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Effect of emerging non-thermal extraction methods on bioactive individual components profile from diverse plant materials

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Abstract
Extraction of bioactive chemicals from plant material is a crucial step in the separation and purification process. Traditional methods such as Soxhlet, heat reflux, and maceration have limitations, leading to the emergence of novel technologies that offer several advantages, including higher extraction yields, preservation of thermo-sensitive structures, and the use of non-organic solvents. These emerging technologies, such as high hydrostatic pressure, pulsed electric fields, and supercritical fluids, enhance mass transfer rates, increase cell permeability, and improve secondary metabolite diffusion, resulting in high-quality extracts with fewer impurities. This research aims to investigate the impact of these emerging extraction methods on the individual profile of bioactive chemicals in plant material.

Keywords: non-thermal extraction, bioactive compounds, high-pressure processing, supercritical extraction, pulse electric field

1. Introduction
Extraction is the initial stage for the recovery (isolation and purification) of essential bioactive chemicals found in herbal materials, and it may be defined as a mass transport phenomenon where components existing in a matrix are moved into the solvent (Lee *et al*., 2011) [1]. The increased interest concerning bioactive components from fruits and vegetables is connected to the consumer preference of natural additives and antioxidants over synthetic ones (Prasad, Yang, Yi, Zhao, & Jiang, 2009) [2]. at general, bioactive substances, such as phenolic compounds, are secondary metabolites of plants, being present at considerably lower levels than constitutive components (lipids, proteins, carbohydrates, and minerals). The fundamental difficulty is that such bioactive chemicals, such as flavonoids and anthocyanins, etc., are found in insoluble structures (for instance, vacuoles of plant cells or bilayers of lipoproteins), which turns its extraction a challenge (Corrales, Toepfl, Butz, Knorr, & Tauscher, 2008) [3]. Many organic components in herbal material are heat sensitive, losing integrity and biological activity via thermal breakdown when treated to heat. The optimal extraction approach is characterized by being adaptable, simple, safe, not very costly, quantitative, non-destructive, and time saving (Lee *et al*., 2011; Zhang, S.-Q., Bi, H., & Liu, C., 2007) [1, 4]. Usually, an extraction process consists in two consecutive steps: (i) combination of the material with the solvent, and (ii) movement of soluble chemicals from the cell into the solvent and its consequent diffusion and extraction (Huang, Hsu, Yang, & Wang, 2013) [5]. The most common extraction procedures include the classic ones, such as Soxhlet, heat reflux, agitation, boiling, leaching-out, and distillation (Huang *et al*., 2013) [5]. However, these techniques are mostly based on the use of mild/high temperatures (50–90 °C) that can cause thermal degradation, are dependent of the correct solvent choice, and the agitation intensity in order to increase the solubility of materials and the mass transfer rate, being reflected on long extraction times, high costs, low extraction efficiency, with consequent low extraction yields (He, Yoon, Park, Park, & Ahn, 2011). Due to these and other problems such as the high prices, high organic solvent consumption, and environmental contamination of the current techniques, it is of interest to develop novel extraction technologies, such as microwave, ultrasounds, supercritical fluids (mainly employing carbon dioxide, SC-CO_2), and high hydrostatic pressure aided extractions (Bursac Kovacevic *et al*., 2018; Giacometti *et al*., 2018; Huang *et al*., 2013) [7, 8, 5]. Nevertheless, some of those new methods still need temperature control (such as microwave-assisted extraction), are confined to the solvents to employ, and are time intensive (Chemat & Cravotto, 2013; Putnik, 2016; Shouquin, Ruizhan, Hua, & Changzheng, 2006) [9, 16, 60].

On the other hand, non-thermal methods may function at refrigerated or room temperatures (RT), guaranteeing that compound denaturation is avoided or at least lessened, as they don't employ high temperatures, facilitating the extraction of such compounds, especially the volatile oils. For so, in this study, the authors intend to examine the effect of such technologies (high hydrostatic pressure, pulsed electric fields, ultrasounds, and supercritical fluid aided extractions) on the bioactive individual chemicals profile from herbal materials.

2. Bio-active Compounds from Plant Materials

Ever since the beginning of human existence, plants have always been a boon for living a healthy life, since they not only give a good place to live, but most importantly, they supply food and bioactive chemicals for therapeutic purposes. In the beginning, plants and plant-related foods were utilised as a source of food and nourishment; subsequently, their therapeutic characteristics were found, which were able to treat ailments. Vinatoru *et al*. 2021 stated that Egyptian papyruses produced oil from coriander and caster.

Additionally, these compounds are classified based on their clinical and toxicological attributes as follows.

2.1 Glycosides

Glycosides are often bound by a mono/oligosaccharide or uronic acids. The component that is bound with saccharide is called glycone and the other part is referred as aglycone, It comprises of pentacyclic triterpenoids/tetracyclic steroids. The key subgroups of glycosides include cardiac glycosides, saponins, anthraquinone, glucosinolates and cyanogenics. Moreover, flavonoids typically appear as glycosides. These glycosides are broken down in intestine following consumption; nevertheless, hydrophobic glycosides tend to be absorbed by the muscle cells. Cardiac glycosides are commonly found in plants such as the Scrophulariaceae family, notably in Digitalis purpura and in *Convallaria majalis* from Convallariaceae family. Additionally, cyanogenic glycosides may be discovered in the Prunus spp. of Rosaceae family as well as saponin, a bitter-tasting component is present in glycosides. These saponin glycosides, found abundantly in the Liliaceas family (Narthesium ossifragum), is made of bigger molecules connected to hydrophilic glycone as well as hydrophobic aglycone, which creates forming quality, and thus it is employed in the creation of soap/detergent. Saponins also play a vital function in modifying immune system and decreasing blood sugar level.

Besides, anthraquinone glycosids discovered in the Rumex crispus and Rheum spp. of polygonaceae family aid in electrolyte secretion as well as induction of water and peristalisis in colon.

2.2 Tannins

Tannins are extensively found in plants, notably in the *Fagaceae* and *Polygonaseae* families. They are mainly split into two categories, including condensed and hydrolysable tannins. Condensed groups of tannins are constituted of larger polymers of flavonoids, while hydrolysable groups of tannins are clusters of monosaccharide (glucose) coupled with various derivatives of catechin. Tannin molecules tend to indiscriminately interact with protein molecules. Larger groups of tannins are used as medication for treating skin bleeding, diarrhea and transudates.

2.3 Mono/Sesqui-Terpenoids and Phenylpropanoids

Synthesis of terpenoids takes occur via a penta-carbon isoprene. In case of monoterpenoids, two units of isoprene are detected, but in sespui-terpenoids there are three units of isoprene. They are generally recognised for their low molecular weight and wide range of categories (more than 25,000). However, phenylpropanoids encompasses group of molecules where the fundamental carbon skeleton begins from nine and more, with strong odor, flavors and are volatile in nature. Generally, these substances are often termed volatile oils, mainly found in the Lamiaceae family. It is utilised as a herbal treatment including antineoplastic, antiviral and antibacterial activities. Besides, it also assists in gastrointestinal stimulation. In addition, diterpenoids are lipophilic non-volatile (odorless) chemical and is a cluster of 4 units of isoprene with a strong taste. It is extensively present in numerous plants including Coffee arabica and generally recognised for its antioxidant capabilities.

2.4 Resins

Resins are composite mixes which consist of both volatile as well as non-volatile attribute chemicals; as well, they are constituted of a lipid soluble group of compounds.

Non-volatile resins consist of diterpenoid and triterpenoid chemicals, whereas volatile resins are equipped with mono/sesquiterpenoids. These resins are generally present in herbaceous plants and are well recognised for their wound healing and antibacterial qualities.

2.5 Alkaloids

Alkaloids, a bitter-tasting and nitrogen-holding chemical is a heterocyclic with limited dissemination in the plant world. The Solanaceae family, includes *Atropa belladonna*, *Datura* spp. as well as *Hyoscyamus niger*, comprises of tropane alkaloids with anticholinergic properties. It is frequently used for relieving muscular discomfort. Besides, pyrrolizidine alkaloids belong to the *Asteraceae* and *Boraginaceae* families, notably in *Senecio spp.* It includes of a wide spectrum of use including treating cancer cells, increasing bone marrow leucocytes and cardiac contractility. In addition, methylxanthine alkaloids are dispersed in *Coffee arabia* as well as *Theobroma cacao.*

2.6. Proteins

Plant proteins have achieved substantial appeal in the sphere of food and medicinal sectors since they are a key source of nourishment for humans and animals. The Euphorbiaceae family as well as Fabaceae and lentils are known to possess a high concentration of protein.

3. Novel techniques for extraction

3.1 Pulsed electric fields assisted extraction.

In the past three decades, pulsed electric fields (PEF) assisted processing has attracted a strong interest in food engineering for enhancement of diffusion extraction, osmotic treatment, pressing extraction and drying suppressing negative impacts of traditional thermal methods (Barba *et al*., 2015; Domagoj *et al*., 2018; Janositz & Knorr, 2010) [12, 13, 14]. PEF technique comprises the application of short duration pulses (from few nanoseconds to several milliseconds) with moderate to high electric field strengths (from 100 to 300 V/cm to 20–80 kV cm^{-1}) and relatively low energy (1–10 kJ/kg) (Koubaa *et al*., 2015) [15]. The extraction of selected molecules by PEF may

be performed by diffusion in solvent (solvent extraction) or by use of pressing techniques (expression) (Vorobiev & Lebovka, 2016) [16]. A PEF apparatus contains a highvoltage pulse generator, a treatment chamber with an appropriate fluid handling system, and a monitoring and controlling system (Alexandre, Moreira, Pintado, & Saraiva, 2017). The product is subjected to electric field pulses in a static or continuous chamber with at least two electrodes, one on high voltage and the other at ground potential, separated by insulating material in various geometric configurations.

The product is subjected to a force per unit charge (the electric field) that is responsible for the cell disintegration (Chemat, Fabiano-Tixier, Vian, Allaf, & Vorobiev, 2015) [18]. At high electric fields (20 kV cm^{-1}), the pathogenic bacteria and quality associated enzymes are inactivated while sensory, nutritional and health-promoting properties of liquid food are preserved or little affected. At low electric fields, the biological membrane is electrically penetrated and loses its semi-permeability temporarily or permanently, enabling a selective recovery of valuable substances from distinct tissues (Barba, Parniakov, *et al*., 2015) [12]. When the cells are subjected to an external electric field, the charge buildup on the membrane surfaces raises the transmembrane potential of both sides of the membrane. This will encourage the formation of holes, which may be reversible or permanent depending on treatment intensity, in weak parts of the membrane. The cell membrane permeability may grow substantially and possibly result in cell disintegration, which is typically a vital processing step in food and bioengineering processes. This cell membrane permeability called "electroporation" or "electro permeabilization" boosts the mass transfer rates promoting the release of intracellular chemicals during the extraction operations (Alexandre, Castro, Moreira, Pintado, & Saraiva, 2017; Barba, Parniakov, *et al*., 2015) [12]. The amount of electroporation will rely on various parameters, such as the plant material compounds, electric-field strength, kind of pulse waveform, treatment time, and number of pulses. The length and number of pulses should be limited to prevent major temperature rises that are usually lower than 3–5 °C (Donsì, Ferrari, & Pataro, 2010) [19].

The principal advantages of PEF assisted extraction (PEFE) against thermal conventional extraction procedures are related with the increased mass transfer, improved extraction yield, decreased processing time, decreased intensity of the conventional extraction parameters (i.e. extraction temperature and solvent concentration), reduction of heatsensitive compounds degradation (e.g., flavors, proteins, etc.), facilitation of purified extract (i.e. reducing grinding), and reduction of energy costs and environmental impact (Barba, Parniakov, *et al*., 2015) [12]. PEF-assisted extraction (PEFE) provides various benefits over typical thermal extraction procedures. One of the key benefits is the greater mass transfer, which leads to higher extraction yield. This is because the electric field pulses induce the cell membrane permeability to rise, allowing for the release of intracellular compounds during the extraction process. This leads in a larger yield of bioactive chemicals compared to typical extraction techniques. Another benefit of PEFE is the shorter processing time. The short duration pulses utilised in PEF-assisted extraction may drastically shorten the extraction time compared to standard approaches. This not only saves time but also decreases energy expenses and environmental effects. PEFE also provides for a decrease in the intensity of typical extraction parameters such as extraction temperature and solvent concentration. This is because the electric field pulses may tear down the cell walls and membranes, making it simpler for the solvent to permeate the plant material and extract the bioactive components. As a consequence, lower temperatures and solvent concentrations may be employed, which decreases the danger of destruction of heat-sensitive components such as tastes and proteins.

PEFE also improves the purification of extracts by minimising the requirement for grinding. The electric field pulses may break down the plant material, making it simpler to extract the bioactive chemicals without the need for considerable grinding. This not only saves time but also decreases the danger of deterioration of heat-sensitive chemicals.

Overall, PEF-assisted extraction is a promising non-thermal extraction approach that offers various benefits over standard thermal extraction methods. It can increase the quality and nutritional content of extracted bioactive chemicals while lowering processing time, energy costs, and environmental effect.

3.1.1 Pulsed electric fields aided extraction impact on bioactive substances profile.

The advantages of PEFE are being proved with the extraction of high-added value compounds from a vast range of fruits and vegetables (apple, carrot, table beet, etc.), food wastes and by-products, leaves (tea, spinach), herbs, mushrooms, and suspensions of cells (yeasts, microalgae, etc.). This extraction technology is appropriate for the selective recovery and extraction of sugar, inulin, starch, proteins, polysaccharides, polyphenols, pigments, taste compounds, phytochemicals, and other high-valued components (Chemat *et al*., 2015; Vorobiev & Lebovka, 2016) [18, 16]. (Barba, Grimi, and Vorobiev (2015) [18] assessed the potential of cell disruption methods such as PEF, for selective extraction of antioxidant chemicals from Stevia rebaudiana Bertoni leaves. The energy inputs of the treatments ranged from 0 to 141 kJ/kg, using water as solvent, and the treatment period was connected with the specific power consumption and all findings were compared to control diffusion trials. These authors noticed that following PEFE, a considerable increase in conductivity (~25% more) and in soluble matter (~33% more) may be attained, boosting both kinetics and extraction yield of soluble matter. Antioxidant activity and total phenolic compounds rose dramatically as compared with the control, about 80 and 50%, respectively. In terms of individual phenolic compounds, chlorogenic and caffeic acids were the primary substances tested.

When compared with control, these chemicals were better extracted by PEFE approximately 93 and 55% respectively. Ferulic and protocatechuic acids were also discovered at the same wavelength with retention durations of 17.69 and 3.38 min being the peak area of 76.46/40.18 and 68.38/ 47.23 for PEFE/control, respectively, which represents an increase of 90 and 45% for each component. The impact of PEFE on bioactive components, colour, and taste of green tea infusions were examined by Zhao, Yang, Wang, and Lu (2009) [2]. These authors found that PEFE is a potential non-thermal pasteurization method that could effectively maintain polyphenols, catechins and natural colour of green tea infusions (p>.05) using an electric field intensity from 20 to 40 kV cm−1 for 200 μs. Moreover, PEFE generated an

increase of 7.5% in the total free amino acids at 40 kV cm^{-1}, being valine, isoleucine, and leucine the primary amino acids responsible for this increase, with an increase of 113, 100, and 66% respectively, when compared to the control. Concerning the taste components of green tea infusions, it was not seen a significant effect of PEFE at 20 or 30 kV cm^{-1}. In relation to the colour, the ΔE values at 20, 30, and 40 kV cm−1 were 0.11, 0.47, and 0.76, respectively, which means that there was no noticeable change in the colour of green tea infusions produced by PEFE at 20 or 30 kV cm−1, and only a slightly noticeable difference was observed between the control and 40 kV cm^{-1}. However, at 40 kV cm−1 for 200 μs the overall concentration of volatiles lost was roughly 10%. Twenty-five volatiles were identified by GC–MS and the authors concluded that there was no significant influence of PEFE at 20 or 30 kV cm^{-1} on taste components of green tea infusions. However, at 40 kV cm^{-1} it was found a reduction of 10% of taste compounds, largely owing to 2-pentanol, cis-3-hexenol, and bionone that fell 30, 14, and 3% respectively, when compared to the control.

Lu, Yin, and Yu (2017a) [22] enhanced the extraction of ginsenosides from ginseng root using PEFE coupled with a commercial enzyme. The enzymes examined were Cellulcast 1.5 L FG, Cellulose, and β-glucosidase, which was the most effective for extracting total saponin following PEF treatment. The best treatment settings were 15 kV cm−1, 10 pulses (10 min.), and enzyme concentration of 2% (w/w), which enabled to produce a yield of total saponin of 38.15 mg/g that was 19% higher than the obtained for heat reflux extraction (after 6 h). The major saponins discovered in the ginseng root extracts were Rb1, Rc, Rb2, Rd, and Re1 + Rg1 being all of them better extracted by PEFE plus the enzyme β-glucosidase, with an increase in extraction yield of 9, 25, 15, 64, and 13%, respectively.

Other authors such as Fincan (2015) [23], Sarkis *et al*. (2015) [24] and Segovia, Luengo, Corral-Pérez, Raso, and Almajano (2015) [25] also used PEFE to extract phenolic components from spearmint, sesame seed cake, and borage, respectively. Fincan (2015) [23] found the highest disintegration index (0.86 ± 0.02) at a PEFE intensity corresponding to 99 pulses of 3 kV cm−1 with a specific energy input of 4102 ± 239 J/kg and the extraction yields produced (total phenolic, antioxidant capacity, and antioxidant activity) were comparable with the heat and microwave treatments. Sarkis *et al*. (2015) [24] concluded that the disintegration index and the polyphenol and protein contents increased with the energy inputs, until 83 kJ/kg was reached, and Segovia *et al*. (2015) concluded that PEFE incremented the total phenolic contents and ORAC values of the extracts between 1.3 and 6.6 times for total phenolic and between 2.0 and 13.7 times for ORAC, compared to the control. Other compounds such as podophyllotoxin were isolated from Podophyllum peltatum likewise utilising PEFE that greatly boosted the concentration of podophyllotoxin up to 47% (Abdullah, Zhao, Mittal, & Baik, 2012) [26].

3.2 Supercritical fluids assisted extraction.

Supercritical fluids are described by being the condition of a material or a solvent when their temperature and pressure are raised above their critical levels. For so, these solvents have unusual characteristics when compared to their typical equivalents, acting somewhat as both gas and liquid (Silva, Rocha-Santos, & Duarte, 2016; Uddin *et al*., 2015) [28]. Due to their particular features, such as high diffusivity and low viscosity, supercritical fluids may be utilised as transporters, allowing to obtain larger solubilities and mass transfer rates than common liquids (Ueno, Tanaka, Machmudah, Sasaki, & Goto, 2008; Da Silva *et al*., 2016) [19]. These qualities may be adjusted by changes in pressure and temperature levels, in order to encourage higher extraction rates, with specifications for target bioactive ingredients (Uddin *et al*., 2015) [28]. For so, the connection between pressure (usually between 200 and 400 bar) and temperature (up to 60 °C) may be controlled in order to enable heat-sensitive chemicals extraction, avoiding their destruction (Silva *et al*., 2016). The characteristics of supercritical fluids may be modified by changes in pressure and temperature levels, in order to stimulate increased extraction rates, with specifications for target bioactive constituents. The link between pressure (typically between 200 and 400 bar) and temperature (up to 60 °C) may be adjusted in order to permit heat-sensitive compounds extraction, avoiding their destruction.

Carbon dioxide is the most utilised supercritical fluid for extraction of bioactive chemicals from plant material or other natural sources (Capuzzo, Maffei, & Occhipinti, 2013) [30]. This particular choice is related to i) being safe for human health and to the environment, ii) it has a mild critical pressure and temperature (73.8 bar and 31.2 °C, respectively), iii) it prevents extracts oxidation, iv) allows to produce a freesolvent final extract due to its easy volatilization, v) it is not expensive and it is efficiently recycled, not producing effluents, and vi) its odourless, colourless, non-flammable and it is inert to most materials (Guclu-Ustundag & Temelli, 2005; Barbosa, de Melo, Coimbra, Passos, & Silva, 2014; Uddin *et al*., 2015; Da Silva *et al*., 2016; Silva *et al*., 2016) [28]. Furthermore, in order to maximize supercritical fluids assisted extraction (SFE), it may be added solvents (typically known as co-solvents) that will help the extraction of polar molecules (Da Silva *et al*., 2016). The most common co-solvent is ethanol, owing to its low boiling point and efficiency to separate from the final extract, and due to its food grade qualities (Uddin *et al*., 2015) [28].

SFE provides various benefits over standard extraction procedures, including good selectivity, minimal toxicity, and the capacity to extract chemicals at low temperatures. SFE has been utilised to extract bioactive chemicals from diverse plant materials, including fruits, vegetables, and herbs. For example, SFE has been employed to extract carotenoids from tomato paste, lycopene from watermelon, and polyphenols from grape seeds. SFE has also been used to extract essential oils from other plants such as rosemary, thyme, and oregano.

Similarly, to other extraction processes, SFE happens in two sequential phases. The first step, the solubilisation of the bioactive chemicals contained in the plant material into the solvent, relies on the absorption of the solvent by the cellular membrane, leading to its degradation and probable breaking, boosting the mass transfer rate (Brunner, 1994) [31]. The second stage is linked to the efficient separation of the bioactive chemicals from the solvent, which are carried to the external surface of the cell wall, and then separated by solvent evaporation (Brunner, 1994; Uddin *et al*., 2015) [31, 28]. The SFE process is reliant on numerous factors, such as temperature, pressure, time of extraction, solvent flow rate, and the matrix properties (Da Silva *et al*., 2016).

3.2.1 SC-CO_2 Impact on bioactive compounds profile

SC-CO_2 allows the extraction of several different bioactive compounds such as those present in essential oils, flavonoids, total phenolic compounds, coumarins, and diterpenoids, from different herbal materials, such as Marchantia convolute, rosemary, sage, Chinese lovage, savory,, Damjanovi ć-Vratnica, Hypericum polyanthemum,, knotweed, giant dodder, Dahurian angelica, spearmint, Cretan barberry, scarlet bee balm,, scarlet bee balm, wild bergamot, thyme, saffron, and sweet wormwood. Rosemary is a well-known fragrant herb used mostly for cooking, having also a range of bioactivities, such as antioxidant and anti-in- flammatory. The components responsible for these actions include the phenolic chemicals, such as carnosic acid, carnosol, and Rosmarinus acid. Peng *et al*. (2007) [34] examined the e ffect of SC-CO_2 of phenolic acids from dried rosemary leaves at 34.5 MPa, 40 – 80 °C for 2 h, at a CO_2 flow rate of 1.0 mL/min. The authors discovered eight main compounds by HPLC analysis, being five identi fied as rosmarinic acid, carnosol, 12-methoxycarnosic acid, carnosic acid, and methyl carnosate. Furthermore, authors observed that temperature can greatly affect the way each compound is extracted, being obtained di fferent concentrations for carnosic acid (36.7, 31.3, and 30.4 mg/g for SC-CO_2 at 40, 60, and 80 °C, respectively) and carnosol (12.3, 7.5, 8.2 mg/g for SC-CO_2 extraction at 40, 60, and 80 °C, respectively) (Peng *et al*., 2007) [34]. On the other hand, rosmarinic acid is more e fficiently extracted at higher temperatures, being achieved values of 3.3 and 3.2 mg/g for SC-CO_2 at 60 °C and 80 °C respectively. It is noteworthy that although different temperatures led to different concentration of the bioactive compounds in the extracts, all the SC-CO_2 conditions led to higher concentrations than conventional extraction with solvents, being observed an increase of about 169% for carnosic acid, and an increase of 127% for carnosol. Likewise, the pressure range may likewise affect the concentration of carnosic acid and carnosol in rosemary leaves.

Vázquez *et al*. (2013) [36] studied SC-CO_2 extraction of these two phenolic acids at 20 and 30 MPa, at 40 °C, for 5 h, and concluded that a higher pressure (30 MPa) leads to an increase of about 80% of carnosic acid compared to the extraction that occurred at 20 MPa, while carnosol is not even quantified in the latter condition. The concentration of extracted chemicals may also be altered by the utilised co-solvent, and its amount. For example, Vicente *et al*. (2013) [37] demonstrated that extraction of phenolic compounds from rosemary leaves by SC-CO2 (15 MPa, 40 °C, for 3 h, with a CO_2 flow rate of 60 g/min) with different amounts of co-solvent can directly affect the extraction of carnosic acid, being obtained higher content when ethanol was employed as co-solvent, in detriment of essential oil compounds (as borneol, bornyl acetate, camphor, 1,8-cineol, and verbenone).Topala and Tataru (2016) [358] examined the composition of essential oils from rosemary and thyme using ATR-FTIR spectroscopy and observed that α-pinene and 1,8-cineole are the primary constituents in rosemary oil, while carvacrol is the predominant component in thyme oil. The interesting discovery of these authors was that after comparison of the spectra of the extract obtained by CO_2 (10 MPa, 40 °C, for 3 h) and the one from extraction with n-hexane, the peaks positions, shapes and intensities of the main speci fic bands in the spectra were quite similar to each other since both extraction techniques used nonpolar solvents (Topala & Tataru, 2016) [35]. Also, Villanueva Bermejo *et al*. (2015) [52] evaluated the e ffect of SC-CO_2 (15 –40 MPa, at 40 °C for 4 h) on the extraction of thymol.

Generally, the authors noted that SC-CO_2 extraction enabled higher concentration of thymol than pressurized liquid extraction (PLE), and in the case of one species, Thymus citriodorus, PLE did not allow thymol extraction. On the other hand, the highest thymol recovery was obtained in the case of Thymus vulgaris at 15 MPa with values of 6.87, 8.00, and 10.27 mg/g, depending on the increase of CO_2 flow rate, which resulted in higher recovery than those produced by increasing of the extraction pressure (Villanueva Bermejo *et al*., 2015) [52]. Different findings were achieved by Petrović *et al*. (2016) [51] who evaluated the impact of SC-CO_2 at 10 and 30 MPa at 40 °C for 1.5 h and found substantially higher results (an increase of 78%) for thymol extraction at 10 MPa, when compared to the procedure at 30 MPa. Additionally, while comparing the extraction at 10 MPa with supercritical CO2 to the conventional Soxhlet extraction using hexane as solvent, the scientists reported an increase of nearly 2000% (Petrović *et al*., 2016) [51]. Nevertheless, it is noteworthy that, while SC-CO2 extraction at 10 MPa and Soxhlet with hexane permitted to identify 64 compounds by GC/FID analysis, the extraction using SC-CO_2 at 30 MPa allowed to identify 80 components, even at extremely low concentrations (Petrović *et al*., 2016) [51].

Rodriguez-Solana, Salgado, Dominguez, and Cortes-Dieguez (2015) compared the extraction of phenolic compounds by Soxhlet and supercritical fluid extraction from different Lamiaceae species. The authors aimed to describe the essential oils by GS-MS analysis and phenolic compounds by HPLC-ESI-MS/MS, and observed that typically, related to the volatile chemicals, there were no significant differences between Soxhlet and SC-CO_2 extraction. Concerning *Mentha piperita L.*, the most prevalent components were I-menthone and menthol, being observe a rise from Soxhlet to SFE of around 1.5 and 5%, respectively. Relatively to Thymus vulgaris L., the chemicals with higher concentration were thymol and n-hexadecanoic acid, with an increase of roughly 2% for the former and 138% for the latter. *For Rosmarinus officinallis L.*, the most abundant chemicals were eucalyptol and camphor (with a drop of roughly 9% and 5% when comparing Soxhlet extraction with SFE, respectively). Finally, with Origanun vulgare, SFE allowed to double the concentration of thymol, with an increase of almost 90%.

3.3 High hydrostatic pressure assisted extraction.

The impacts of high hydrostatic pressure (HHP) in biotechnology have been increasingly studied in the last decades, being this technology already successfully applied in the processes of pasteurization for gentle food preservation and pharmaceutical compounds processing (Considine, Kelly, Fitzgerald, Hill, & Sleator, 2008) [57]. High hydrostatic pressure assisted extraction (HPE) follows the same principles of HHP (isostatic and Le Chatelier's principles), can use refrigerated or room temperatures, at pressure levels that range from 100 to 600 MPa that usually do not majorly affect the covalent bonds, thus avoiding thermal degradation (Robert & Alexander, 2018) [58]. Nevertheless, it may induce certain structural changes in structurally fragile materials, such as cell deformation, cell membrane damage and protein partial denaturation, and the temperature can increase only about 3 °C per 100 MPa via adiabatic heating, during the compression

phase (Us-Fda, 2000) [59]. HPE enables the extraction of heat-sensitive compounds, without major damage or denaturation, and has been recognized as an environmentally friendly technology by the Food and Drug Administration, since it does not produce effluents and its energy spend is controlled to a minimum (Us-Fda, 2000; Xi, 2006b) [59]. Another HPE benefit is the potential of mixing multiple solvents (and solvent ratios), with varied polarity, enabling the extraction of different compounds, as well as to modify the quantity of impurities present in the final extract (Shouqin, Junjie, & Changzhen, 2004). The two most utilised solvents are water and ethanol (pure or in combination) due to their distinct polarity and the convenience of evaporation and recycling of the ethanol (which, when compared to other organic solvents is considered non-toxic and non-expensive) (Shouqin, Xi, & Changzheng, 2005) [61, 10]. Due to those characteristics, ethanol was generally chosen in detriment of methanol, chloroform, and n-butanol, even though the last ones presented relatively higher extraction yields depending on the class compound (Chen, Meng, Zhang, & Liu, 2009; Prasad *et al*., 2009; Prasad, Yang, Yi, *et al*., 2009; Shouqin *et al*., 2005; Xi, 2006a) [62, 2,, 10].

HPE presents many other advantages comparatively to conventional extraction techniques, such as short time processing (the differential pressure between the inner and the outer cell can be very large, allowing the solvent to permeate through the broken cells very quickly), low energy consumption (energy is only necessary to generate the pressure in the first phase of HPE), high solubility when under high pressure, high amount of solvent inside the cell, leading to easier permeation due to wall and membrane breakage, causing a high rate of mass transfer and consequent high extraction yield (Shouqin *et al*., 2004). The damages caused in cell membranes are due to the appearance of hollow openings, development of smaller particles from the broken plant tissue, etc., as can be seen by scanning electron microscopy of ginseng samples (Chen *et al*., 2009; Predrag *et al*., 2018;, *et al*., 2009) [63] and light and scanning electron microscopies of dried pollen grains (Altuner, Çeter, & Alpas, 2012) after HPE. According to the mass transfer theory, the rate of mass transfer equals to pressure by resistance of mass transfer (i.e. pressured cells exhibit enhanced permeability) (Yan, 2002) [65]; and based on the phase behaviour theory, dissolution is quicker at higher pressure levels (Sadus, 2012) [66].

HPE comprehends three key stages: (1) pressure boost stage: that includes the mixture of the raw plant material with the solvent, and the time until achieving the target pressure inside the cell, and the consequent equilibrium between inside and outside the cell (that can be very short); (2) pressure maintaining stage: treatment under high pressure (100–600 MPa) for a determined and appropriate period of time; and (3) pressure relief stage: quick pressure release (from target pressure to atmospheric pressure in only a few seconds) that causes cell expansion and fluid circulation, resulting in significant cell and membrane damage (leading to higher permeation), followed by concentration/purification of the compound of interest (Huang *et al*., 2013; Shouqin *et al*., 2005) [5, 10].

The key factors to consider for HPE are, in order of importance: extraction temperature, pressure level, solvent and its concentration, ratio of solvent to raw material, and holding pressure time (Chen *et al*., 2009) [2]. The extraction temperature is of extreme importance owing to the effective extraction of thermo-sensitive chemicals. A change in temperature may destroy the phenolic-matrix connections and affect the membrane structure of plant cells making them less selective by the coagulation of lipoproteins (Prasad, Yang, Zhao, *et al*., 2009) [2].

The pressure level may vary according to the compounds of interest, and was noted that typically, the greater the hydrostatic pressure is, the more solvent can enter into the cells and subsequently, more chemicals can permeate out to the solvent (Xi *et al*., 2009). Also, the solvent choice (and its concentration) is intimately connected to the components to extract; it should be non-toxic, and simple to evaporate from the final extract. The ratio of solvent to raw material is another important parameter to consider, since the dissolution of bioactive components into the solvent is a physical process, and when the solvent volume is high enough, there is a much higher probability to enter in contact with the compounds of interest, leading to higher extraction yields, while the contrary can lead to solvent saturation and lower extraction yields.

Finally, the pressure holding time is the duration of time required to achieve the equilibrium of solvent between the interior and outside of the cells (Xi *et al*., 2009).

3.3.1 High pressure assisted extraction effect on bioactive compounds profile.

After HPE, some differences were observed, in several studies in herbal materials such as the extraction of ginsenosides from ginseng (Lee *et al*., 2011; Shin *et al*., 2010; Shouquin *et al*., 2006) [1, 70, 60], salidroside from rhodiola (Bi, Zhang, Liu, & Wang, 2009; Zhang, S.-Q., Bi, H., & Liu, C., 2007) [2, 4], p-coumaric acid from pinyin (Hong-Sen, ShouQin, Xiao-Pei, Li-Li, & Qing, 2008), catechins and caffeine from green tea (Xi, 2009; Xi *et al*., 2010), deoxyschisandrin and y-schisandrin from Magnolia berry (Liu, Zhang, & Wu, 2009) [62], podophyllotoxin and 4′-demethylpodophyllotoxin from hance (Zhu, Liu, Xu, Lin, & Wang, 2012), and total phenolic compounds and flavonoids from Korean barberry and deodeok (He *et al*., 2010; He *et al*., 2011; Lee, He, & Ahn, 2010, *et al*., 2009) [69].

In green tea there are a considerable number of phenolic chemicals, such as caffeine and catechins, with demonstrated biological action. Xi (2009) evaluated the impact of caffeine extraction by HPE from green tea leaves and compared the results with traditional extraction techniques. This work allowed to infer that HPE for just 1 min, at 500 MPa and RT gave similar extraction yields of caffeine (4.0%) as extraction at RT for 20 h (4.2%), ultrasonic extraction for 90 min (4.1%), and heat reflux for 45 min (3.9%), being HPE the most efficient approach. The same authors extracted phenolic components from dry green tea leaves using HPE and by HPLC were able to identify and quantify the key components (caffeine, epigallocatechin gallate, epicatechin gallate, epigallo catechin, epicatechin, and gallic acid) (Xi *et al*., 2010). The authors reported that the concentrations present in the final extract were greatly influenced by the pressure level (as pressure increased, the concentration of phenolic compounds increased as well), and that the extraction yields achieved with HPE (at 400 MPa of pressure) for only 15 min at RT were like those of organic solvent extraction for over 2h (Xi *et al*., 2010). Using deodeok roots as matrix, it was feasible to extract several free phenolic acids such as vanillic acid (20.4–40.7 μg/ mL), which was the most abundant,

followed by p-hydroxybenzoic acid, p-coumaric acid, vanillin, and p-hydroxybenzaldehyde (He *et al*., 2010; He *et al*., 2011). However, it was not seen an increase in the concentration with the rise of pressure (100–500 MPa), suggesting that increasing pressure might change the polarity, leading to a decrease of polar chemicals extraction (He *et al*., 2011). An interesting result obtained by He *et al*. (2010), also with deodeok roots extracts, was that after fermentation with different probiotic strains, it was observed a different total number of peaks, being only 65 common to all HPE extracts, indicating the production of new metabolites during fermentation, and its preservation after HPE, and also that some flavonoids, such as quercetin, rutin, and kaempferol can be degraded to phenolic acids by bacterial growth. After HPE (600 MPa, for 5 min, at RT, using water as solvent) for the extraction of total ginsenosides from Korean Panax ginseng, it was observed a clear increase for all the seven standard's ginsenosides studied and an additional two unknown higher peaks, when compared to control (extraction at RT, for 24 h) (Shin *et al*., 2010) [70]. Also in fresh ginseng, a total of 39 volatiles were identified (three acids, two alcohols, four aldehydes, four ketones, one furan, one pyran, and twenty-four terpenoids), being the most of them identified in the fresh ginseng extract after HPE, while only 29 were identified in the extract after heat assisted extraction (Lee *et al*., 2011) [1]. These results proposed that the chemicals important for fragrance may be destroyed during heat processing, and that HPE can generate extracts with a high number of various components and produce extracts with minimal change in taste (Lee *et al*., 2011) [1]., *et al*. (2009) [63] have evaluated the extraction of total phenolic compounds from Korean barberry and compared the obtained yields by different extraction procedures, such as the traditional for 24 h at 60 °C, HPE at 500 MPa, for 5 min at RT, and HPE aided by sonication (HPWS). These authors observed that extracts obtained after HPWS showed a higher variety of HPLC peaks, probably since the combination of HPE and ultrasonification allowed the solvent to better penetrate the matrix, enhancing the solubility of the target analytes, being obtained an increase of total phenolic yield from 324.89 mg GAE/g by HPE, to 401.45 mg GAE/g by HPWS. Lee *et al*. (2010) [69] also evaluated the impact of the combination of HPE with probiotic fermentation. These scientists extracted total phenolic components using HPE at 500 MPa for 30 min and then fermented them using Bifidobacterium longum B6 and Lactobacillus paracasei at 37 °C for 6 days (Lee *et al*., 2010) [69]. The findings demonstrated that HPE alone allows to produce greater total phenolic yields than the conventional extraction or the combination of HPE plus fermentation. These results may be connected to the fact that HPE alone permitted the extraction of more than the doubling of p-hydrobenzoic acid and a general rise in vanillic acid, p-hydrobenzaldehyde, vanillin, and ferulic acid (Lee *et al*., 2010) [69].

Conclusion

Non-thermal technologies assisted extractions offer a promising alternative to traditional extraction methods for obtaining high-quality extracts with improved biological activities. The advantages of these methods, such as rapidity, convenience, and low or room temperature operation, make them highly efficient and effective for extracting heat-sensitive compounds and a variety of bioactive components from different matrixes. These technologies have already demonstrated their efficiency in the extraction of phenolic compounds, flavonoids, carotenoids, caffeine, and other bioactive components, which have potential applications in the food, pharmaceutical, and nutraceutical industries. Overall, the development and application of non-thermal technologies assisted extractions represent a significant advancement in the field of natural product extraction and hold great promise for the future.

References

1. Lee HS, Lee HJ, Yu HJ, Ju W, Kim Y, Kim CT *et al*. A comparison between high hydrostatic pressure extraction and heat extraction of ginsenosides from ginseng (Panax ginseng CA Meyer). Journal of the Science of Food and Agriculture. 2011;91(8):1466–1473. https://doi.org/10.1002/jsfa.4334
2. Prasad NK, Yang B, Zhao M, Wang BS, Chen F, Jiang Y. Effects of highpressure treatment on the extraction yield, phenolic content and antioxidant activity of litchi (Litchi chinensis Sonn.) fruit pericarp. International Journal of Food Science & Technology. 2009;44(5):960–966. https://doi.org/10.1111/j.1365-2621.2008.01768.x
3. Corrales M, Toepfl S, Butz P, Knorr D, Tauscher B. Extraction of anthocyanins from grape by-products assisted by ultrasonics, high hydrostatic pressure or pulsed electric fields: A comparison. Innovative Food Science & Emerging Technologies. 2008;9(1):85–91. https://doi.org/10.1016/j.ifset.2007.06.002.
4. Zhang SQ, Bi H, Liu C. Extraction of bio-active components from Rhodiola sachalinensis under ultrahigh hydrostatic pressure. Separation and Purification Technology. 2007;57(2):277–282. https://doi.org/10.1016/j.seppur.2007.04.022.
5. Huang HW, Hsu CP, Yang BB, Wang CY. Advances in the extraction of natural ingredients by high pressure extraction technology. Trends in Food Science & Technology. 2013;33(1):54–62. https://doi.org/10.1016/j.tifs.2013.07.001.
6. He X, Yoon WB, Park SJ, Park DS, Ahn J. Effects of pressure level and processing time on the extraction of total phenols, flavonoids, and phenolic acids from Deodeok (Codonopsis lanceolata). Food Science and Biotechnology. 2011;20(2):499–505. https://doi.org/10.1007/s10068-011-0069-7.
7. Bursac Kovacevic D, Barba FJ, Granato D, Galanakis CM, Herceg Z, DragovicUzelac V, Putnik P. Pressurized hot water extraction (PHWE) for the green recovery of bioactive compounds and steviol glycosides from Stevia rebaudiana Bertoni leaves. Food Chemistry. 2018;254:150–157. https://doi.org/10.1016/j.foodchem. 2018.01.192.
8. Giacometti J, Bursać Kovačević D, Putnik P, Gabrić D, Bilušić T, Krešić G, Režek Jambrak A. Extraction of bioactive compounds and essential oils from mediterranean herbs by conventional and green innovative techniques: A review. Food Research International. 2018;113:245–262. https://doi.org/10.1016/j.foodres.2018. 06.036.
9. Chemat F, Cravotto G. Microwave-assisted Extraction for Bioactive Compounds - Theory and Practice. S: Springer, 2013.
10. Shouqin Z, Xi J, Changzheng W. High hydrostatic

pressure extraction of flavonoids from propolis. Journal of Chemical Technology & Biotechnology. 2005;80(1):50–54. https://doi.org/10.1002/jctb.1153.
11. Vinatoru M. An overview of the ultrasonically assisted extraction of bioactiveprinciples from herbs. Ultrason. Sonochem. 2001;8:303–313.
12. Barba FJ, Parniakov O, Pereira SA, Wiktor A, Grimi N, Boussetta N. *et al*. Current applications and new opportunities for the use of pulsed electric fields in food science and industry. Food Research International. 2015;77:773–798. https:// doi.org/10.1016/j.foodres.2015.09.015
13. Domagoj G, Francisco B, Shahin R, Taghi GSM, Milivoj R, Predrag P, Danijela BK. Pulsed electric fields as an alternative to thermal processing for preservation of nutritive and physicochemical properties of beverages: A review. Journal of Food Process Engineering. 2018;41(1):e12638. https://doi.org/10.1111/jfpe.12638.
14. Janositz A, Knorr D. Microscopic visualization of pulsed electric field induced changes on plant cellular level. Innovative Food Science & Emerging Technologies,2010;11(4):592–597. https://doi.org/10.1016/j.ifset.2010.07.004.
15. Koubaa M, Roselló-Soto E, Šic Žlabur J, Režek Jambrak A, Brnčić M, Grimi N. *et al*. Current and new insights in the sustainable and Green recovery of nutritionally valuable compounds from Stevia rebaudiana Bertoni. Journal of Agricultural and Food Chemistry. 2015;63(31):6835–6846. https://doi.org/10.1021/acs. jafc.5b01994.
16. Vorobiev E, Lebovka N. Selective extraction of molecules from biomaterials by pulsed electric field treatment. In D. Miklavcic (Ed.). Handbook of electroporation. Cham: Springer International Publishing, 2016, 1-16.
17. Alexandre EMC, Brandão TRS, Silva CLM. Emerging technologies to improve safety and quality of fruits and vegetables. In A. Sobral (Ed.). Novel technologies in food science – Their impact on products, consumer trends and environment. 2012, 261–297. USA: Springer.
18. Chemat F, Fabiano-Tixier AS, Vian MA, Allaf T, Vorobiev E. Solventfree extraction of food and natural products. TrAC Trends in Analytical Chemistry. 2015;71:157–168.
19. Donsì F, Ferrari G, Pataro G. Applications of pulsed electric field treatments for the enhancement of mass transfer from vegetable tissue. Food Engineering Reviews. 2010;2(2):109–130.
20. Vorobiev E, Lebovka N. Selective extraction of molecules from biomaterials by pulsed electric field treatment. In D. Miklavcic (Ed.). Handbook of electroporation. Cham: Springer International Publishing, 2016, 1-16.
21. Zhao W, Yang R, Wang M, Lu R. Effects of pulsed electric fields on bioactive components, colour and flavour of green tea infusions. International Journal of Food Science & Technology. 2009;44(2):312–321. https://doi.org/10.1111/j.1365-2621. 2008.01714.x.
22. Lu CW, Yin YG, Yu QY. Optimized Extraction of Ginsenosides from Ginseng root (Panax ginseng C.A. Meyer) by Pulsed Electric Field combined with Commercial Enzyme. Journal of Food Processing and Preservation. 2017a;41(1):e12766. https://doi.org/10.1111/jfpp.12766.
23. Fincan M. Extractability of phenolics from spearmint treated with pulsed electric field. Journal of Food Engineering. 2015;162:31–37.
24. Sarkis JR, Boussetta N, Blouet C, Tessaro IC, Marczak LDF, Vorobiev E. Effect of pulsed electric fields and high voltage electrical discharges on polyphenol and protein extraction from sesame cake. Innovative Food Science & Emerging Technologies. 2015:29:170–177. https://doi.org/10.1016/j.ifset.2015.02.011.
25. Segovia FJ, Luengo E, Corral-Pérez JJ, Raso J, Almajano MP. Improvements in the aqueous extraction of polyphenols from borage (Borago officinalis L.) leaves by pulsed electric fields: Pulsed electric fields (PEF) applications. Industrial Crops & Products. 2015;65:390–396. https://doi.org/10.1016/j.indcrop.2014.11. 010.
26. Abdullah SH, Zhao S, Mittal GS, Baik OD. Extraction of podophyllotoxin from Podophyllum peltatum using pulsed electric field treatment. Separation and Purification Technology. 2012;93:92–97. https://doi.org/10.1016/j.seppur.2012.04.002.
27. Silva FVM, Martins A, Salta J, Neng NR, Nogueira JMF, Mira D, *et al*. Phytochemical profile and anticholinesterase and antimicrobial activities of supercritical versus conventional extracts of Satureja montana. Journal of Agricultural and Food Chemistry. 2009;57(24):11557–11563. https://doi.org/10.1021/ jf901786p.
28. Uddin MS, Sarker MZI, Ferdosh S, Akanda MJH, Easmin MS, Bt Shamsudin SH, *et al*. Phytosterols and their extraction from various plant matrices using supercritical carbon dioxide: A review. Journal of the Science of Food and Agriculture. 2015;95(7):1385–1394. https://doi.org/10.1002/jsfa.6833.
29. Ueno H, Tanaka M, Machmudah S, Sasaki M, Goto M. Supercritical carbon dioxide extraction of valuable compounds from citrus junos seed. Food and Bioprocess Technology. 2008;1(4):357–363. https://doi.org/10.1007/s11947-007-0015-0.
30. Capuzzo A, Maffei ME, Occhipinti A. Supercritical fluid extraction of plant flavors and fragrances. Molecules. 2013;18(6):7194–7238. https://doi.org/10.3390/ molecules18067194.
31. Brunner G. Supercritical gases as solvents: Phase equilibria. Gas extraction: An introduction to fundamentals of supercritical fluids and the application to separation processes. New York: Steinkopff-Verlag, 1994, 59-146.
32. Cao H, Xiao JB, Xu M. Comparison of volatile components of Marchantia convoluta obtained by supercritical carbon dioxide extraction and petrol ether extraction. Journal of Food Composition and Analysis. 2007;20(1):45–51. https://doi.org/10. 1016/j.jfca.2006.06.004.
33. Xiao JB, Chen JW, Xu M. Supercritical fluid CO2 extraction of essential oil from Marchantia convoluta: Global yields and extract chemical composition. Electronic Journal of Biotechnology. 2007;10(1):141–148. https://doi.org/10.2225/vol10-issue1- fulltext-3.
34. Peng CH, Su JD, Chyau CC, Sung TY, Ho SS, Peng CC, Peng RY. Supercritical fluid extracts of rosemary leaves exhibit potent anti-inflammation and anti-tumor effects. Bioscience, Biotechnology, and Biochemistry.

2007;71(9):2223–2232. https://doi.org/10.1271/bbb.70199.
35. Topala CM, Tataru LD. ATR-FTIR study of thyme and rosemary oils extracted by supercritical carbon dioxide. Revista de Chimie. 2016;67(5):842–846.
36. Vázquez E, García-Risco MR, Jaime L, Reglero G, Fornari T. Simultaneous extraction of rosemary and spinach leaves and its effect on the antioxidant activity of products. The Journal of Supercritical Fluids. 2013;82:138–145. https://doi.org/10.1016/j.supflu.2013.07.004.
37. Vicente G, Molina S, Gonzalez-Vallinas M, Garcia-Risco MR, Fornari T, *et al*. Supercritical rosemary extracts, their antioxidant activity and effect on hepatic tumor progression. Journal of Supercritical Fluids. 2013;79:101–108. https://doi.org/10.1016/j.supflu.2012.07.006.
38. Arranz E, Jaime L, Lopez Hazas MC, Vicente G, Reglero G, Santoyo S. Supercritical sage extracts as anti-inflammatory food ingredients. Industrial Crops and Products. 2014;54:159–166. https://doi.org/10.1016/j.indcrop.2014.01.021.
39. Wang L, Song Y, Liu X, Cheng Y, Qu H. Development and validation of a method for the determination of tanshinones in supercritical fluid extraction products by HPLC. Journal of Liquid Chromatography & Related Technologies. 2008;31(4):543–554. https://doi.org/10.1080/10826070701812772.
40. Yang B, Chen J, Lee FSC, Wang X. GC-MS fingerprints for discrimination of Ligusticum chuanxiong from Angelica. Journal of Separation Science. 2008;31(18):3231–3237. https://doi.org/10.1002/jssc.200800332.
41. Vidović S, Zeković Z, Marošanović B, Todorović MP, Vladić J. Influence of pre-treatments on yield, chemical composition and antioxidant activity of Satureja montana extracts obtained by supercritical carbon dioxide. The Journal of Supercritical Fluids. 2014;95:468–473. https://doi.org/10.1016/j.supflu.2014.10.019.
42. Zeković Z, Pintać D, Majkić T, Vidović S, Mimica-Dukić N, Teslić N, *et al*. Utilization of sage by-products as raw material for antioxidants recovery - Ultrasound versus microwave-assisted extraction. Industrial Crops and Products. 2017;99:49–59. https://doi.org/10.1016/j.indcrop.2017.01.028.
43. Biljana DV, Svetlana P, Lu T, Regina S. Effect of matrix pretreatment on the supercritical CO2 extraction of Satureja montana essential oil. Chemical Industry and Chemical Engineering Quarterly. 2016;22(2):201–209.
44. Beňová B, Adam M, Pavlíková P, Fischer J. Supercritical fluid extraction of piceid, resveratrol and emodin from Japanese knotweed. The Journal of Supercritical Fluids. 2010;51(3):325–330. https://doi.org/10.1016/j.supflu.2009.10.009
45. Manpong P, Douglas S, Douglas PL, Pongamphai S, Teppaitoon W, Kaewprakaisangkul O. Response surface methodology applied to the extraction of phenolic compounds from Jatropha curcas Linn. Leaves using supercritical CO2 with a methanol CO-solvent. Journal of Food Process Engineering. 2011;34(5):1661–1681. https://doi.org/10.1111/j.1745-4530.2009.00552.x.
46. Mitra P, Barman PC, Chang KS. Coumarin extraction from Cuscuta reflexa using supercritical fluid carbon dioxide and development of an artificial neural network model to predict the coumarin yield. Food and Bioprocess Technology. 2011;4(5):737–744. https://doi.org/10.1007/s11947-008-0179-2.
47. Wang LH, Mei YH, Wang F, Liu XS, Chen Y. A novel and efficient method combining SFE and liquid–liquid extraction for separation of coumarins from Angelica dahurica. Separation and Purification Technology. 2011;77(3):397–401. https://doi.org/10.1016/j.seppur.2010.12.020.
48. Kukula-Koch W, Aligiannis N, Halabalaki M, Skaltsounis AL, Glowniak K, Kalpoutzakis E. Influence of extraction procedures on phenolic content and antioxidant activity of Cretan barberry herb. Food Chemistry. 2013;138(1):406–413. https://doi.org/10.1016/j.foodchem.2012.10.045.
49. Sovova H, Sajfrtova M, Topiar M. Supercritical CO2 extraction of volatile thymoquinone from Monarda didyma and M. fistulosa herbs. The Journal of Supercritical Fluids. 2015;105:29–34. https://doi.org/10.1016/j.supflu.2015.01.004.
50. Wei MC, Yang YC, Chiu HF, Hong SJ. Development of a hyphenated procedure of heat-reflux and ultrasound-assisted extraction followed by RP-HPLC separation for the determination of three flavonoids content in Scutellaria barbata D. Don. Journal of Chromatography B. 2013;940:126–134. https://doi.org/10.1016/j.jchromb.2013.09.015.
51. Petrović NV, Petrović SS, Džamić AM, Ćirić AD, Ristić MS, Milovanović SL *et al*. Chemical composition, antioxidant and antimicrobial activity of Thymus praecox supercritical extracts. The Journal of Supercritical Fluids. 2016;110:117–125. https://doi.org/10.1016/j.supflu.2016.01.001.
52. Villanueva Bermejo D, Angelov I, Vicente G, Stateva RP, Rodriguez García-Risco M, Reglero G *et al*. Extraction of thymol from different varieties of thyme plants using green solvents. Journal of the Science of Food and Agriculture. 2015;95(14):2901–2907. https://doi.org/10.1002/jsfa.7031.
53. Nerome H, Ito M, Machmudah S, Wahyudiono KH, Goto M. Extraction of phytochemicals from saffron by supercritical carbon dioxide with water and methanol as entrainer. The Journal of Supercritical Fluids,.2016;107:377–383. https://doi.org/10.1016/j.supflu.2015.10.007.
54. Martinez-Correa HA, Bitencourt RG, Kayano ACAV, Magalhães PM, Costa FTM, *et al*. Integrated extraction process to obtain bioactive extracts of Artemisia annua L. leaves using supercritical CO2, ethanol and water. Industrial Crops and Products. 2017;95:535–542. https://doi.org/10.1016/j.indcrop.2016. 11.007.
55. Villanueva Bermejo D, Angelov I, Vicente G, Stateva RP, Rodriguez García-Risco M, Reglero G, *et al*. Extraction of thymol from different varieties of thyme plants using green solvents. Journal of the Science of Food and Agriculture. 2015;95(14):2901–2907. https://doi.org/10.1002/jsfa.7031.
56. Petrović NV, Petrović SS, Džamić AM, Ćirić AD, Ristić MS, Milovanović SL, *et al*. Chemical composition, antioxidant and antimicrobial activity of Thymus praecox supercritical extracts. The Journal of Supercritical Fluids. 2016;110:117–125.

https://doi.org/10.1016/j.supflu.2016.01.001.
57. Considine KM, Kelly AL, Fitzgerald GF, Hill C, Sleator RD. Highpressure processing - effects on microbial food Microbiology Letters.2008;281(1):1–9. https://doi.org/10.1111/j.1574-6968.2008. 01084.x.
58. Robert S, Alexander M. Continuous versus discontinuous ultra-high-pressure systems for food sterilization with focus on ultra-high-pressure homogenization and high-pressure thermal sterilization: A review. Comprehensive Reviews in Food Science and Food Safety. 2018;17(3):646–662. https://doi.org/10.1111/1541-4337.12348.
59. US-FDA. Kinetics of microbial inactivation for alternative food processing technologies - High pressure processing, 2000. http://www.fda.gov/Food/Food Science Research Safe Practices for Food Processes/ucm101456.htm.
60. Shouquin Z, Ruizhan C, Hua W, Changzheng W. Ginsenoside extraction from Panax quinquefolium L. (American ginseng) root by using ultrahigh pressure. Journal of Pharmaceutical and Biomedical Analysis. 2006;41(1):57–63. https://doi.org/10. 1016/j.jpba.2005.10.043.
61. Shouqin Z, Xi J, Changzheng W. High hydrostatic pressure extraction of flavonoids from propolis. Journal of Chemical Technology & Biotechnology. 2005;80(1):50–54. https://doi.org/10.1002/jctb.1153.
62. Chen R, Meng F, Zhang S, Liu Z. Effects of ultrahigh pressure extraction conditions on yields and antioxidant activity of ginsenoside from ginseng. Separation and Purification Technology. 2009;66(2):340–346. https://doi.org/10.1016/j.seppur.2008. 12.026.
63. Qadir SA, Kwon MC, Han JG, Ha JH, Chung HS, Ahn J, Lee HY. Effect of different extraction protocols on anticancer and antioxidant activities of *Berberis koreana* bark extracts. Journal of Bioscience and Bioengineering. 2009;107(3):331-338. https://doi.org/10.1016/j.jbiosc.2008.11.021.
64. Altuner EM, Çeter T, Alpas H. High hydrostatic pressure processing: A method having high success potential in pollen protein extraction. High Pressure Research. 2012;32(2):291–298. https://doi.org/10.1080/08957959.2012.678341.
65. Yan HX. Separation engineering. Beijing: China Petrochemical Press; c2002.
66. Sadus RJ. High pressure phase behaviour of multicomponent fluid mixtures. Amesterdam: Elsevier Science; c2012.
67. Huang HW, Hsu CP, Yang BB, Wang CY. Advances in the extraction of natural ingredients by high pressure extraction technology. Trends in Food Science & Technology. 2013;33(1):L54–62. https://doi.org/10.1016/j.tifs.2013.07.001.
68. Chen R, Meng F, Zhang S, Liu Z. Effects of ultrahigh pressure extraction conditions on yields and antioxidant activity of ginsenoside from ginseng. Separation and Purification Technology. 2009;66(2):340–346. https://doi.org/10.1016/j.seppur.2008. 12.026.
69. Lee HY, He X, Ahn J. Enhancement of antimicrobial and antimutagenic activities of Korean barberry (*Berberis koreana* Palib.) by the combined process of high-pressure extraction with probiotic fermentation. Journal of the Science of Food and Agriculture. 2010;90(14):2399–2404. https://doi.org/10.1002/jsfa.4098.
70. Shin JS, Ahn SC, Choi SW, Lee DU, Kim BY, Baik MY. Ultra high pressure extraction (UHPE) of ginsenosides from Korean Panax ginseng powder. Food Science and Biotechnology. 2010;19(3):743–748. https://doi.org/10.1007/s10068-010- 0104-0.
71. Zhu Q, Liu F, Xu M, Lin X, Wang X. Ultrahigh pressure extraction of lignan compounds from *Dysosma versipellis* and purification by high-speed counter-current chromatography. Journal of Chromatography B, 2012;905:145–149. https://doi.org/10. 1016/j.jchromb.2012.08.016.
72. He X, Kim SS, Park SJ, Seong DH, Yoon WB, Lee H, *et al*. Combined effects of probiotic fermentation and high-pressure extraction on the antioxidant, antimicrobial, and antimutagenic activities of deodeok (*Codonopsis lanceolata*). Journal of Agricultural and Food Chemistry. 2010;58(3):1719–1725. https://doi. org/10.1021/jf903493b.