first identified in “CH-19 Sweet” peppers (Kobata, Todo, Yazawa, Iwai & Watanabe, 1998). The only structural difference between capsinoids and capsaicinoids is the type of bond between the benzene backbone and the carbon chain of the molecule. In capsinoids this bond is ester-type, while in capsaicinoids it is an amide-type (Kobata et al., 1998). The lack of pungency, characteristic of these compounds, makes them interesting for application in the food and pharmaceutical industries, since the strong pungency is a limiting factor for the use of capsaicinoids (Luo et al., 2011). The determination of pungency or quantification of the different capsaicinoids present in peppers is crucial for industrial purposes. The contents of capsaicinoids and carotenoids in *Capsicum* peppers oleoresin are factors that determine their commercial value and are also related to their proper application as food ingredients. Pepper pungency can be determined by capsaicinoid quantification or sensory evaluation, expressed as Scoville Heat Unit (SHU).

The physiological and pharmacological activities of capsinoids are very similar to those of capsaicinoids, mainly regarding antioxidant capacity (Rosa et al., 2002), anticarcinogenic potential (Friedman et al., 2018), anti-obesity effect (Joseph, Johannah, Kumar, Syam, Maliakel & Krishnakumar, 2020), the ability to improve glucose metabolism (Kwon et al., 2013; Liu et al., 2019), to increase body temperature and oxygen consumption in humans (Ohnuki, Haramizu, Watanabe, Yazawa & Fushiki, 2001; Ohyama, Nogusa, Shinoda, Suzuki, Bannai & Kajimura, 2016), to reduce total adipose tissue (Kim et al., 2014), as well as being potent anti-inflammatory agents *in vivo* (Sancho et al., 2002). Benefits on human health of *Capsicum* and derivatives main compounds are shown in Fig. 2.

Another class of bioactive compounds found in *Capsicum* peppers are carotenoids, which are responsible for the different color varieties (Agostini-Costa, Gomes, Melo, Reifschneider & Ribeiro, 2017). Carotenoids are lipophilic pigments with C-40-based isoprenoid structure with different end groups ( $\beta$ ,  $\epsilon$ ,  $\kappa$ ). They are classified into oxygen-free carotenes, such as  $\alpha$ -carotene and  $\beta$ -carotene and oxygen-containing xanthophylls, such as  $\beta$ -cryptoxanthin, zeaxanthin, violaxanthin and capsanthin (Britton, 1995). The red carotenoids are mainly capsanthin and capsorubin, which are exclusive to the *Capsicum* genus (Hornero-Méndez, Guevara & Mínguez-Mosquera, 2000), along with capsanthin 3,6-epoxide (Deli, Molnár, Matus, Tóth & Steck, 1996) and capsanthone (Deli, Matus, Molnár, Tóth, Steck & Pfander, 1995) as minor components. Carotenoids in *Capsicum* peppers may vary in composition and

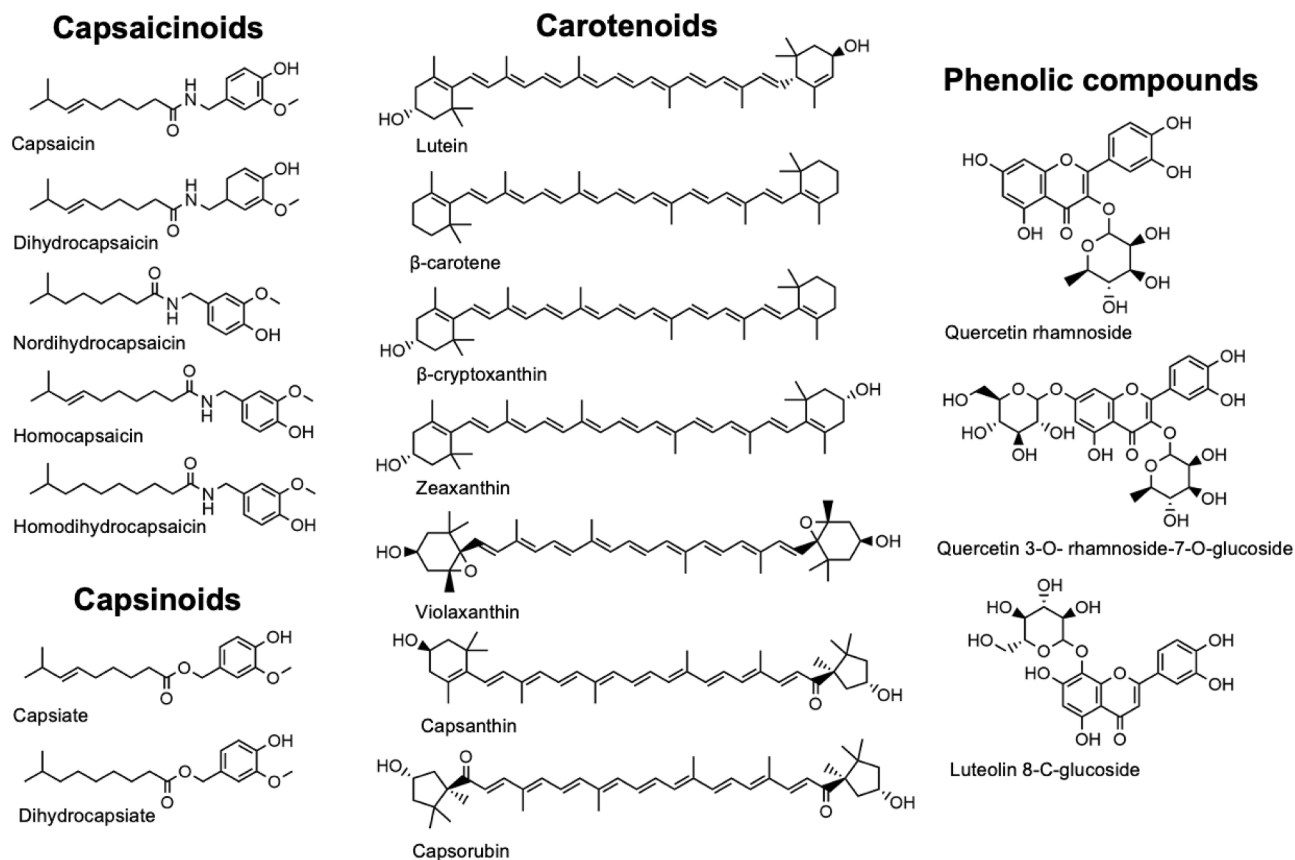


Fig. 1. Chemical structure of main bioactive compounds found in *Capsicum* ssp. Peppers.

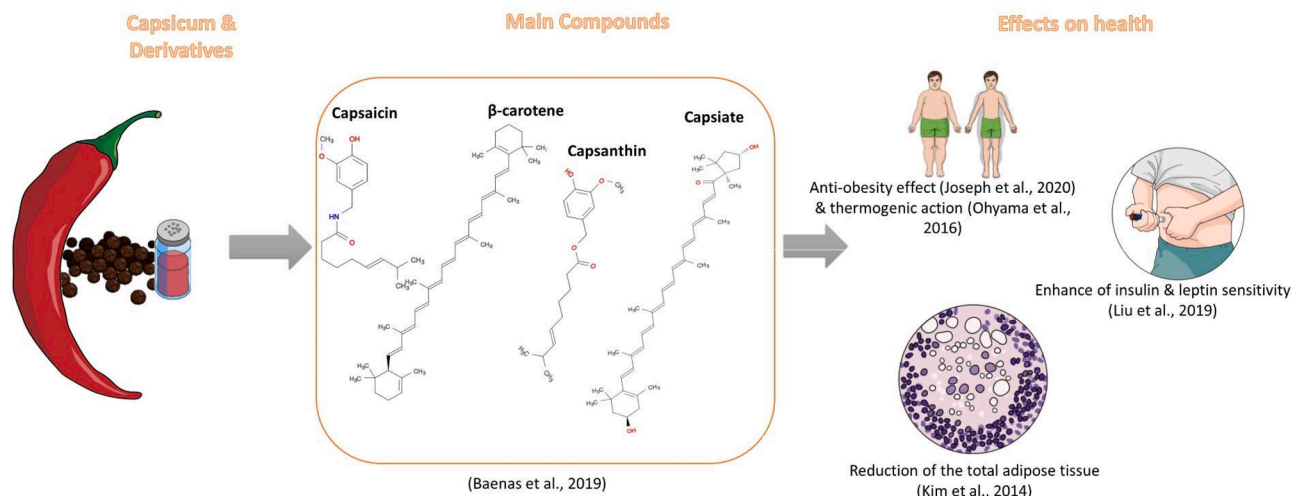


Fig. 2. Schematic illustration of Capsicum and derivatives compounds and their benefits on human health.

content, mainly due to the maturation stage and genetic aspects, but are also influenced by cultivation practices and processing conditions. Carotenoids showed excellent antioxidative (Matsufuji, Nakamura, Chino & Takeda, 1998; Nishino et al., 2015) and anticancer (Deli et al., 1995; Molnár et al., 2012; Murakami et al., 2000) activities. Additionally, a positive link between higher dietary intake and tissue concentrations of carotenoids and lower risk of chronic diseases is suggested, based on epidemiological studies (Johnson, 2002; Rao & Agarwal, 2011).

Capsicum peppers are also known as good sources of phenolic compounds, predominantly hydroxybenzoic and hydroxycinnamic

acids, flavonoids and their glycosides (Morales-Soto, Gómez-Caravaca, García-Salas, Segura-Carretero & Fernández-Gutiérrez, 2013). Phenolic compounds are chemically defined as substances having an aromatic ring with one or more hydroxyl substituents, including their functional groups, which are secondary metabolites often synthesized by plants. They are widely distributed in plants, performing various functions such as protection against UV rays, and acting as attractive pollination (Naczek & Shahidi, 2004). In fruits of Capsicum peppers, phenolic compounds confer color, flavor and aroma, besides being involved in the mechanisms of protection against oxidative agents (Padilha, Pereira, Munhoz,

Vizzoto, Valgas & Barbieri, 2015; Baenas et al., 2019). Thus, the content of phenolic compounds can be a good indicator of antioxidant capacity in peppers. Physiological properties, such as antiallergenic, anti-arteriogenic, anti-inflammatory, antimicrobial, antithrombotic, cardioprotective and vasodilator are attributed to phenolic compounds. Moreover, their main effect is related to their antioxidant action in food matrices (Balasundram, Sundram & Samman, 2006). Flavonoids and their glycoside derivatives are the most abundant group of phenolic compounds found in Capsicum pepper fruits, and some compounds noteworthy are quercetin rhamnoside, quercetin 3-O-rhamnoside-7-O-glucoside, and luteolin 8-C-glucoside (Morales-Soto et al., 2013; Park et al., 2012; Marín, Ferreres, Tomás-Barberán, & Gil, 2004; Jeong et al., 2011, Aguiar et al., 2019).

Vitamins and minerals are also part of the composition of Capsicum peppers. As for the vitamin content, they have high levels of vitamin C, E ( $\alpha$ -tocopherol), provitamin A and folate (Navarro, Flores, Garrido & Martínez, 2006; Guil-Guerrero, Martínez-Guirado, Reboloso-Fuentes & Carrique-Pérez, 2006; Kantar et al., 2016). The vitamin contents found in the fruits of Capsicum peppers depend on several factors, such as variety, maturation stage, harvest time, post-harvest handling and processing and storage conditions (Baenas et al., 2019). Vitamins C and E can decrease the levels of free radicals and quelling peroxidation reactions in the human organism, being associated with the reduction of the risk of arteriosclerosis, cardiovascular diseases and some types of cancers (Navarro et al., 2006). Minerals usually found in peppers 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 amounts vary significantly with variety, maturity stage and environmental changes during growth (Rubio, Hardisson, Martín, Báez, Martín & Álvarez, 2002; Guil-Guerrero et al., 2006).

Based on the rich nutritional composition of fruits of Capsicum peppers, there is an increasing interest in the development of sustainable industrial processes that enable the maximum use of this plant material, such as supercritical fluid-based industrial processes.

### Supercritical fluid extraction to obtain bioactive compound from Capsicum peppers

The interest in new extraction processes of bioactive compounds for analytic and industrial purposes has arisen in the past two decades, driven by the increasing number of scientific papers demonstrating the efficacy of such compounds against several diseases (Herrero, Castro-Puyana, Mendiola & Ibañez, 2013) and by the needs of using environmentally friendly techniques (Dias, Aguiar & Rostagno, 2021). The target compounds in natural products, including peppers, are traditionally obtained after exhaustive extraction of the sample using solid-liquid extraction techniques (Wijngaard, Hossain, Rai & Brunton, 2012). Solid-liquid extraction techniques can be divided into convective or classic techniques such as Soxhlet extraction, maceration, stirring-assisted, and hydrodistillation; and the non-convective or modern techniques that include pulsed-electric field extraction, UAE, EAE, MAE, SFE, and PLE (Azmir et al., 2013; Baenas et al., 2019; Viganó & Martínez, 2015). Non-convective extraction techniques present some advantages over the classical ones, such as the use of less amount of solvents, short extraction times, high-throughput, specificity, extraction under environmentally friendly conditions and scalability (Azmir et al., 2013; Baenas et al., 2019; Herrero et al., 2013). This review will focus on supercritical fluids and fluids mixtures extraction processes because they have the additional advantage of enhanced target molecule specificity and speed due to physicochemical properties of the solvent, such as density, diffusivity, viscosity and dielectric constant, which are controlled by varying pressure and temperature of the extraction system (Wijngaard et al., 2012).

Supercritical fluid extraction has been extensively used to obtain target compounds from a variety of matrices at laboratory and industrial

scale. In the laboratory-scale, the usual motivations are to recover the target analyte for quantification and provide optimal extraction conditions for these compounds with a view to scaling-up to commercial applications (Wijngaard et al., 2012).

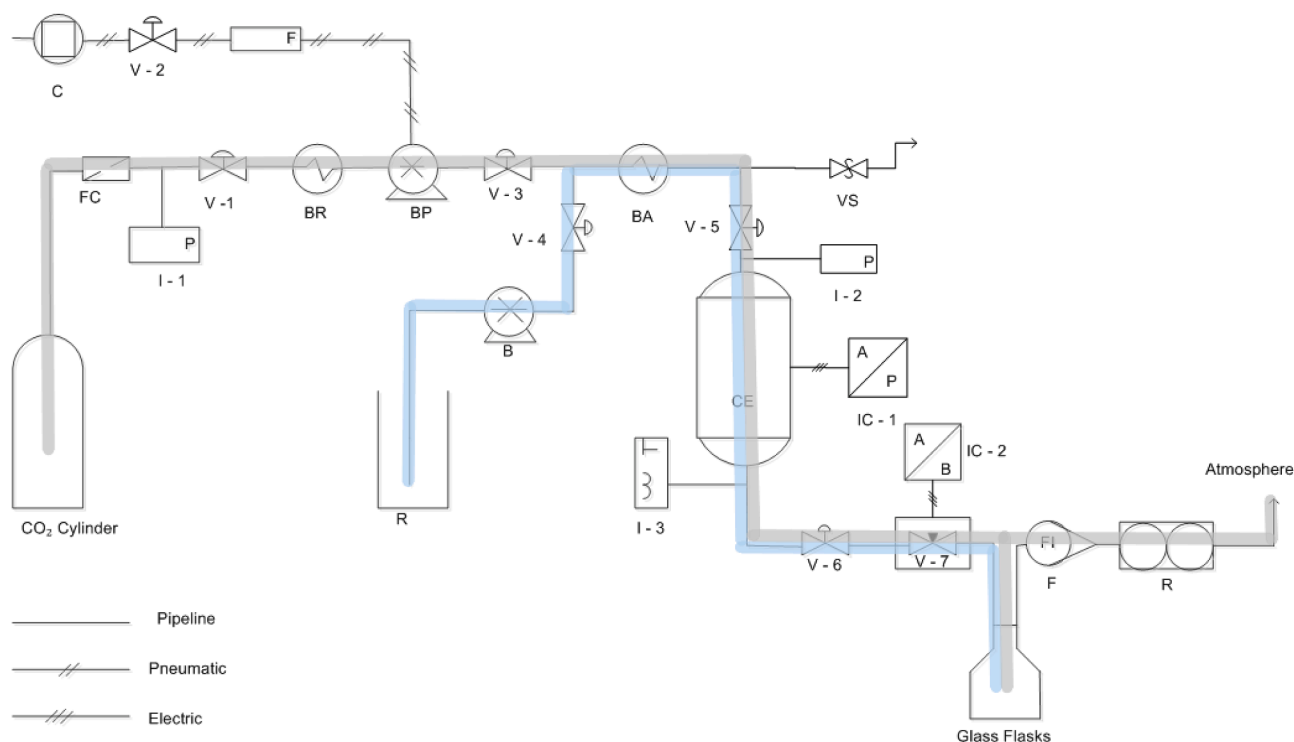
In order to define the SFE principle, it is important to understand what a supercritical fluid is. Pure substances can be found in nature in three states: solid, liquid and gas. The supercritical state is distinctive and can only be attained if a substance is subjected to temperature and pressure beyond its critical point. The critical point of a substance is defined as a characteristic temperature ( $T_c$ ) and pressure ( $P_c$ ) above which distinct gas and liquid phases do not exist (Herrero et al., 2013). Processes based on supercritical fluids take advantage that the fluid behaves as a gas, with gas properties of diffusion, viscosity and surface tension, and as liquid, assuming the density and solvation properties of liquids. In addition to these properties, the supercritical fluid cumulates tunability of thermodynamic and transport properties with favorable techno-economical features (Caputo, Fernández, Saldaña & Galia, 2013).

A large variety of solvents is available for use as supercritical fluid, including carbon dioxide, nitrous oxide, ethane, propane, *n*-pentane, ammonia, fluorofom, sulfur hexafluoride and water. However, carbon dioxide ( $\text{CO}_2$ ) is the most chosen solvent, as it can easily reach supercritical conditions ( $T_c$  of 31.1 °C and  $P_c$  of 74 bar) and has clear advantages (e.g., low toxicity, inflammability and cost and high purity) over other fluids (Zougagh, Valcárcel & Ríos, 2004). Moreover, separation of solute from solvent can easily be achieved by depressurization of the supercritical fluid, and the recycling and reuse of supercritical  $\text{CO}_2$  are possible, thus minimizing waste generation (Azmir et al., 2013). Supercritical  $\text{CO}_2$  extraction processes present an important advantage over low-pressure methods based on the tunability properties, i.e., the supercritical  $\text{CO}_2$  selectivity can be adjusted by varying temperature and pressure to obtain fractions containing specific compounds (Viganó et al., 2016). A disadvantage of using supercritical  $\text{CO}_2$  (sc- $\text{CO}_2$ ) as solvent is its low polarity, which makes it ideal for lipid, fat and non-polar substances, but unsuitable for most pharmaceuticals and drug samples. Such limitation can be overcome by using modifiers or co-solvents such as ethanol and water (Azmir et al., 2013; Wijngaard et al., 2012).

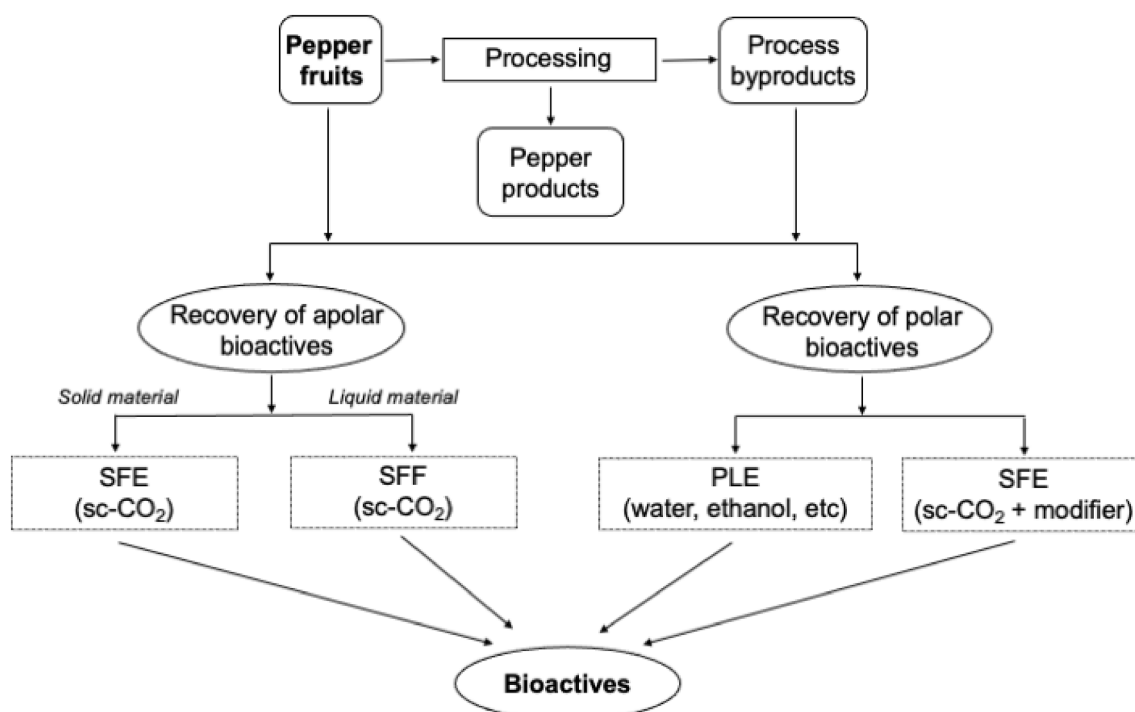
The basic SFE process is carried out in solid matrixes through the continuous contact between the solvent and the solid phase. In most cases, the solid is placed in a fixed bed and the solvent flows through it. After the extraction procedure, the solvent loaded with the extracted solute leaves the extractor and migrates to a precipitator separator, where it is precipitated. The precipitation of the solute is made by simple pressure reduction (Aguiar, Osorio-Tobón, Silva, Barbero & Martínez, 2018). A lab-scale SFE unit is represented in Fig. 3.

The main variables influencing the SFE efficiency are temperature, pressure, particle size and moisture content of feed material, flow rate of  $\text{CO}_2$  and solvent-to-feed ratio (Dias, Aguiar & Rostagno, 2021). However, most studies focus efforts on the study of temperature and pressure effects. The temperatures used in SFE are generally between 40 and 70 °C. The lower limit is due to the proximity of the critical temperature of  $\text{CO}_2$ , and the upper limit affects the density of the solvent. Lower densities are achieved with increasing temperature, resulting in lower extraction yield and high energy consumption. Regarding pressure, most works explore the range from 100 to 500 bar. Pressure has the opposite effect of temperature on  $\text{CO}_2$  density, i.e., increasing the pressure the density of  $\text{CO}_2$  increases, and consequently, high solvation capacity is reached. Pressures above the presented range lead to high energy costs and lower pressures approach of the critical  $\text{CO}_2$  pressure (Viganó & Martínez, 2015).

Regarding the recovery of bioactive compounds from Capsicum peppers, pure sc- $\text{CO}_2$  is used to extract preferentially nonpolar compounds, as shown in Fig. 4. Capsicum oleoresin is the nonpolar extract with the greatest industrial interest due to its applications in the food and pharmaceutical industries. The traditional extraction process of



**Fig. 3.** Example of an extraction unit for single SFE and PLE process, and sequential extraction (SFE + PLE); highlighted gray line (—) indicates the components used for the SFE and highlighted blue line (—) indicates the components used for the PLE; V-1 to V-6: block valves; V-7: micrometer valve; VS: safety valve; C: compressor; F: air filter; FC: CO<sub>2</sub> filter; BR: cooling bath; BP: CO<sub>2</sub> pump; BA: heating bath; CE: jacketed extraction column; R: solvent reservoir; B: HPLC pump; I-1 and I-2: pressure indicators; I-3: temperature indicators; IC-1 and IC-2: temperature controller; F: flow meter; R: flow totalizer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 4.** Basic paths of fresh pepper/residue processing and the subsequent bioactive compounds recovery through high-pressure extraction technologies.

peppers oleoresin consists of extraction from dried and ground pepper with organic solvents, usually *n*-hexane (Aguiar, Sales, Coutinho, Barbero, Godoy & Martínez, 2013). However, the presence of solvent

residues in the extract is strictly controlled by legislation due to *n*-hexane toxicity. The lipophilic nature of the compounds found in peppers oleoresin, and therefore their high solubility in *sc*-CO<sub>2</sub>, make SFE a

suitable technology for obtaining this extract, besides having environmental and quality advantages over the conventional techniques, as already mentioned.

The research on obtaining oleoresin and other bioactive compounds from peppers with supercritical fluids began in the late 1970 s (Hubert & Vitzthum, 1978) and since then, many scientific papers have been published. Different experimental strategies were used to obtain Capsicum pepper extracts with supercritical technology, such as the use of different solvents (CO<sub>2</sub> and propane), use of modifiers together with sc-CO<sub>2</sub> to change the polarity range of the extracted bioactive compounds, processes in multiple stages for obtaining different classes of compounds, intensification of the SFE process by the simultaneous application of ultrasound waves, studies of oleoresin solubility in sc-CO<sub>2</sub> and cost estimations of SFE processes. Next, we will comment on the main studies in each of the areas mentioned above.

### Supercritical fluid extraction with pure solvents (CO<sub>2</sub> and propane) and CO<sub>2</sub> plus modifiers

The first published articles on SFE of bioactive compounds from Capsicum peppers investigated the use of pure CO<sub>2</sub>/propane and the addition of modifiers. Initially, extraction processes with multiple stages were proposed to recover fractions of different compounds, such as fractions rich in capsaicinoids and carotenoids. Tables 1 and 2 summarize relevant studies regarding the application of SFE to obtain extracts from peppers using pure solvents (CO<sub>2</sub> and propane) and CO<sub>2</sub> plus modifiers as solvents, respectively.

Yao, Nair and Chandra (1994) extracted capsaicin and dihydrocapsaicin using sc-CO<sub>2</sub> and organic solvents at low pressures from *Capsicum annuum* var. Scotch Bonnet. The proposed extraction process consisted of two steps at 50 °C: the first at 405 bar for 30 min and the

**Table 1**

Main studies using pure sc-CO<sub>2</sub> and/or subcritical propane to extract bioactive compounds from peppers.

Raw material	Extract/isolated compound	Solvent	Extraction condition	Reference
<i>C. annuum</i> var. Scotch Bonnet	Capsaicin and dihydrocapsaicin	CO <sub>2</sub>	SFE in two stages: 405 bar/50 °C/30 min and 608 bar/50 °C/90 min	Yao, Nair and Chandra (1994)
Sweet paprika, chilli sweet	Aroma and colour fractions	CO <sub>2</sub>	SFE in two stages: 500 to 700 bar/60 °C	Lack and Seidlitz (1996)
Paprika	Aroma and color fractions	CO <sub>2</sub>	SFE in two stages: 150 bar/40 °C and 400 bar/40 °C	Škerget, Knez and Novak (1998)
Paprika <i>C. annuum</i>	Carotenoids, tocopherols and capsaicinoids	CO <sub>2</sub> Subcritical propane	CO <sub>2</sub> : 100–400 bar/35 and 55 °C Propane: 50 bar/25 °C	Gnayfeed, Daood, Illes and Biacs (2001)
Paprika <i>C. annuum</i> L.	Oleoresin, carotenoids, tocopherols and capsaicinoids	CO <sub>2</sub> Subcritical propane	CO <sub>2</sub> : 35–55 °C/100–400 bar Propane: 25 °C/50–80 bar Solvent rate: 1.0 to 1.5 mL/min	Daood, Illés, Gnayfeed, Mészáros, Horváth and Biacs (2002)
Jalapeño pepper <i>C. annuum</i> L.	Oleoresin	CO <sub>2</sub>	120 bar (4 h) and 320 bar (3 h)/40 °C	del Valle, Jiménez and de la Fuente (2003)
Chilli	Oleoresin	CO <sub>2</sub> Subcritical propane	CO <sub>2</sub> : 300 bar/35, 40, 50 and 60 °C Subcritical propane: 40 bar/35, 40, 50 and 60 °C	Catchpole, Grey, Perry, Burgess, Redmond and Porter (2003)
Chilli pepper var. Byedige	Capsaicinoids Colour components	CO <sub>2</sub>	100 to 400 bar/40, 60 and 80 °C	Perva-Uzunalić, Škerget, Weinreich and Knez (2004)
Red pepper <i>C. frutescens</i>	Oleoresin	CO <sub>2</sub>	150 to 230 bar/40 °C Superficial velocity: 0.041 to 0.081 cm/s	Duarte, Moldão-Martins, Gouveia, Costa, Leitão and Bernardo-Gil (2004)
Red pepper <i>C. annuum</i>	Oleoresin	CO <sub>2</sub>	320–540 bar/40 °C Particle diameter: 0.273 to 3.90 mm Superficial velocity: 0.057–0.125 cm/s	Uquiche, del Valle and Ortiz (2004)
<i>Capsicum annuum</i> L.	Capsidiol	CO <sub>2</sub>	100, 200, 250, 300, 350, 400 and 500 bar/40, 50 and 60 °C CO <sub>2</sub> flow rate: 0.5, 1 and 2 cm <sup>3</sup> /min Particle diameter: 116, 231, 463 and 655 μm	Salgın, Üstün, Mehmetoğlu and Çalimli (2005)
Paprika <i>Capsicum annuum</i> L.	Oleoresin	CO <sub>2</sub>	450 bar/50 °C CO <sub>2</sub> flow rate: 7 kg/h Extraction time: 200 to 600 min	Nagy and Simándi (2008)
Paprika Aleva N.K. variety	Oleoresin	CO <sub>2</sub>	200, 300 and 400 bar/40 °C CO <sub>2</sub> flow rate: 3.59 g/min	Tepić, Zeković, Kravić and Mandić (2009)
Malagueta pepper <i>Capsicum frutescens</i>	Oleoresin	CO <sub>2</sub>	150, 250 and 350 bar/40, 50 and 60 °C CO <sub>2</sub> flow rate: 1.98x10 <sup>-4</sup> kg/s Extraction time: 320 min	Aguiar, Sales, Coutinho, Barbero, Godoy and Martínez (2013)
Red pepper <i>Capsicum frutescens</i>	Oleoresin	CO <sub>2</sub>	150 bar/40 °C	Silva and Martínez (2014)
Biquinho pepper <i>Capsicum chinense</i>	Oleoresin	CO <sub>2</sub>	150, 200 and 250 bar/40, 50 and 60 °C CO <sub>2</sub> flow rate: 2.15 × 10 <sup>-4</sup> kg/s Solvent/Feed: 420 kg CO <sub>2</sub> /kg feed	Aguiar, Santos, Coutinho, Barbero, Godoy and Martínez (2014)
Malagueta pepper <i>Capsicum frutescens</i> L.	Oleoresin	CO <sub>2</sub>	150 bar/40 °C Solvent/Feed: 600 kg CO <sub>2</sub> /kg feed Extraction time: 60 to 24 min US power: 200 to 360 W Particle diameter: 0.23, 0.94 and 1.43 mm	Santos, Aguiar, Barbero, Rezende and Martínez (2015)
Dedo de moça pepper <i>Capsicum baccatum</i> L. var. pendulum	Oleoresin	CO <sub>2</sub>	150, 200 and 250 bar/40, 50 and 60 °C US power: 200, 400 and 600 W Extraction time: 40, 60 and 80 min CO <sub>2</sub> flow rate: 1.7569 × 10 <sup>-4</sup> kg/s	Dias, Sergio, Santos, Barbero, Rezende and Martínez (2016)
<i>Capsicum frutescens</i>	Oleoresin	CO <sub>2</sub>	100 bar/35 °C/30 min	Farahmandfar, Asnaashari and Sayyad (2017)

SFE: supercritical fluid extraction; US: ultrasound.



**Table 2**  
Main studies using sc-CO<sub>2</sub> plus modifiers to extract bioactive compounds from peppers.

Raw material	Extract/isolated compound	Extraction solvent/modifier	Extraction condition	Reference
<i>C. frutescens</i> L. <i>C. annuum</i> L.	Capsaicinoids	CO <sub>2</sub> Modifiers: methanol, acetic acid, water	SFE in static and dynamic methods 45 to 75 °C CO <sub>2</sub> flow rate: 1.0 mL/min CO <sub>2</sub> density: 0.75 to 0.9 g/ mL	Peusch, Müller-Seitz, Petz, Müller and Anklam (1997)
Paprika <i>C. annuum</i> L.	Oleoresin	CO <sub>2</sub> Modifier: 1% (w/w SCF-CO <sub>2</sub> ) ethanol and acetone	Continuous and discontinuous SFE 40 °C/138, 206, 276, 345, 413, and 483 bar CO <sub>2</sub> flow rate: 5.8 g/min CO <sub>2</sub> extraction volumes: 50, 100 and 200 L 331 bar/60 °C	Jarén-Galán, Nienaber and Schwartz (1999)
Capsicum annuum	Oleoresin	CO <sub>2</sub> Modifier: 20% ethanol	Extraction time: 5 min static/20 min dynamic	Richins, Hernandez, Dungan, Hambly, Holguin and O'Connell (2010)
Red pepper Capsicum annuum L.	Seed oil	CO <sub>2</sub> Modifier: ethanol	Box–Behnken factorial design Pressure: 150, 225 and 300 bar Temperature: 35, 45 and 55 °C Modifier concentration: 0, 7.5 and 15% CO <sub>2</sub> flow rate: 2000 mL/h 200, 240 and 300 bar/ 45 and 60 °C Extraction time 90 and 120 min modifier flow rate: 300 mL/h	Li, Song, You, Sun, Xia and Suo (2011)
Capsicum annuum L. variety Piquillo by- products	Oleoresin	CO <sub>2</sub> Modifier: ethanol	CO <sub>2</sub> flow rate: 2000 mL/h 200, 240 and 300 bar/ 45 and 60 °C Extraction time 90 and 120 min modifier flow rate: 300 mL/h	Romo- Hualde, Yetano- Cunchillos, González- Ferrero, Sáiz- Abajo and González- Navarro (2012)
Capsicum annuum L.	Carotenoids and phenolic fractions	CO <sub>2</sub> Modifier: ethanol	Carotenoids fraction 400 and 700 bar/40 and 60 °C (180 min) CO <sub>2</sub> flow rate: 10 kg/h Phenolic fraction Ethanol + CO <sub>2</sub> (50% w/w) and pure ethanol 300 and 500 bar/50 and 80 °C (180 min)	Venturi, Sanmartin, Taglieri, Andrich and Zinnai (2017)
Dried capsicum fruit	Capsaicinoids	CO <sub>2</sub> Modifier: ethanol	240 to 400 bar/ 30 to 50 °C CO <sub>2</sub> flow rate: 20 L/h (90 min)	Yan, Zhao, Tao, Zou and Xu (2018)

SFE: supercritical fluid extraction.

second at 608 bar for 90 min. The sc-CO<sub>2</sub> extraction yields for capsaicin (3.2%) and dihydrocapsaicin (0.58%) were approximately 6.4-fold higher than those obtained with organic solvent extraction. Later, Lack and Seidlitz (1996) investigated the sc-CO<sub>2</sub> extraction of color and aroma fractions from paprika, applying a two-stage process. The investigated pressures ranged from 500 to 700 bar at a fixed temperature of 60 °C. The authors found that the increase in pressure did not influence the color value. Still, the extraction time or the CO<sub>2</sub> throughput could be reduced to 50% with increased extraction pressure.

Peusch et al. (1997) determined the concentration of capsaicinoids in extracts obtained with sc-CO<sub>2</sub> from paprika and chili pepper. The authors observed that the SFE technique proved to be efficient and the yields obtained were comparable to those resulting from extraction with organic solvents. Škerget, Knez and Novak (1998) separated paprika components (aromatics and colorants) by employing a two-stage sc-CO<sub>2</sub> extraction process. They determined the optimal operating pressure and temperature (150 bar and 40 °C) for the recovery of aromatic compounds; as for the separation of coloring agents, the optimal pressure condition was 400 bar. The authors also correlated their findings with solubility data of β-carotene in CO<sub>2</sub> (Škerget & Knez, 1997), which were in the range from 0.6 to 5.5 g/m<sup>3</sup> (100–300 bar, 25 and 40 °C). Jarén-Galán, Nienaber and Schwartz (1999) studied the preparation of extracts from paprika, focusing on obtaining pigments (capsorubin, capsanthin, zeaxanthin, β-cryptoxanthin, and β-carotene). They investigated continuous and discontinuous extraction with sc-CO<sub>2</sub> and traditional methods with acetone and hexane. At constant pressure, increasing the extraction volume (50 to 200 L), as well as at constant extraction volume and increasing the pressure (140 to 480 bar), promoted an increase in the capsanthin concentration of the extract. The best conditions for the discontinuous extraction were: the first step at 137 bar, which was able to extract the oil fraction almost completely; followed by a second step at 413 or 482 bar, which produced the highest extraction yield of pigments, 2-fold higher than the pigment concentration obtained by traditional extraction methods.

Besides CO<sub>2</sub>, Gnayfeed et al. (2001), Daood et al. (2002) and Catchpole et al. (2003) also investigated the use of propane as a high-pressure solvent to obtain bioactive compounds from Capsicum peppers. In the work performed by Gnayfeed et al. (2001), paprika was subjected to extraction with sc-CO<sub>2</sub> and subcritical propane under different conditions of pressure and temperature, and the extracts obtained were evaluated in terms of global yield, carotenoid, tocopherol and capsaicinoids contents. The results indicated that the different extraction conditions affected the global extraction yield when CO<sub>2</sub> was used as a solvent. In contrast, the propane extraction yields remained fairly constant and the extraction conditions influenced the quantitative distribution of the bioactive compounds in the extract. For instance, sc-CO<sub>2</sub> was inefficient in the extraction of diesters of xanthophylls even at 400 bar and 55 °C, whereas capsaicinoids and tocopherols were easily extracted at these conditions. Under mild conditions, subcritical propane was better than sc-CO<sub>2</sub> in the extraction of carotenoids and tocopherols, but less efficient in the extraction of capsaicinoids. Daood et al. (2002) determined the contents of carotenoids, tocopherols and capsaicinoids in paprika extracts obtained with sc-CO<sub>2</sub> and subcritical propane. The results were similar to those obtained previously by Gnayfeed et al. (2001): highest carotenoid recovery in extract and most of the capsaicinoid extraction efficiency were achieved with sc-CO<sub>2</sub> at 400 bar and 35 and 55 °C, respectively; while subcritical propane led to low extraction efficiency of capsaicinoids and extracts with color content 4–5 times higher than that of sc-CO<sub>2</sub>. Catchpole et al. (2003) extracted spices (including Capsicum chili powder) using CO<sub>2</sub>, propane and dimethyl ether to determine the global yield and extraction efficiency of selected pungent components. The authors found that yields of capsaicin obtained by sc-CO<sub>2</sub> and dimethyl ether were similar and approximately twice that extracted by propane.

The sc-CO<sub>2</sub> extraction kinetics of pre-pelletized Jalapeño peppers was studied by del Valle, Jiménez and de la Fuente (2003). The authors

evaluated the effect of sample particle size ( $D_p$ ) and solvent superficial velocity ( $U_s$ ) under conditions of 40 °C and 120 or 320 bar on extraction kinetics. The extraction rate increased with decreasing  $D_p$  and with increasing  $U_s$  at 120 bar. The values of the external mass transfer coefficient ( $k_f$ ) were directly proportional to  $U_s$  and inversely proportional to  $D_p$  and pressure. Besides, the authors found that the pseudosolubilities of Capsicum oleoresin were in the same order of magnitude as corresponding capsaicin solubilities. The influence of operating parameters (pressures from 100 to 400 bar and temperatures of 40, 60 and 80 °C) on the SFE ( $\text{CO}_2$  as solvent) of capsaicinoids and colorants from chili peppers was studied by Perva-Uzunalić et al. (2004). The results indicated that the total extraction yield and capsaicinoid extraction efficiency increased with pressure at constant temperature. The highest global yield (12.8%) was obtained at 400 bar and 40 °C, in which approximately 96% of capsaicinoids and 80% of colorants were recovered. Duarte et al. (2004) investigated the influence of sc- $\text{CO}_2$  superficial velocity and pressure on oleoresin and capsaicinoids extraction from red peppers. A central non-factorial composite design was used to optimize the extraction process. At 10 min of extraction, an optimal value of the oleoresin yield (5.2% w/w) was determined for a pressure of 215 bar, and superficial velocity of 0.071 cm/s and an optimal value of the capsaicinoids yield (0.252% w/w) was observed at 205 bar and 0.064 cm/s. Uquiche, del Valle and Ortiz (2004) studied the kinetics of extracting oleoresin from pelletized red pepper with sc- $\text{CO}_2$  at 40 °C as a function of particle size (0.273 to 3.90 mm), pressure (320 to 540 bar) and superficial solvent velocity (0.57 to 1.25 mm/s). The solute partition between the solid matrix and the solvent ( $K$ ) was estimated from the initial slope of cumulative plots of oleoresin yield versus specific solvent mass. The  $K$  value did not depend on particle diameter and superficial velocity. The authors also observed that the yield of oleoresin and carotenoid pigments increased, and  $K$  decreased with the increasing of extraction pressure.

In addition to compounds such as pigments, capsaicinoids and tocopherol, sc- $\text{CO}_2$  was also studied to obtain capsidiol, which is a phytoalexin produced by Capsicum peppers in response to fungal infection. Salgin et al. (2005) evaluated the effect of temperature, pressure,  $\text{CO}_2$  flow rate, particle diameter and initial concentration of capsidiol on solubility, initial extraction rate and extraction yield of SFE. The authors reported that the optimum extraction conditions among those evaluated were temperature of 40 °C, pressure of 400 bar, solvent flow rate of 2.0  $\text{cm}^3/\text{min}$  and particle diameter of 116  $\mu\text{m}$ .

Later, Nagy and Simándi (2008) investigated the effects of sample particle size, moisture and initial oil contents on the efficiency of SFE of paprika. The authors observed that a decrease in particle size increased extraction efficiency. Moisture content between 7 and 18% had a negligible effect on the extractability of oil; however, above 18%, the presence of water decreased the oil extraction efficiency. Tepić et al. (2009) conducted experiments to examine the influence of conventional (hexane) and sc- $\text{CO}_2$  extractions of paprika on the quality of oleoresin. The extraction yield for hexane was 12.8%, whereas for sc- $\text{CO}_2$  it was 10.6, 10.6, and 10.3% at 200, 300, and 400 bar, respectively. The authors confirmed that the organic solvent was less selective than sc- $\text{CO}_2$ , since the analyses of fatty acid composition showed that oleoresin consisted mostly of linoleic acid. On the other hand, sc- $\text{CO}_2$  was not appropriate to recover pigments, reaching 44.9% of the total obtained by the conventional hexane extraction. In 2010, Fernández-Ronco et al. published a study evaluating the effect of pressure (140 to 300 bar) and temperature (40 to 60 °C) on the yield and commercial value of the oleoresin of Capsicum peppers, obtained by SFE through the response surface methodology (RSM). The analysis by RSM evidenced the effect of the factors on the variables and found that linear terms could describe almost all the responses in the correlations. Therefore, linear correlations were proposed over the pressure and temperature range studied. The operational condition of 300 bar and 60 °C was selected as the best to obtain the oleoresin among the studied conditions.

Richins et al. (2010) described a process for the extraction of red

pigments using sc- $\text{CO}_2$ . The optimal SFE process consisted of two stages. First, 20% ethanol as a modifier for 5 min static, followed by 20 min dynamic at 60 °C and 331 bar. Then, the modifier was removed, and the sample as re-extracted using the same process conditions of the first stage. The authors stated that the proposed method could reduce the use of hazardous solvents for the extraction of pigments.

Capsicum pepper seeds and by-products were also submitted to SFE to obtain bioactive compounds. Li et al. (2011) applied a Box–Behnken factorial design to optimize the SFE conditions of pressure, temperature and concentration of modifier (ethanol) in the recovery of the oily fraction of Capsicum fruits seeds. The optimum conditions were pressure of 271.7 bar, temperature of 47.67 °C and concentration of modifier of 8.11 % vol., which led to an oil yield of 18.4%. Romo-Hualde et al. (2012) proposed an extraction process followed by the stabilization of vitamins from red pepper by-products. SFE was used for the extraction step, and the experimental condition of 60 °C, 240 bar and particle size of 0.2 to 0.5 mm resulted in the highest extraction yield of red-colored oleoresin. Subsequently, the SFE extract was microencapsulated by spray-drying using arabic gum as wall material to avoid the degradation of vitamin over the storage time.

The SFE process for obtaining bioactive compounds from Capsicum peppers native to the Brazilian territory was studied by Aguiar et al. (2013) and Aguiar et al. (2014). Initially, the authors selected a pepper variety with a high concentration of capsaicinoids and evaluated the SFE process under different experimental conditions of pressure and temperature. Malagueta pepper showed the highest levels of capsaicinoids (1516  $\mu\text{g}/\text{g}$  fresh fruit). For the capsaicin and dihydrocapsaicin contents, SFE at 150 bar and 40 °C led to the best yields (Aguiar et al., 2013). After that, the authors studied the effect of SFE pressure and temperature on the recovery of capsaicinoids and capsinoids from Biquinho peppers and compared its performance with low-pressure extraction techniques using organic solvents (hexane, ethanol, acetone and methanol). The extraction yields varied depending on the solvent used for the low-pressure techniques. For total extraction yield, the best condition was Soxhlet extraction using methanol as solvent. In terms of capsaicinoids and capsinoids, the best extraction yields were obtained with maceration using ethanol as solvent and Soxhlet extraction using acetone as solvent, respectively. Although SFE has provided low extraction yields (0.0049–0.0134 g extract/g freeze-dried pepper) compared to low-pressure techniques, the extract obtained at 60 °C and 15 MPa showed a high concentration of capsinoids (28.5 mg/g extract). Regarding the global extraction yield, the best conditions to extract capsaicinoids and capsinoids were 40 and 50 °C at 15 MPa, with values of 0.004 and 0.17 g/g freeze-dried pepper, respectively. According to the authors, the solubilities of capsaicinoids in  $\text{CO}_2$  at 15 MPa and 50 °C are probably higher than those of other compounds found in pepper oleoresin, such as triacylglycerols and carotenoids. The same behavior was also observed for the capsinoids because those compounds have a similar chemical structure to capsaicinoids, with an ester group instead of the amide moiety (Kobata et al., 1998); thus, their solubility in sc- $\text{CO}_2$  must be close to those of capsaicinoids. The results indicated that low-pressure techniques are more efficient in extracting capsaicinoids and capsinoids. However, the extracts obtained by SFE have higher concentrations of these compounds, depending on the polarity of  $\text{CO}_2$  at the applied conditions (Aguiar et al., 2014).

The mass transfer phenomenon during the red pepper SFE was evaluated by Silva and Martínez (2014). The authors performed experiments at 150 bar and 40 °C, varying solvent flow rate, particle diameter and extraction bed volume. The highest extraction rates were obtained with high solvent flow rates, low particle diameters and low extraction bed volume. A classical model based on the concept of intact and broken cells was applied to experimental SFE curves, and model parameters were obtained. Two modeling strategies were used: a simultaneous fitting, creating a set of parameters for pairs of duplicates, and a multiple fitting that adjusts a single value for the solute concentration in unbroken cell for curves with equal particle diameter. The multiple fitting

approach presented good results on the application of Sovová's model (Sovová, 1994) to represent SFE curves, since the adjusted extraction curves were close to the experimental data.

Farahmandfar, Asnaashari and Sayyad (2017) compared the extraction of *Capsicum frutescens* peppers using sc-CO<sub>2</sub> to ultrasound-assisted and traditional methods in terms of phenolic, tocopherol and anthocyanin contents; antioxidant activity and the ability of the extract to stabilize soybean oil. Results indicated that sc-CO<sub>2</sub> extraction method was able to preserve the phenolic, tocopherol and anthocyanin contents of peppers and remarkably protect the oil from lipid oxidation. A two-step SFE process composed of a preliminary sc-CO<sub>2</sub> extraction of carotenoids followed by the recovery of polyphenols using sc-CO<sub>2</sub> plus ethanol as modifier from chili pepper and tomato by-products was proposed by Venturi et al. (2017). The authors concluded that chili pepper and tomato were good sources of bioactive antioxidant compounds, and the extraction process from chili pepper was faster than that from tomato under identical operating conditions. Yan et al. (2018) extracted capsaicin and dihydrocapsaicin from *Capsicum* fruits by SFE using CO<sub>2</sub>, and further separated capsaicinoids from the extracts using a two-step enrichment method. The developed process was successfully applied in the purification of capsaicin and dihydrocapsaicin from capsaicinoid crystal.

#### Supercritical fluid extraction assisted by ultrasound (SFE-US)

In the last years, investigations applying SFE assisted by ultrasound to obtain extracts from *Capsicum* peppers were published. Ultrasound-assisted extraction is a technique that applies lower temperatures and shorter extraction times that, when coupled to SFE, can reduce the costs of the extraction process. Ultrasonic waves can enhance the accessibility of the solvent into the vegetable matrix through the rupture of the cell walls of the matrix samples, improving the extraction yields, as well as the increment of the mass transfer coefficients (Dias, Aguiar, & Ros-tagno, 2021).

Santos et al. (2015) applied SFE-US to extract capsaicinoids from malagueta pepper (*Capsicum frutescens* L.) at 150 bar, 40 °C and ultrasound power of 600 W for 60 min. The authors observed an increase in the extraction yield of up to 77% in comparison to SFE without ultrasound. Additionally, they concluded that ultrasound promoted disturbances in the vegetable matrix, leading to the release of extractable material on the solid surface. However, the capsaicinoids and phenolics profiles did not change with the ultrasound application. Dias et al. (2016) performed the capsaicinoids extraction of dedo de moça pepper (*Capsicum baccatum* L. var. *pendulum*) by SFE-US. The process was evaluated at pressures of 150, 200 and 250 bar; temperatures of 40, 50 and 60 °C; and ultrasonic powers of 200, 400 and 600 W during 40, 60 and 80 min of extraction. The authors found that at 250 bar, 40 °C, 600 W and 80 min, the use of ultrasound raised the extraction yield to 45% and the capsaicinoids yield increased up to 12%.

#### Scale-up and cost estimations of SFE from *Capsicum* peppers

Although SFE is well established in some industrial applications, information about its economic viability is still not readily available, which can lead to a certain reluctance of companies to implement SFE in industrial scale, especially in Latin America (del Valle, Jiménez & de la Fuente, 2003). Thus, the evaluation of the economic viability of SFE processes from vegetable and animal matrices is important to encourage the application of this technology in industrial scale. The cost estimation for the production of *Capsicum* oleoresin by sc-CO<sub>2</sub> extraction was investigated by Rocha-Uribe, Novelo-Pérez and Ruiz-Mercado (2014) and Aguiar et al. (2018).

Rocha-Uribe et al. (2014) developed an equation to estimate the costs of industrial-scale SFE systems. They further applied it to calculate the cost of manufacturing (COM) of habanero pepper oleoresin in extraction cells with capacity ranging from 5 to 400 L. A COM of 600 US

\$/kg was calculated based on SFE experimental data obtained in a 0.1 L extraction cell. The authors concluded that SFE to obtain habanero oleoresin presented a good perspective for industrial application, since the estimated selling price of the product was 7000 US\$/kg. Later, Aguiar et al. (2018) performed an economic evaluation of the SFE of capsaicinoids-rich oleoresin from malagueta pepper, considering both oleoresin and total capsaicinoids yields. Based on the results of the SFE simulation, the authors concluded that for the studied conditions (150 bar and 40 °C), the lowest cost of manufacturing based on the total capsaicinoids concentration in the extracts was achieved at 240 min for a 2x0.5 m<sup>3</sup> unit. The COM obtained under this condition (125.41 US \$/kg) was lower than the estimated commercialization price of the extract (223 US\$/kg), which suggests that producing malagueta oleoresin on a large scale by SFE can be economically applicable.

#### Phase equilibrium

Solubility information is of great importance for the estimation of some characteristics of a compound, such as toxicity, bioavailability, metabolism and crystallization (crystal size and morphology). The determination of oleoresin and capsaicinoids solubility in supercritical media is important to choose the appropriate solvent, aiming to optimize the operation conditions (Long, Li, Song & Du, 2011; de la Fuente, Valderrama, Bottini, & del Valle, 2005).

Since *Capsicum* oleoresin is a multicomponent product surrounded by many other compounds (e.g., triglycerides, diglycerides, monoglycerides, fatty acids, carotenoids and capsaicinoids/capsinoids), its solubility can vary in comparison with that of pure capsaicin. A good characterization of the oleoresin and its behavior is crucial to obtain the critical constants to predict the experimental data. Effects of  $\beta$ -carotene on the capsaicin solubility under sc-CO<sub>2</sub> were evaluated for a  $\beta$ -carotene-capsaicin-CO<sub>2</sub> system (Skerget & Knez, 1997). The authors found that  $\beta$ -carotene solubility was not affected by different capsaicin concentrations, whereas capsaicin solubility decreased for higher  $\beta$ -carotene concentrations. In this case, the excess of  $\beta$ -carotene decreased the capsaicin melting point from 60 to 40 °C at 100 bar, and thus its solubilization in the system.

The effects of water and ethanol on the capsaicin solubility under sc-CO<sub>2</sub> were determined by Duarte, Crew, Casimiro, Aguiar-Ricardo and Ponte (2002) from a quaternary system (CO<sub>2</sub> + ethanol + water + capsaicin). Experiments were conducted at pressures of 120–180 bar and temperatures of 40 and 50 °C. The authors observed that for a system richer in water, the less solute-solvent affinity caused a lower capsaicin concentration in the liquid phase, but higher capsaicin content was found in the gas phase. On the contrary, lower separation factors were obtained for a system richer in ethanol, showing that ethanol prevents the extraction of capsaicin to the gaseous phase. Ethanol acts as a co-solvent to carbon dioxide and water, which results in increased solubility of capsaicin in the liquid and gas phases. Nevertheless, this effect is more significant in the aqueous phase, and lower equilibrium concentrations of capsaicin are achieved when extracting richer ethanol mixtures with carbon dioxide. Representative values of capsaicin solubility expressed in terms of mass of capsaicin per mass of carbon dioxide in the gaseous phase at 40 °C and pressures between 12 and 18 MPa ranged from 12.9x10<sup>-6</sup> to 31.5x10<sup>-6</sup> for water-rich mixtures and from 0.16x10<sup>-6</sup> to 0.69x10<sup>-6</sup> for ethanol-rich mixtures.

Fernández-Ronco, Gracia, De Lucas and Rodríguez (2011) evaluated the equilibrium data for the separation of *Capsicum* oleoresin in sc-CO<sub>2</sub> at different pressures (90–130 bar) and temperatures (42–65 °C). The authors observed that the oleoresin solubility increased with pressure in the gas phase due to the rise in the solvent density. Besides, they noticed a small dependence of oleoresin solubility with temperature in the gas phase, whereas in the oil phase the CO<sub>2</sub> solubility decreased with temperature. This behavior can be explained because temperature exerts a decrease in the solvent density and an increase in the vapor pressure of the system. A similar trend was found by Elizalde-Solis and Galicia-Luna

(2006), Kwon et al. (2011) and Fernández-Ronco, Ortega-Noblejas, Gracia, De Lucas, García and Rodríguez (2010) when evaluating the capsaicin solubility in sc-CO<sub>2</sub> from Capsicum peppers.

### Pressurized liquid extraction (PLE) and sequential extraction process (SFE + PLE) as strategies to recovery bioactive compounds from Capsicum peppers

Bioactive compounds can be obtained from fresh peppers or residues from their industrial processing and different high-pressure strategies can be applied, depending on the characteristics of the products of interest. When the objective is the recovery of nonpolar compounds, SFE (CO<sub>2</sub> as solvent) is indicated for solid feeds and supercritical fluid fractionation (SFF) for liquid feeds. On the other side, if the objective is the recovery of compounds with polar characteristics, PLE (using polar solvents) and SFE (CO<sub>2</sub> + polar modifiers) are the most appropriate. Fig. 4 presents the recommended paths of fresh pepper/residue processing and the subsequent recovery of bioactives through high-pressure extraction technologies. In the following sections, we will present the application of PLE and sequential extraction process (SFE + PLE) techniques as alternatives to recover bioactive compounds from Capsicum peppers.

#### Pressurized liquid extraction (PLE)

As previously discussed, supercritical fluid extraction using pure CO<sub>2</sub> as solvent can produce nonpolar extracts. To overcome such limitation and obtain polar extract fractions, pressurized liquid extraction (PLE) can be efficiently employed. Such extraction technique is also known as accelerated solvent extraction (ASE), pressurized hot solvent extraction (PHSE) or pressurized fluid extraction (PFE). According to Herrero et al. (2013), despite several differences in the basic principles of SFE and PLE, these techniques have in common the operation under medium-to-high pressures.

Mustafa and Turner (2011) published a very comprehensive review addressing PLE. According to these authors, PLE is defined as a technique that involves extraction using liquid solvents at elevated temperature and pressure, which enhances the extraction performance when compared to techniques carried out at near room temperature and atmospheric pressure. High solubility and mass transfer are achieved by using the solvents at temperatures above their atmospheric boiling point, maintaining the solvents in the liquid phase by using high pressure, which implies in: i) an increase in the capacity of solvents to solubilize solutes, ii) an increase in diffusion rates, iii) better disruption of solute-matrix bonds, iv) a decrease in viscosity of the solvent and v) decrease in surface tension (Wijngaard et al., 2012). Nevertheless, when dealing with bioactive compounds, temperature has to be carefully examined and optimized, since it is widely known that high temperatures might have negative effects on the bioactivity of thermolabile compounds (Herrero et al., 2013).

The main solvents used in PLE are methanol, isopropanol, acetone, hexane and ether. However, water and ethanol have been increasingly employed in the extraction of polyphenols, such as flavonoids and phenolic acids (Viganó & Martínez, 2015). According to Mustafa and Turner (2011), the use of solvent mixtures of two substances can enhance the extraction by improving the solubility and increasing the interaction with the target compound, i.e., one substance improves the solubility and the other, the solute desorption. Some other PLE variables have been reported to possess a weak effect on extraction efficiency, e.g., pressure and time; regarding pressure, works have pointed out a null influence of the extraction pressure beyond the point at which the solvent is maintained liquid, and pressure range used applied between 35 and 200 bar; about time, there is a dependency on the PLE mode – static or dynamic –, since in the static mode the efficiency is limited by solubility of solute in the solvent, whereas time is an important variable in dynamic mode because fresh solvent is continuously introduced into the

extraction cell (Herrero et al., 2013). Moreover, not very common additives as non-ionic surfactants solutions, protective antioxidants, CO<sub>2</sub> and drying agents can also be used to improve PLE efficiency.

The PLE process could be explained in two stages; the first is called solubility-controlled and the second is known by diffusion-controlled. In samples in which the diffusion-controlled is predominant, there are strong interactions between matrix and analytes or long diffusion paths for the analytes to pass through the sample matrix. In this case, the temperature of the solvent and particle size might be critical factors to enhance the extraction efficiency. On the other hand, in solubility-controlled sample matrices the analyte-matrix interactions are quite weak, and the extraction rate mainly depends on the partitioning of the analyte between the matrix and the extraction solvent. In this case, the efficiency is enhanced by using more frequent replacement with the fresh extraction solvent (Mustafa & Turner, 2011).

Regarding the application of PLE for the extraction of bioactive compounds from Capsicum peppers an important study was performed by Barbero, Palma and Barroso (2006). The authors developed an analytical PLE method to obtain capsaicinoids from Capsicum peppers. They studied the extraction variables: temperature, solvent (methanol, ethanol and water), different percentages of water in methanol (0–20%) and ethanol (0–20%) and the number of extraction cycles. The optimized PLE conditions were pressure of 100 atm (101 bar), temperature of 200 °C, pure methanol as solvent and one extraction cycle.

#### Sequential extraction process (SFE + PLE)

Alongside with the need of enhancing the extraction performance, there is an increasing demand in recent years for industrial green and sustainable extraction processes. Thus, developing and applying sustainable extraction processes means not causing harm to the environment, avoiding damage and depletion of resources (Herrero & Ibañez, 2018). Based on the mentioned principles of sustainable extraction processes, the full use of raw material is highly recommended, minimizing waste generation and maximizing the products obtained from a single raw material. However, natural raw materials exhibit complexity in the composition, which means that a single extraction process would not be able to solubilize several classes of compounds, even because selective extraction methods are expected.

To overcome this drawback, many researchers have proposed process integration to perform a sequence of extractions. Such strategy is also known as a multistep process (Basesmezet et al., 2017), integrated operation processes, multi-unit operation processes (Herrero & Ibañez, 2018), biorefining (Kitrytė, Bagdonaitė & Venskutonis, 2018) and fractionation (Kitrytė, Povilaitis, Kraujalienė, Šulniūtė, Pukalskas & Venskutonis, 2017). This method consists in submitting the same raw material to different extraction techniques and/or the same extraction technique, but at different extraction conditions, in a successive way to obtain different fractions of extract. Interestingly, such choice allows obtaining lipophilic extract fractions rich in minor lipids, fractions containing compounds of higher polarity and further to separate fractions of strongly bonded compounds in the matrix. Fig. 3 shows a schematic representation of an SFE + PLE sequential process unit.

The strategy of performing sequential high-pressure extractions, as defined above, was successfully applied to obtain capsinoids and phenolics compounds from biquinho peppers (*Capsicum chinense*) by Aguiar et al. (2019). In the first step, the non-polar fraction was extracted with sc-CO<sub>2</sub> for the recovery of capsinoids. Then, the sample previously extracted by SFE was submitted to PLE using mixtures of ethanol and water (50, 75 and 100% ethanol) at different temperatures (45, 55 and 65 °C) to recover compounds of higher polarity, mainly phenolics. The SFE yield was 4.75% and the capsiate concentration in the extract was 8.67 mg/g oleoresin. In the PLE stage, the solvent composition influenced the extract yield and quality. Considering the extracted phenolic compounds, the highest concentration of rutin isomer (441 µg/g extract) was obtained with pure ethanol, for vicenin-2,

the best solvent was 50% ethanol (299 µg/g extract), whereas for the extraction of total phenolics 75% ethanol was the most effective solvent. The authors concluded that sc-CO<sub>2</sub> extraction followed by PLE is an interesting alternative to obtain bioactive compounds from Capsicum peppers.

### Trends in encapsulation technologies for food application and delivery of Capsicum and derivatives compounds

As discussed in section 2, Capsicum peppers and their derivatives have a series of bioactive compounds that confer numerous benefits to human health. However, these compounds can present some unappealing characteristics such as susceptibility to oxidation, low bioaccessibility, and the spicy sensory profile (in the case of hot peppers). Therefore, encapsulation techniques have been employed to overcome these drawbacks and develop food-grade formulations rich in Capsicum peppers compounds for safe intake and improved bioaccessibility (Aguiar, Silva, Rezende, Barbero & Martínez, 2016; Aguiar et al., 2021). Encapsulation processes consist of the entrapment of gas, liquid droplets, or solid particles in a thin film. The particles with a size ranging from 1 to 1000 µm are formed with one or more cores surrounded by a single or double-layer (Nazzaro, Orlando, Fratianni & Coppola, 2012). Different materials have been applied to encapsulate bioactive compounds, such as carbohydrates, proteins, or lipids (Jafari, 2017).

Many microencapsulation techniques are extensively employed to encapsulate food ingredients, for instance, spray drying, spray chilling, complex coacervation, ionic gelation, and emulsification. The food industry largely employs the spray drying process due to its low cost, ease of scaling-up, and versatility. In this technique, a liquid emulsion is atomized during a short time of contact with a high-temperature air stream that transforms this liquid into powders with distinct characteristics, like a different size distribution, spherical or polyhedral geometry, teeth concavities in the surface, smooth or rough structure, and surface with or without pores formation (Jafari, 2017). Advantages already mentioned in the literature for spray-dried powders are related to high solubility in water, resistance to low or high pH, protection of volatiles, increased bioavailability, and they are therefore appealing ingredients to apply in food products (Jafari, Assadpoor, He & Bhandari, 2008; Vulić et al. 2019).

Many studies have been carried out to encapsulate Capsicum peppers compounds by spray-drying. As an example, a study involving a combination of chili seed oil extract by sc-CO<sub>2</sub> followed by a spray drying technique was employed to retard the oxidation of oil and then prevent unpleasant taste. The authors used starch sodium octenyl succinate and maltodextrin as emulsifiers and carrier agents, respectively. In turn, microparticles with polyhedral shape, diameter varying from 3 to 20 µm, and a high oil encapsulation efficiency reaching over 94% were obtained (Wang, Liu, Wen, Li, Wang & Ni., 2017).

In another study, Rybak et al. (2020) produced red bell peppers juice (rich in compounds with antioxidant properties) in powder by spray drying. Results showed an average of 2244 mg of total phenolics content/100 g dry matter, a content varying from 605 to 643 mg of β-carotene/100 g dry matter content, and a concentration of vitamin C ranging from 2.2 to 3.6 mg/100 g dry matter content. Similarly, extract from *Capsicum pubescens* in powder also produced by spray drying showed high polyphenols content and high antioxidant activity (Mendes et al., 2020).

Apart from the entrapment of compounds, the spray drying technique combined with wall materials can produce particles resistant to digestion phases. For instance, phenolic compounds and carotenoids from fresh red pepper waste were microencapsulated by spray drying using whey protein as an encapsulating agent. As a result, carotenoids were released in small amounts at simulated gastrointestinal fluids, pointing to resistance against digestive enzymes. In contrast, phenolic compounds were degraded only in the intestinal phase, which was desirable (Vulić et al., 2019).

Capsicum oleoresin emulsions have been formulated by different techniques, especially by methods able to produce nanoemulsions with a mean droplet diameter less than 500 nm, which means a product with a better bioaccessibility of compounds and less spicy taste (Singh et al., 2017; Akbas, Soyler & Oztop, 2018).

Several high-energy methods are employed to produce nanoemulsions, such as ultrasonication, microfluidization, high-pressure, and homogenization. They are chosen according to the droplet size required, type of emulsifier or surfactant used, solid concentration, process parameters, and product application (Zhang, Zhang & McClements, 2020). A range of examples of Capsicum oleoresin nanoemulsions has been documented in the scientific literature. For instance, Akbas, Soyler and Oztop (2018) obtained nanoemulsions by high-pressure homogenization and ultrasonication with droplets smaller than 80 nm. In sequence, the same authors (Akbas, Soyler & Oztop, 2019) prepared nanoemulsions using pre-homogenization with Ultra-Turrax followed by microfluidization. The produced Capsicum oleoresin nanoemulsions showed high antimicrobial activity and droplet size around 35 nm, confirming that the microfluidization technique can make smaller droplet sizes due to the high energy input.

The use of natural emulsifiers is also recommended due to the demand for healthier products. For this reason, the study by Aguiar et al. (2021) evaluated the encapsulation of Capsicum oleoresin by microfluidization using natural emulsifiers (whey protein, pea protein, quillaja saponin and sunflower lecithin). The results showed a reduction of droplet size with the increase of emulsifier concentration. Furthermore, after 15 days of storage at 4 °C, all nanoemulsions were stable for their capsaicin content, mean particle diameter and surface potential, indicating that natural emulsifiers are good alternatives for stabilizing Capsicum peppers derivatives.

Emulsions with smaller droplets can improve the stability of compounds essential to food and pharmaceutical applications mainly because of their bioaccessibility. For example, an interesting study by Kim et al. (2014) showed that mice fed with Capsicum oleoresin nanoemulsions had a more significant reduction of weight when compared to those provided with non-encapsulated oleoresin. The authors concluded that the nanoemulsions could promote better absorption of capsaicinoids by the intestine, improving the thermogenic action of capsaicinoids, which led to mice fat reduction.

Thus, the encapsulation of extracts obtained from Capsicum peppers is an excellent alternative for stabilizing extracts rich in bioactive compounds. Additionally, the encapsulation process can be chosen to optimize the incorporation of Capsicum pepper bioactives in food and pharmaceuticals. However, regarding the positive effects of encapsulation of peppers derivatives on human health, more studies are still necessary to elucidate the action mechanisms and develop systems that meet specific product demands.

### Future perspectives

The current social awareness about the sustainable use of natural resources and the development of industrial processes that cause less impact on the environment, associated with the increasing demand for natural ingredients instead of synthetic substitutes, results in the growing market for functional products obtained with clean technologies.

Capsicum peppers and derived products, such as oleoresin, purified extracts and fractions enriched in bioactive compounds, are potential ingredients for food, pharmaceutical and cosmetic industries. In this sense, the standardization of the cultivation and the production of the derived ingredients conditions in terms of flavor, color (carotenoids content) and pungency (capsaicinoids content) are crucial for the successful application of these ingredients. Furthermore, for the industrial process of obtaining Capsicum derived products, it is necessary to create a solid base for the supply of fresh peppers, with a constant volume of production (to guarantee the availability of fresh pepper to be

processed) associated with cultivation carried out with rigid norms to maintain the quality (in qualitative and quantitative terms of the bioactive compounds) of pepper fruits (Aguiar et al., 2018). On the other hand, food and pharmaceutical industries need to develop new effective green processes, which could achieve the expectations of consumers and result in minimum manufacturing costs. In this sense, a reduction of the amount of organic solvent waste and energy required for the extraction and purification steps, along with the development of higher value derived product formulations, seems to be a good strategy to fulfill the market requirements and increase economic benefits to producers and agribusiness.

The use of high-pressure technology for the processing of Capsicum peppers meets the main sustainability requirements, since it performs well when using GRAS (Generally Recognized as Safe) solvents such as CO<sub>2</sub>, ethanol and water, besides minimizing the use of solvents. High-pressure extraction plants should present flexibility regarding the extraction of different products from Capsicum peppers. The development of refined multistep sequential extraction processes to obtain extracts with bioactive compounds of different classes should be a focus of the food and pharmaceutical industries (Aguiar et al., 2020). Furthermore, to increase the purity of the extracts as well as their commercial value, high-pressure processes as SFE can be coupled to additional downstream separation techniques, such as a membrane separation, adsorption columns or pervaporation processes, avoiding the depressurization step.

Finally, the recovery of bioactive compounds from Capsicum peppers through supercritical fluid technology and fluid mixtures has a wide field to be studied. A more in-depth investigation of the thermodynamic/equilibrium behavior of the solute/solvent systems is recommended, as well as the modeling of the solutes behavior in sub- and supercritical conditions. Besides, the scale-up and the economic analysis of the single and combined extraction processes for different peppers varieties are also necessary for a successful industrial application.

## Declaration of Competing Interest

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

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