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REVIEW ARTICLE

Enhancement of Bioactivity of Natural Extracts by Non-Thermal High Hydrostatic Pressure Extraction

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Abstract

Natural extracts, like those obtained from medicinal herbs, dietary plants and fruits are being recognized as important sources of bioactive compounds with several functionalities including antioxidant, anticancer, and antimicrobial activities. Plant extracts rich in phenolic antioxidants are currently being successfully used for several pharmaceutical applications and in the development of new foods (i.e., functional foods), in order to enhance the bioactivity of the products and to replace synthetic antioxidants. The extraction method applied in the recovery of the bioactive compounds from natural materials is a key factor to enhance the bioactivity of the extracts. However, most of the extraction techniques have to employ heat, which can easily lead to heat-sensitive compounds losing their biological activity, due to changes caused by temperature. Presently, high hydrostatic pressure (HHP) is being increasingly explored as a cold extraction method of bioactive compounds from natural sources. This non-thermal high hydrostatic pressure extraction (HHPE) technique allows one to reduce the extraction time and increase the extraction of natural beneficial ingredients, in terms of nutritional value and biological activities and thus enhance the bioactivity of the extracts. This review provides an updated and comprehensive overview on the extraction efficiency of HHPE for the production of natural extracts with enhanced bioactivity, based on the extraction yield, total content and individual composition of bioactive compounds, extraction selectivity, and biological activities of the different plant extracts, so far studied by extraction with this technique.

Keywords Natural extract · High hydrostatic pressure · Extraction · Antioxidant activity · Phenolic compounds

Abbreviations

HPP	High pressure processing
HHP	High hydrostatic pressure
HHPE	High hydrostatic pressure extraction
CE	Conventional extraction
HRE	Heat reflux extraction
LRT	Leaching at room temperature
UE	Ultrasonication extraction

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Introduction

Oxidative damage of biomolecules (*e.g.*, lipids, proteins, and DNA) plays a major role in the development of chronic and degenerative illnesses such as cancer, autoimmune disorders, aging, cataracts, rheumatoid arthritis, cardiovascular, and neurodegenerative diseases. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally synthesized *in situ*, or externally supplied through foods, and/or supplements [1, 2].

The natural extracts of medicinal herbs, fruits, vegetables, spices, and others have been recognized as natural sources of antioxidants due to the presence of bioactive ingredients, including in most cases phenolic compounds [3]. Several studies have indicated that the plants containing a high-level of phenolic antioxidants possess a good range of bioactivities, including antioxidant, antiviral, antiinflammatory, and anticancer properties [4–6]. Moreover, they have shown higher antioxidant activity *in vitro* than vitamin E, vitamin C as well

as butylated hydroxytoluene (BHT), a widely used synthetic antioxidant [7, 8]. Therefore, plant extracts rich in phenolics are currently being successfully used in several pharmaceutical applications and in the development of new foods (*i.e.*, *functional foods*), in order to enhance the bioactivity of food products and to replace synthetic antioxidants [9, 10].

Total phenolics content is often considered as an indicator of the antioxidant activity of plant extracts [11, 12]. However, other studies have referred that the antioxidant activity does not necessarily always correlate with the level of total phenolics compounds, but sometimes with the content of particular individual phenolics [9]. For example, the antioxidant activity of pomegranate peel extract has been associated with the predominant phenolics in the form of ellagitannins, mainly ellagic and gallic acids, and punicalagin [13]. According to Guimarães et al. [14], the bioactivity of wild fruits proved to be more related to the phenolic compounds profile than to the amounts present in each extract [14]. It has been suggested that both phenolic content and antioxidant activity information must be discussed when evaluating the antioxidant/bioactive potential of extracts [9]. In fact, the levels of total and individual phenolics compounds vary depending on the plant parts used as starting material and can be altered by storage conditions and the extraction procedure [15].

The aim of an efficient extraction procedure is to provide the maximum yield of substances with the highest functional properties [16], enhance the bioactivity of the extracts, increase pollution prevention [17], and shorten extraction time [18]. However, most of the extraction techniques have to employ heat, which is most likely detrimental to the bioactivity of the extracts, due to heat promoted reactions [19]. The conventional extraction (CE) is time consuming and laborious, has low selectivity, and/or low extraction yield [20]. The combination of long extraction times and high temperature increases the chance of oxidation of phenolics which decreases the yield of phenolics in the extracts [7]. Moreover, the plant cell walls contain polysaccharides (*e.i.*, cellulose, hemicellulose, and pectins) which act as barriers to the release of the intracellular bioactive compounds. Thus, alternative extraction methods, which are able to efficiently disrupt the cells and to recover these active secondary metabolites from raw plant materials are a key factor to enhance the bioactivity of plant extracts [21, 22].

Non-thermal high pressure processing (HPP), operating at room or at refrigeration temperature, is an alternative to thermal pasteurization with the advantage of providing foods with similar characteristics to the raw unprocessed foods [23], while retaining/improving important nutritive and functional properties [24]. HPP was recognized by the Food and Drug Administration (FDA) as an environmentally friendly technology and currently is being increasingly studied as a very promising cold extraction method of bioactive compounds from natural materials [25].

High hydrostatic pressure extraction (HHPE) is considered a good alternative in comparison to CE techniques, such as soxhlet, heat reflux, infusion, and distillation, since the extraction of compounds can be done in shorter time, the process may be performed at room temperature (avoiding thermal degradation of thermosensitive molecules), and it can improve the extraction efficiency in terms of higher extraction yields, less solvent consumption, and higher purity of the extracts [21]. Recently, it has been shown that HHPE has obvious superiority in obtaining higher quality of natural antioxidant substances [21], which can lead to the production of extracts with enhanced bioactivities [26]. The present paper aims to review the extraction efficiency of the HHPE based on the extraction yield, total content, and individual composition of bioactive compounds, extraction selectivity, and biological activities of the different plant extracts so far studied by extraction with this technique. It is important to highlight that this paper is focused specifically on the extracts instead of purified bioactive components, as some information regarding purified components can be found elsewhere [25, 27, 28].

Extraction Process of HHPE

The HHPE process is performed in a HHP processing unit (Fig. 1), basically consisting of a high hydrostatic vessel and the pressure generating system. The raw material is mixed with the appropriate solvent and hermetically sealed in a sterile high-density-polyethylene bag [29]. Furthermore, the samples are pressurized in the vessel of different volume ranges from <8 mL (laboratory scale) to the current maximum volume reaching 525 L (industrial scale equipment) [30, 31]. In HHPE the hydrostatic pressure is applied in the range of 100 to 600 MPa or even more, up to 1000 MPa for short time periods [32].

The pressure is generated by pumping liquid medium (*i.e.*, water in industrial equipment, silicon oil, ethanol, glycerol, or a mixture of these fluids with water in laboratory equipment) into the pressure chamber. When the desired pressure is reached, the pump is stopped and the pressure is maintained during the required holding time to extract and dissolve the active components by the solvent action, and then the system is depressurized [27].

The Principle and Mechanism of HHPE for Enhancing Extraction of Bioactive Compounds

One main advantage of using low/room temperature during HHPE results in the retention of thermo-sensitive components, such as bioactive compounds [33]. It is generally accepted that HHP mainly affects non-covalent bonds

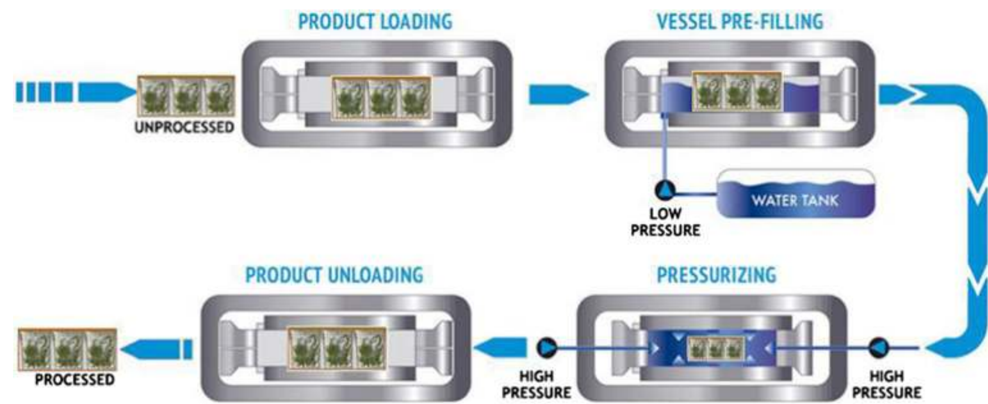

Fig. 1 Schematic diagram of an HHPE technique in an HPP unit (Courtesy of Hyperbaric Company). The sample material (*e.g.* fresh, dried, and powdered) is mixed with an appropriate solvent and hermetically sealed in a high-density-polyethylene bag. The sample is extracted in vessels under pressure in the range of 100–1000 MPa for a short time [28]

(hydrogen, electrostatic, Van der Waals, and hydrophobic bonds) [27], which means that low molecular weight compounds, such as many bioactive compounds (*e.g.*, vitamins, pigments, flavor ingredients, flavonoids) are less affected [34, 35] and thus the HHPE treatment can preserve most of the bioactive compounds better [21]. The level of pressure is one of the most important parameters of the extraction process, due to its direct correlation with the solubility of bioactive compounds. Jun et al. [36] stated that increasing pressure increased solubility of the soluble constituents and enhanced the equilibrium concentration in the extract [36]. In a later study, the authors reported, that the pressure had direct mechanical effect on the disruption of organelle and blend of cellular contents [21]. When the pressure is released, the cell wall disrupts and releases the cytoplasm, which contains a high concentration of the target materials and removes them into the solvent. Both effects are thought as the major reason for the high efficiency of the HHPE method. To understand the structural changes involved in the HHPE, Fig. 2 displays the micrographs with structural features of untreated, HHPE and CE (reflux extraction) samples of *Radix Angelica sinensis*. After HHPE, the surface of the sample was greatly destroyed and the texture was crumbled (Fig. 2b), the tissue became porous and some micro-fractures and hollow openings were generated, while the surface of the CE sample (Fig. 2c) was complete and compact. Moreover, severe damage on cell walls and cellular organelles were observed after HHPE (Fig. 2e) while the CE sample remained, basically, unchanged (Fig. 2f). The destruction of cells and tissues by HHPE most probably facilitates mass transfer between cellular contents and the surrounding solvent and subsequently improves extraction efficiency [37]. The rate at which the pressure is applied and released is important for the cell rupture, thus a short extraction period is enough to harvest a highly concentrated extract [26]. Moreover, a recent study by Yan and Xi [21] refers that HPP pre-treatments can be a possible way to improve HHPE, since the former cause cellular disruption, favoring cell fracture by the latter [21]. The recovery of bioactive compounds in the HHPE process depends on processing factors like extraction pressure, temperature, time, type and concentration of solvent, and solvent-to-solid ratio, which are considered the main HHPE parameters [25]. For instance, the recovery of phenolic compounds from watercress was maximized when high pressure (600 MPa), high ethanol concentration (100%) and short extraction time (3.1 min) were applied. The solvent was found to be the most relevant variable on the HHPE of phenolic compounds from watercress [38]. Indeed, different solvents can be used in HHPE; therefore, it is possible to extract compounds with different polarities differentially. The pH value of the solvent can be reduced during the HHPE leading to the enhancement of the extraction effectiveness of some bioactive compounds, such as, for instance, anthocyanins, since most of these compounds are more stable at $pH < 4$ [39]. Hence, the medium plays an important role in the extraction of bioactive compounds, but also in the antioxidant activity of the obtained extracts.

Enhanced Antioxidant and Anticancer Activity of Natural Extracts by HHPE

Some studies examined the optimal extraction conditions of HHPE in order to maximize the bioactivity of the natural extracts from different plant materials. The main parameters considered were extraction yield and total and individual content of bioactive compounds (mostly phenolic compounds), but also the extraction selectivity and the different biological activities of the extracts. The works so far reported in the literature, dealing with the biological activity of natural extracts obtained by HHPE, are presented in Table 1, including the extraction conditions used and the main results obtained that are discussed below.

Green Tea Extract

Green tea is increasingly popular worldwide, mainly due to its wide range of bioactive properties including antioxidant and anticarcinogenic effects. Studies have suggested that the most

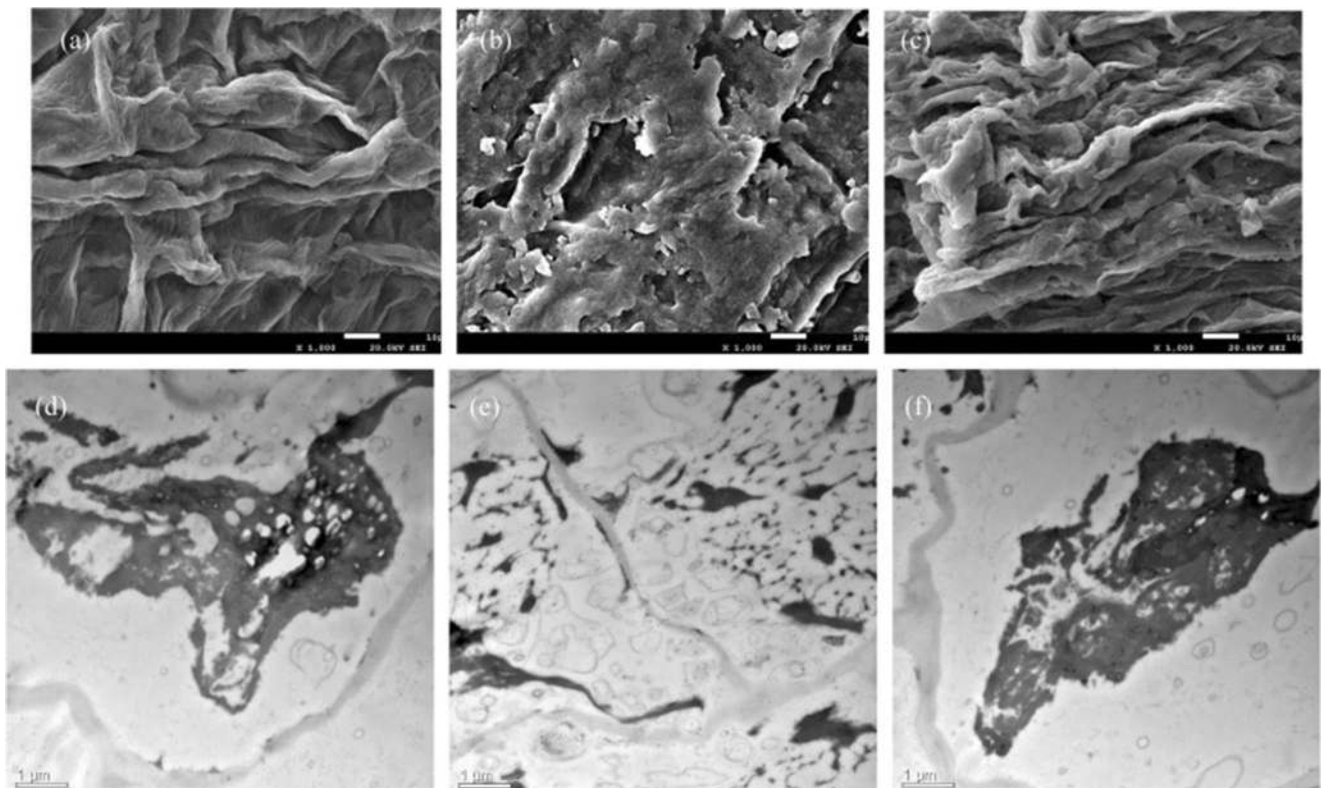

Fig. 2 Scanning electron micrographs (a, b, c) and transmission electron micrographs (d, e, f) of the untreated, HHPE and CE (reflux extraction) samples of green tea leaves, respectively; (a, d) untreated samples; (b, e) HHPE samples (300 MPa for 10 min); (c, f) CE. Adapted from [37] with permission

favorable effects of green tea extracts are attributable to the green tea polyphenolic compounds, mainly catechins. However, a heating treatment during the extraction can decrease the antioxidant activity of green tea due to oxidation, thermal degradation, epimerization, and polymerization of these compounds [48]. Xi and Wang [40] investigated the potential of the HHPE of green tea leaves, aiming to produce extracts containing a higher level of polyphenolics with enhanced antioxidant activity [40]. In comparison with CE, the green tea extract obtained by HPE at 490 MPa, at room temperature, and during a shorter time (15-fold less), possessed significantly higher α-diphenyl-β-picrylhydrazyl radical (DPPH) scavenging activity (Table 1). Furthermore, Xi et al. [41] studied the effect of HHPE at different pressures (150, 250, 350, and 450 MPa) on the total phenolics content, extraction yields, and the antioxidant activity of green tea extracts [41]. The results showed that the phenolics and the antioxidant activities of extracts were greatly influenced by high pressure. The total phenolics content and the antioxidant activity of the extract obtained by HPE at 450 MPa was higher than by conventional heat reflux extraction (HRE) (Table 1). In both studies just presented, the higher content of phenolic compounds in the green tea leaves was indicated as the cause for the higher antioxidant activity of the extracts. Thus, it has been concluded that HHPE can be a tool to improve the antioxidant activity of green tea extract.

However, the increased antioxidant activity is not necessarily due only to the high total phenolic content in the extract. For instance, for a green tea extract with a high amount of phenolics with antioxidant properties, 78% of the antioxidant activity of the extracts was attributed to the particular presence of individual phenolics of the extracts, such as catechins and catechin gallate esters [48, 49].

Extract of Propolis and Litchi Fruit Pericarp

Propolis, the natural resinous substance produced by honeybees from various plant sources, is considered a good source of natural antioxidants such as aromatic acids, phenolic compounds, especially flavonoids (flavones, flavonols, and flavonones), and phenolic acids [50]. HHPE enhanced the antioxidant activity of an ethanolic extract of propolis, with only 1 min of extraction time (Table 2). The CE methods like HRE and leaching at room temperature (LRT) were applied during 240 and 10,080 min compared with only 1 min for HHPE, respectively. Even so, the antioxidant activity of the ethanolic extract of propolis obtained by HHPE (86.6%) was very similar to the results obtained for the tert-butylhydroquinone (87.6%), a synthetic antioxidant compound commonly used in processed foods. The higher *in vitro* antioxidant activity of this extract was correlated with higher total

Table 1 Characterization of plant extracts obtained by high hydrostatic pressure extraction (HHPE), combined process of HHPE with probiotic fermentation, conventional solvent extraction (CE), and ultrasound extraction (UE)

Extract	Initial material	Extraction method	Pressure (MPa)	Time	Temperature (°C)	Solvent concentration (% raw material:solvent [g/mL])	Extraction yield of crude extract (%)	Total phenolic content mg/g DW	Antioxidant activity (solid-liquid concentration of sample [μg/mL])		Other biological activities (solid-liquid concentration of sample [μg/mL] or content of bioactive compounds)		Reference
Green tea	Dried/24 h/ hot air oven at 50 °C/powdered	HHPE	490	15 min	25	50% EtOH (1:20)		583.8	DPPH (%)	85.6			[40]
		CE		4 h	85	50% EtOH (1:20)		440	DPPH (%)	58.6			
	Dried/24 h/ hot air oven at 50 °C/powdered	HHPE	150	5 min	25	50% EtOH (1:20)	23.4	383.4	DPPH (%) Total antioxidant capacity	51.8 (50) 61.8 (100) 1.04 (100)			[41]
		HHPE	450	5 min	25	50% EtOH (1:20)	35.6	578.2	DPPH (%) Total antioxidant capacity	83.23 (50) 88.36 (100) 0.99 (100)			
		CE		4 h	100	50% EtOH (1:20)	38.7	439.4	Total antioxidant capacity	0.77 (100)			
Chilean papaya (*Vasconcellea pubescens*)	Papaya seeds (5 g)	HHPE	500	5 min	RT	80% MeOH	5.39	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	41.44	[42]
				10 min	RT	80% MeOH	5.92	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	57.48	
				15 min	RT	80% MeOH	6.49	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	54.97	
		UE		5 min	RT	80% MeOH	4.19	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	32.32	
				10 min	RT	80% MeOH	4.23	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	38.81	
				15 min	RT	80% MeOH	4.75	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	47.82	
		CE		30 min		80% MeOH	3.94	[Fig. 4]	DPPH (%)	[Fig. 3]	Sulforaphane (mg/g seeds)	9.14	
Longan fruit pericarp *(Dimocarpus longan* L.)	Dried/24 h/ hot air oven at 60 °C)/ powdered	CE		4 h	85	50% EtOH (1:20)		440	DPPH (%)	58.6	Anticancer activity (%) human cell lines: SGC 7901 HepG2 A549	37.6 (50) −0.22 (100) 11.96 (100)	[43]
	Dried/24 h/ hot air oven at 50 °C/powdered	HHPE	150	5 min	25	50% EtOH (1:20)	23.4	383.4	DPPH (%) Total antioxidant capacity	51.8 (50) 61.8 (100) 1.04 (100)	Anticancer activity (%) (human cell lines): SGC 7901 HepG2 A549	30.58 (50) −0.54 (100) NA (100)	
	Dried/24 h/ hot air oven at 60 °C)/ powdered	HHPE	450	5 min	25	50% EtOH (1:20)	35.6	578.2	DPPH (%) Total antioxidant capacity	83.23 (50) 88.36 (100) 0.99 (100)	Tyrosinase inhibitory activity (%)	23.6 (100)	[44]
		CE		4 h	100	50% EtOH (1:20)	38.7	439.4	Total antioxidant capacity	0.77 (100)	Tyrosinase inhibitory activity (%)	19.5 (100)	
		HHPE	500	30 min	30	50% EtOH	17.7	20.8	DPPH (%)	78 (50)			[45]

Table 1 (continued)

Extract	Initial material	Extraction method	Pressure (MPa)	Time	Temperature (°C)	Solvent concentration (% raw material:solvent [g/mL])	Extraction yield of crude extract (%)	Total phenolic content mg/g DW	Antioxidant activity (solid-liquid concentration of sample [μg/mL])		Other biological activities (solid-liquid concentration of sample [μg/mL] or content of bioactive compounds)		Reference
	Dried/36 h/ hot air oven at 60 °C)/ powdered					(1:50)			Reducing power Total antioxidant capacity Superoxide anion scavenging (%) Lipid peroxidation inhibitory activity (%)	3.1 (100) 0.91 (100) 61.6 (100) 90.7 (100)			
		UE		30 min	30	50% EtOH (1:50)	14.1	16.1	DPPH (%) Reducing power Total antioxidant capacity Superoxide anion scavenging (%) Lipid peroxidation inhibitory activity (%)	55 (50) 2.8 (100) 0.73 (100) 56 (100) 68.3 (100)			
		CE		30 min	30	50% EtOH (1:50)	7.2	12	DPPH (%) Reducing power Total antioxidant capacity Superoxide anion scavenging (%) Lipid peroxidation inhibitory activity (%)	52 (50) 2.8 (100) 0.80 (100) 55.6 (100) 68 (100)			
Longan fruit pericarp *(Dimocarpus longan* L.)	Dried/24 h/ hot air oven at 60 °C/powdered	HHPE	500	2.5 min	30	50% EtOH (1:50)	17.8	21	DPPH (%) Superoxide anion scavenging (%)	77 (100) 61.6 (100)			[32]
		CE		12 h	30	50% EtOH (1:50)	14.8	14.2	DPPH (%) Superoxide anion scavenging (%)	76.6 (100) 56.6 (100)			
Korean barberry *bark (Berberis koreana)*	Fresh	HHPE	500	5 min	25	water (1:10)	11.41	324.89	Inhibitory activity on xanthine oxidase (%)	56.68	Anticancer activity IC_{50} (μg/mL) (human cell lines) [a]: A549 AGS MCF-7 Hep 3B Cytotoxic activity in normal human kidney cells HEK293 IC_{50} (μg/mL) [a] NK cell activity (cells/mL)	340.26 276.01 147.99 159.60 1549.94 12.4×10^4	[29]

Table 1 (continued)

Extract	Initial material	Extraction method	Pressure (MPa)	Time	Temperature (°C)	Solvent concentration (% raw material:solvent [g/mL])	Extraction yield of crude extract (%)	Total phenolic content mg/g DW	Antioxidant activity (solid-liquid concentration of sample [μg/mL])		Other biological activities (solid-liquid concentration of sample [μg/mL] or content of bioactive compounds)		Reference
		HHPE	500	15 min	25	water (1:10)	11.04	317.35	Inhibitory activity on xanthine oxidase (%)	55.6	Anticancer activity IC_{50} (μg/mL) (human cell lines) [a]: A549 AGS MCF-7 Hep 3B Cytotoxic activity in normal human kidney cells HEK293 IC_{50} (μg/mL) [a] NK cell activity (cells/mL)	423.61 489.90 204.23 282.22 1996.52 11.9×10^4	
		CE		24 h	60	water (1:20)	8.39	244.16	Inhibitory activity on xanthine oxidase (%)	44.3	Anticancer activity IC_{50} (μg/mL) (human cell lines) [a]: A549 AGS MCF-7 Hep 3B Cytotoxic activity in normal human kidney cells HEK293 IC_{50} (μg/mL) [a] NK cell activity (cells/mL)	729.01 170.45 128.32 718.50 1282.79 10.4×10^4	
Litchi fruit pericarp *(Litchi chinensis* Sonn.*)*	Dried/36 h/ hot air oven at 80 °C/ powdered	HHPE	500	2.5 min	30	85% EtOH +15% HCl (5:200)	29.3		DPPH (%) Superoxide anion scavenging (%)	74 58 (100)			[46]
Red grape skin (*Vitis vinifera* L.)	Stored frozen before utilization	HHPE	600	30 min 60 min 90 min	70	50% EtOH (1:4.5)			Antioxidant capacity (TE mol TE g^{-1} DM)	286.08 548.49 716.67			[47]

[a] The IC_{50} values (the extract concentration reducing the absorbance in treated cells by 50%, with respect to untreated cells) were calculated by the LOGIT method

[b] The EC_{50} represents the effective concentration required to scavenge DPPH radicals by 50%

[c] The $EC_{0.5}$ represents the effective concentration required to achieve an absorbance of 0.5

[d] RT, room temperature

polyphenolics and flavonoids contents. The ethanolic extract of propolis obtained by HHPE provided higher total flavones, flavonols, flavanones, and dihydroflavonols contents, in comparison to HRE (Table 2). Interestingly, HRE resulted in a similar extraction yield of total polyphenols (6.51%) compared to HHPE (6.43%), but the total content of polyphenols was significantly lower in HRE samples. It has been reported that the high ethanol concentration [95% (*v*/v)] used in HRE, results in the extraction of larger amounts of non-polar components and in the decrease of total polyphenols and flavonoids contents [51].

Similarly, Prasad et al. [52] reported a higher extractability of flavonoids from litchi fruit pericarp (*Litchi chinensis* Sonn.) by HHPE [52]. HHPE enhanced the flavonoid extraction yield up to 2.6-fold and up to 10-fold, in comparison with ultrasonication extraction (UE) and CE, respectively. The major flavonoids identified in the extract of litchi pericarp tissues by HHPE at 200 MPa, HHPE at 400 MPa and CE were epicatechin and epicatechin gallate along with catechin and procyanidin B2 as the minor compounds (Table 3). The increasing pressure correlated with the increasing amount of each compound. HHPE at 400 MPa significantly improved the level of catechin to 0.016 mg/g DW and consequently provided the highest total content of flavonoids in the extract, fostering the conclusion that HHPE was more effective in the extraction of polyphenols. However, the antioxidant activity and total phenolic content of the extract were comparable among the three extraction methods [52]. In another study by the same author, he reported an increased extraction yield of the litchi fruit pericarp by HHPE (29.3%) during only 2.5 min, in comparison with CE (19.9%) and UE (23%), but similarly with no significant difference in total phenolic content and antioxidant activity between these extraction methods. In spite of this, the aspect of the extract obtained by HHPE was clear, while those obtained by CE and UE were cloudy and dark. Aside from the selectivity and increased content of the individual components of the bioactive ingredients involved in the extract, HHPE can influence the overall aspect of the extract, which may lead to the production of a natural extract of higher quality [46].

Schisandra chinensis Extract

Schisandra chinensis (Turcz.) Baill is used as a medical remedy due to its health-promoting properties, such as antioxidant and anticarcinogenic effects. The main active components associated with the bioactive effects of this plant are mainly lignans, including deoxyschisandrin, γ-schisandrin, and schisandrin, among others [28]. Liu et

Table 2 The *in vitro* antioxidant activity of ethanolic extract of propolis obtained by high hydrostatic pressure extraction (HHPE), leaching at room temperature (LRT), and heat reflux extraction (HRE) in relation to its extraction yield, total polyphenols, and individual flavonoids content

Extract	Initial material	Extraction method	Extraction conditions	Extraction yield [a]			Total content [b]			Antioxidant activity (%) [c]	
				Total polyphenols	Flavonone and flavonol	Flavanone and dihydroflavonol	Total polyphenols	Flavonone and flavonol	Flavanone and dihydroflavonol	DPPH	β-carotene linoleic acid system
Ethanolic extract of propolis	Frozen at −20 °C, ground	HHPE	500 MPa, 1 min, 25 °C, 75% EtOH (1:3.5)	6.43	5.10	0.68	290.4	230.4	30.7	86.8	75.5
		LRT	7 days, 25 °C, 70% EtOH (1:3.5)	6.35	4.70	0.64	296.0	232.1	31.6	87.1	74.6
		HRE	4 h, 85 °C, 95% EtOH (in water) (1:4)	6.51	4.66	0.71	247.7	167.9	21.8	80.6	67.2

Adapted from [51]

[a] Expressed as a percentage, g/g crude propolis

[b] Expressed as mg/g of an ethanolic extract of propolis

[c] Antioxidant activity at a sample concentration of 15 μg/mL

Table 3 Main individual flavonoids in litchi fruit pericarp extract (*Litchi chinensis* Sonn.) obtained by high hydrostatic pressure extraction (HHPE) at 200 and 400 MPa, conventional solvent extraction (CE), and ultrasound extraction (UE)

Extract	Initial material	Extraction conditions	Extraction method	Individual flavonoids (mg/g DW)				
				Epicatechin	Epicatechin gallate	Catechin	Procyanidin B_2	Total content
Litchi fruit pericarp (*Litchi chinensis* Sonn.)	Dried/36 h/ hot air oven at 80 °C/ powdered	30 min, 25 °C, 85% EtOH+ 1.5% HCl	HHPE-200	0.32	0.19	0.0016	0.14	0.6516
			HHPE-400	0.348	0.2527	0.0160	0.1346	0.7513
			CE	0.0414	0.0121	0.0002	0.0175	0.0712
			UE	0.16	0.06	0.0020	0.0731	0.2951

Adapted from [52]

al. [16] applied HHPE, HRE and UE extraction to *Schisandra chinensis* Baill aiming to increase the content of the active components and the antioxidant activity of the plant extract [17]. HHPE extracts possessed the highest antioxidant activity that was associated with the highest extraction yield of deoxyschisandrin and γ-schisandrin. The optimum extraction conditions were 400 MPa pressure, 90% ethanol-water solution, 90:1 liquid:solid ratio, and 5 min extraction time. In fact, the HHPE provided the highest extraction yield of these active compounds within 5 min, which was about 115 and 15 min shorter than HRE and UE, respectively. Thus, besides the advantage of HHPE to improve the antioxidant activity of the *Schisandra chinensis* extract, this extraction was the most economical extraction method for deoxyschisandrin and γ-schisandrin. The HHPE of *Schisandra chinensis* may provide an opportunity in the field of the discovery of new drugs based on lignans that constitute the main secondary metabolites of this plant.

Sargassum muticum Extract

The brown seaweed *Sargassum muticum* is rich in bioactive polysaccharides, which has several health benefits associated with it, such as antioxidant activity. Rodrigues et al. [53] evaluated the potential and the effectiveness of HHPE to obtain extracts concentrated in bioactive sulfated polysaccharides from *S. muticum* and tested the antioxidant activity of the extract [53]. The results demonstrated that the extraction yield ranged between 32 and 40.4% resulting in average increases of 3.6 to 4.8-fold for total sugars and sulfated sugars, as compared to CE. Extracts displayed improved antioxidant activities, yet maximum values were achieved at 300 MPa for 5–5.5 min and 1 g of dry seaweed for yield. HHPE increased extractability and bioactivity from the seaweed *S. muticum*, providing extracts with higher content in polysaccharides, which can be used as ingredients to develop novel functional foods.

Longan Fruit Pericarp and Korean Barberry Extracts

An extract of longan (*Dimocarpus longan* L.) fruit pericarp (LFP) has been reported to possess antioxidant, antiinflammatory, anticarcinogenic, and antihyperglycemic activities, mainly due to a great source of high quality phenolic compounds (*i.e.*, gallic acid, and ellagic acid, and corilagin) [54, 55]. Antioxidant model systems, including DPPH and superoxide anion scavenging [32, 43–45], lipid peroxidation inhibitory activity [43, 45], total antioxidant capacity scavenging [44, 45], and reducing power [45] were used to determine the antioxidant activity of the LFP extract obtained by HHPE and CE techniques (Table 1). The extract obtained by HHPE, at a pressure of 500 MPa, with 50% ethanol, at 30 °C for only 2.5 and 30 min, possessed the highest total phenolics content and antioxidant activity in comparison with CE, and UE methods (Table 1). The antioxidant activities correlated positively with the total content of phenolics present in the extracts. However, these results fail to report on the identities and content of the individual phenolics involved in the extracts obtained by HHPE and other methods. Nevertheless, a relationship between the intake of polyphenols and reduced risk of certain cancers has been found. The alteration of tyrosinase (EC 1.14.18.1), an enzyme involved in the production of melanin, has been referred as responsible for a part of the histopathological features which are unique to malignant melanoma. Its inhibition activity might be dependent on the hydroxyl group of the phenolic compounds that can form a hydrogen bond to a site of the enzyme, leading to lower enzymatic activity. The extract of LFP obtained by HHPE showed superior results indicating an almost 2-fold increase of total phenolics content and consequently higher tyrosinase inhibitory activity, compared to CE (Table 1) [44]. Three polyphenolic compounds, namely, gallic acid, ellagic acid, and corilagin were identified as the major phenolic acids in the LFP extract. The content of individual phenolics varied with increasing pressure (Table 4) [44]. The extract obtained by HHPE at 500 MPa contained an almost 2-fold higher amount of total phenolic acids (10.5 mg/g DW) when compared to those obtained by CE (5.4 mg/g DW).

HHPE extracts possessed excellent selectivity for corilagin in the LFP extract. According to the content of individual phenolic acids after HHPE, the corilagin content was 9.6 mg/g DW at 500 MPa, which was higher than the 2.3 mg/g DW obtained by CE (ethanol extraction using 50% ethanol for 30 min at 30 °C) (Table 4) [44]. In another study by this author, the corilagin content in LFP extract obtained by HHPE (at 500 MPa) was higher in comparison to the one obtained by UE and about 4-fold more in comparison to the extract obtained by CE (Table 4) [45]. This compound has been recognized as a potent antitumor herbal medicine, since it has been successfully applied for the inhibition of ovarian cancer cell growth [56]. The extracts of LFP by HHPE and CE were tested against some cancer cell lines. It has been found that the LFP extract obtained by HHPE was more effective to inhibit human cancer cell lines, like human gastric cancer cell lines (SGC-7901), and human lung carcinoma (A549), compared to CE (with ethanol), and even higher for SGC-7901 in comparison to Cisplatin, a commercial chemotherapy drug (Table 1) [43]. Likewise, the extract of the Korean barberry *(Berberis koreana*) obtained by HHPE at 500 MPa for 5 min (HHPE-5) demonstrated an enhanced *in vitro* inhibitory activity on the human cell lines, like A549 and human hepatocellular carcinoma (Hep3B) than the CE (Table 1). Moreover, this extract showed a higher exhibition effect on natural killer (NK) cell growth, compared to HPE at 500 MPa for 15 min, and CE. Generally, the NK cells have cytolytic activity against several tumors and it has been found that some bioactive compounds of plant origin can modulate the activity of the NK, which can be exploited for cancer prevention and treatment [57]. In both studies just presented, HHPE increased the anticancer activity of the extracts. The more efficient anticancer activity was verified in the extracts with the higher phenolic content. However, different and possibly useful compounds could be extracted using the HHPE rather than CE, which could contribute to the higher bioactivity of the extracts. Therefore, further investigation of the identification and effects of individual components is necessary to improve the extraction efficiency of HHPE.

Papaya Seeds and Fig Extracts

Papaya seeds are discarded after the fruit has been consumed, but they contain many bioactive compounds such as polyphenols, carotenoids and vitamin C. Moreover, some of these phytochemicals protect major biomolecules from oxidation caused by free radicals, thus preventing the onset of many chronic diseases, such as cancer, diabetes, and obesity. Exclusively, papaya is a unique fruit in the Caricaceae family, containing sulforaphane (SFN), belonging to the family of isothiocyanates [58]. The SFN is a compound considered to be an important and active substance for reducing the risk of cancer [59]. Briones-Labarca et al. [42] applied HHPE, UE, and CE to papaya by-products like papaya seeds, aiming to study their effect on the bioactive compounds. The results showed that HHPE was more effective than UE and CE methods as the former led to a higher extraction yield of SFN in a much shorter extraction time. The content of SFN in the papaya seed extract increased significantly in 353.4, 528.9 and 501.4% for HHPE at 500 MPa for 5, 10 and 15 min, respectively, and 253.6, 324.6, and 423.2% for UE by 5, 10 and 15 min, respectively, relative to CE (agitation for 1 h). Moreover, the extract obtained by HHPE showed the highest antioxidant capacity, total phenolic content, and flavonoid content (Figs. 3 and 4). The phenolic compounds and flavonoids have been suggested as being the primary contributors to the antioxidant activity of papaya seed extract. However, their individual identification has not been investigated yet. Nevertheless, these findings raise the possibility that HHPE can produce natural extracts enriched with bioactive compounds (*i.e.*, the natural anticancer compound SFN), which can have potential application in the pharmaceutical industry.

Similarly, Alexandre et al. [60] applied HHPE to obtain fig by-product derived extracts and its impact was evaluated as to antioxidant activity and total phenolic, tannin, and flavonoid compounds [60]. HHPE led to an increase of 8–13% of antioxidant activity and an increase of 8–11% of total phenolic, flavonoid, and tannin contents when compared to extracts

Table 4 The main individual phenolic acids identified in Longan fruit pericarp (*Dimocarpus longan* Lour.) extract using different high hydrostatic pressure extractions (HHPE-200, HHPE-300, HHPE 400, and HHPE-500 MPa), conventional solvent extraction (CE), and ultrasound extraction (UE)

Extract	Initial material	Extraction method	Individual phenolic acids (mg/g DW)				Reference
			Gallic acid	Ellagic acid	Corilagin	Total content	
Longan fruit pericarp (*Dimocarpus longan* Lour.)	Dried/24 h/ hot air oven at 60 °C)/ powdered	HHPE-200	0.1	0.8	5.9	6.8	[44]
		HHPE-300	0.7	0.9	7.2	8.8	
		HHPE-400	0.08	0.9	8.2	9.1	
		HHPE-500	0.01	0.9	9.6	10.5	
		CE	2.2	0.9	2.3	5.4	
	Dried/36 h/ hot air oven at 60 °C)/ powdered	HHPE-500	0.0140	0.926	9.65	10.59	[45]
		CE	2.25	0.977	2.37	5.597	
		UE	0.0125	0.0.345	7.91	8.2675	

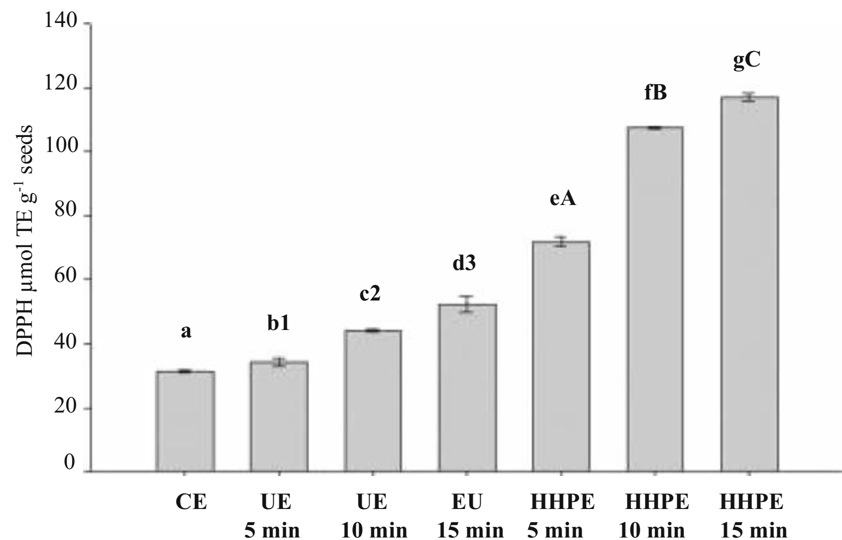

Fig. 3 Antioxidant capacity as DPPH (μmol TE g^{-1} seeds) from Chilean papaya seeds extracted by CE (conventional extraction), UE (ultrasound extraction), and HHPE (high hydrostatic pressure extraction). Different letters above the bars indicate significant differences between mean values ($p \leq 0.05$). Adapted from [42] with permission

performed at 0.1 MPa. The amount of almost all bioactive compounds extracted from processing fig by-product can be increased using high pressure together with an optimized ethanol concentration and extraction time. Moreover, independently of ethanol concentration and extraction time, HHPE resulted always in improved extraction, up to a maximum of 35% for total flavonoids at 600 MPa, 40% ethanol, and 30 min of extraction time. The exploitation of high pressure for extracting bioactive compounds from an industrial fig by-product for their application in food and pharmaceutics is a promising field.

Korean Ginseng Roots and *Opuntia* Cactus Extracts

Ginsenosides are the principal bioactive components present in ginseng and are responsible for several pharmacological activities, such as immunosuppressive, antiinflammatory, immunological adjuvant, anticarcinogenic, and wound-healing activities. In extraction, enzymes can be used for transformation of the major ginsenosides into more pharmacologically active minor ginsenosides. However, currently available enzyme preparations cannot completely hydrolyze plant cell walls, thus limiting the extraction yields of these compounds [61]. Palaniyandi et al. [62] investigated a combination of HHPE and various enzyme combinations to obtain extracts of Korean ginseng roots (*Panax ginseng* C.A. Meyer) with enhanced levels of specific minor ginsenosides, like the Rg1 and Rb1 [62]. The use of enzymes like cellulase+amylase+pectinase (enzymes concentration, 0.5 + 2 + 2 U/mL, respectively) with combination of HHPE at 100 MPa allowed for the efficient extraction of ginsenosides Rg1 and Rb1 from fresh ginseng roots (under optimized temperature, pH, and processing time, like 45 °C, pH 4.8, and 12 h, respectively). The treatment with enzymes and HHPE could destroy the cell wall and enhance the extraction of bioactive metabolites from

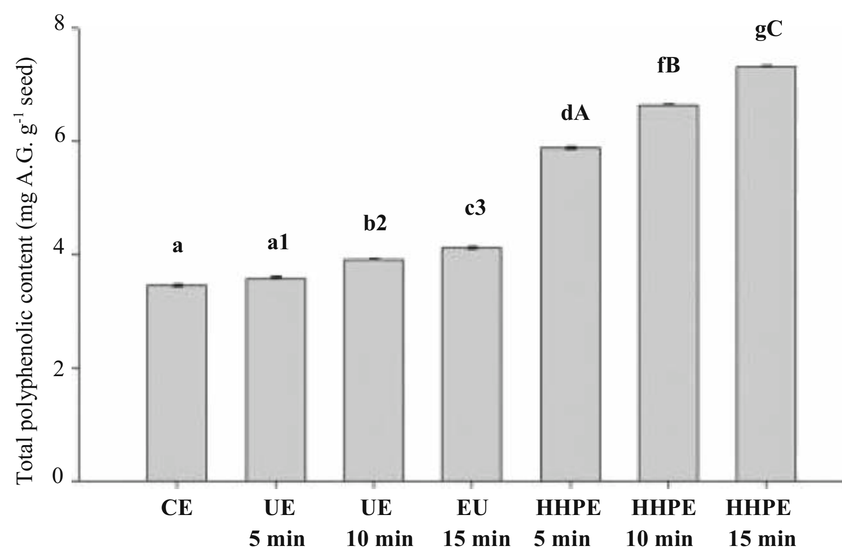

Fig. 4 Comparison of total phenolic content from Chilean papaya seeds extracted by CE (conventional extraction), UE (ultrasound extraction), and HHPE (high hydrostatic pressure extraction). Different letters above the bars indicate significant differences between mean values ($p \leq 0.05$). Adapted from [42] with permission

ginseng tissue. Indeed, the stability and activity of most enzymes are not altered at pressures lower than 100 MPa [19].

Moreover, an enhanced extraction of bioactive components from *Opuntia* cactus (*Opuntia humifusa*) was observed in the combination of HHPE with enzymes in comparison with HHPE only, enzyme only treatment under atmospheric pressure, and CE. The cactus homogenate in water treated with polysaccharide-degrading enzymes (Rapidase–Viscozyme mixture) under high pressure selectively increased the amount of the active components (*i.e.*, taxifolin, quercetin, and isorhamnetin) (Table 5) and enhanced the radical scavenging activity against ABTS and DPPH radicals [63]. In both studies presented above, HHPE with enzyme combination could provide a cheap and eco-friendly method for preparing the natural extracts enriched with pharmacologically active compounds.

Enhanced Antibacterial and Antimutagenic Activity of Plant Extracts by HHPE

Fermentation using live, safe, and non-pathogenic probiotic stains has been suggested as a process that can improve functional and biological properties such as antioxidant and antimicrobial activities of natural extracts, through a microbial conversion of some bioactive compounds and the production of secondary metabolites [64].

The potential application of the combined process of HHPE with probiotic fermentation was investigated as a technique for the enhancement of biological activities of Korean barberry (*Berberis koreana*) [65] and deodeok (*Codonopsis lanceolata*) extracts [66].

Samples of deodeok were anaerobically fermented with *Lactobacillus acidophilus* ADH (LAF-HHPE), *Bifidobacterium longum* B6 (BLF-HHPE), *Lactobacillus rhamnosus* GG (LRF-HHPE), and *Lactobacillus paracasei* (LPF-HHPE) at 37 °C for 10 days and subjected afterwards to 500 MPa at 50 °C for 30 min. Differently, the Korean barberry samples were first subjected to high pressure at 500 MPa for 30 min and then the extracts were fermented with *Bifidobacterium longum* B6 (HHPE-BLF) and *Lactobacillus paracasei* (HHPE-LPF) at 37 °C for six days.

The Korean barberry and deodeok extracts obtained by HHPE without fermentation (HHPE-NF) showed the highest total phenolics content and antioxidant activity (deodeok extract), in comparison to those obtained by CE non-fermented extraction (CE-NF) and probiotic fermentation in combination with HHPE.

In the HHPE-NF Korean barberry extract, the highest amounts of phenolic acids were observed, with *p*-hydroxybenzoic acid being predominant, followed by vanillic acid, vanillin, and *p*-hydroxybenzaldehyde. These compounds were reduced in the combined HHPE-fermented extracts, probably because the phenolic acids could be further decarboxylated by microbial enzymes produced during the probiotic fermentation. Comparable results were found in all deodeok extracts obtained by HHPE (fermented or not fermented), indicating that the HHPE efficiently extracts and recovers phenolic acids, especially the hydroxybenzoic acids.

In spite of this, the HHPE-fermented extracts of both the Korean barberry and the deodeok showed better antibacterial and mutagenic activities, in comparison to only HHPE and CE. Korean barberry showed significantly higher antibacterial activity against a β-lactam resistant *Staphylococcus aureus* and a β-lactam sensitive *Staphylococcus aureus*, as well as antimutagenic activity when compared to CE-NF and HHPE-NF [65]. Similarly, the fermented-HHPE extracts of deodeok exhibited the highest antimutagenic activities against TA 100, TA 1537 and TA 98 mutants of *Salmonella typhimurium* and a significant antibacterial activity against *Listeria monocytogenes, S. aureus, Shigella boydii* and *S. typhimurium* [66], possibly due to the production of specific secondary metabolites produced during the fermentation

Table 5 The main individual flavonols identified in *Opuntia* cactus (*Opuntia humifusa*) extract using heat extraction, high hydrostatic pressure extractions (HHPE) at 100, 200 and 300 MPa, enzyme-assisted extraction (EAE), and the combination of HHPE and EAE (HHPE-EAE)

Extract	Initial material	Extraction method	Extraction conditions	Flavonols (μg/mL)			
				Quercitrin	Taxifolin	Quercetin	Isorhamnetin
Opuntia cactus (*Opuntia humifusa*)	Fresh samples	Heat Extraction	Water bath, 2 h, 95 °C	54.21	97.67	18.43	15.36
		HHPE-100	Homogenate in water,1 h, 40 °C	55.08	94.62	19.34	14.21
		HHPE-200		50.73	96.37	20.10	13.89
		HHPE-300		51.67	96.66	17.88	14.05
		EAE	[Rapidase-Viscozyme mixture, 1/3 (v/v)]	21.87	163.79	43.27	23.32
		HHPE-EAE-100	Homogenate in water +[Rapidase-Viscozyme mixture, 1/3 (v/v)]/ 1 h, 40 °C	23.45	179.21	47.21	32.12
		HHPE-EAE-200		20.26	181.96	50.34	30.27
		HHPE-EAE-300		18.90	188.33	52.43	34.12

Adapted from [63]

process. The combination of fermentation and HHPE may improve the antimicrobial and antimutagenic effectiveness of the referred extracts. However, more studies are needed to elucidate the mechanism of microbial conversion of the extracts and to identify bioactive metabolites produced during the HHPE and fermentation process.

Conclusion

The application of HHPE to natural materials shows several advantages when compared to the traditional extraction methods. HHPE operates at room or reduced temperature, which can protect the natural extracts from heat influence and thus improve their bioactivity. Under high pressure, the differential pressure between the interior and the exterior of cell membranes is so large, that it can lead to rapid permeation and a faster equilibrium of concentration between the cell interior and its exterior, while increased solubility can also occur for several compounds. Moreover, at shorter extraction times, the natural plant extracts possessed higher antioxidant, and anticarcinogenic activities, which proportionally correlated with the higher total phenolic content. Furthermore, HHPE of plant materials can selectively increase the main individual bioactive compounds of great importance in the extract, such as corilagin and the sulforaphane, which have been considered to be effective antitumor compounds. The use of HHPE in order to obtain bioactive compounds from raw materials is a very promising recent extraction technique for the extraction of bioactive compounds from natural materials and improving the bioactivity of natural extracts associated with better nutritional benefits and therapeutic potential. The natural extracts obtained by HHPE can provide a source of antioxidant phenolic compounds for the food and pharmaceutical industries, to replace artificial chemical antioxidants as well as to enhance the bioactivity of biomolecules.

However, while the effect of pressure on the total phenolic content and biological activities of the extracts has been researched, there is still a lack of experimental data for most bioactive compounds (*e.g.*, individual phenolics) responsible for the enhanced biological activities of the HHPE natural extracts. Further studies are needed to identify these compounds and assess the way in which they contribute to these activities. In addition, more research is needed to demonstrate the bioactivity of HHPE extracts with *in vivo* studies, to confirm their bioavailability and potential health benefits. Since the research in the field of HHPE is taking its first steps, deeper studies are needed to ascertain the full potential of HHPE.

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Compliance with Ethical Standards

Permission to used material already published was carried out and granted.

Conflict of Interest The authors declare that they have no conflict of interest.

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