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Review

Cavitation Technology—The Future of Greener Extraction Method: A Review on the Extraction of Natural Products and Process Intensification Mechanism and Perspectives

Debabrata Panda and Sivakumar Manickam *

Department of Chemical and Environmental Engineering, Faculty of Science and Engineering, University of Nottingham Malaysia, 43500 Semenyih, Selangor, Malaysia; pandad89@yahoo.com

* Correspondence: Sivakumar.Manickam@nottingham.edu.my; Tel.: +60-389-248-156

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Abstract: With growing consumer demand for natural products, greener extraction techniques are found to be potential alternatives especially for pharmaceutical, nutraceutical, and cosmetic manufacturing industries. Cavitation-based technology has drawn immense attention as a greener extraction method, following its rapid and effective extraction of numerous natural products compared to conventional techniques. The advantages of cavitation-based extraction (CE) are to eliminate the application of toxic solvents, reduction of extraction time and to achieve better extraction yield, as well as purity. The cavitational phenomena enhance the extraction efficiency via increased mass transfer rate between the substrate and solvent, following the cell wall rupture, due to the intense implosion of bubbles. This review includes a detailed overview of the ultrasound-assisted extraction (UAE), negative pressure cavitation (NPC) extraction, hydrodynamic cavitation extraction (HCE) and combined extractions techniques which have been implemented for the extraction of high-value-added compounds. A list of essential parameters necessary for the maximum possible extraction yield has been discussed. The optimization of parameters, such as ultrasonic power density, frequency, inlet pressure of HC, extraction temperature and the reactor configuration denote their significance for better efficiency. Furthermore, the advantages and drawbacks associated with extraction and future research directions have also been pointed out.

Keywords: Cavitation-based extraction; ultrasound-assisted extraction; negative pressure cavitation extraction; hydrodynamic cavitation extraction; natural products

1. Introduction

Extraction of numerous products and their applications is prevalent from ancient time. Extraction is an essential part of the production line in food, cosmetic, pharmaceutical and nutraceutical industries and hence the advancement in extraction technology will bring significant benefits in terms of energy consumption, pollution abatement, as well as producing a better quality of extract. Novel techniques, such as cavitation-based extraction (CE) are currently one of the most investigated areas because of its economic advantages and potential for large-scale implementation soon. Ultrasound-assisted extraction (UAE), microwave-assisted extraction (MWE), sub-critical and supercritical fluid extraction (SFE) and enzyme assisted extraction are some of the novel greener extraction alternatives employed in these years. Cavitation-based extraction (CE) can be categorized as ultrasound-assisted extraction (UAE), negative pressure cavitation (NPC) extraction and hydrodynamic cavitation extraction (HCE). CE can be an ideal greener extraction alternative following its numerous advantages over conventional methods. Reduced energy and solvent consumption, enhanced extraction yield, better quality of the extract, reduction in extraction time and convenient work procedures are some of the advantages. Conventional extraction techniques, such as Soxhlet extraction, maceration, infusion, solid-liquid extraction (SLE) require longer processing time and may require a large number of toxic solvents. The safety concerns associated with the usage of organic solvent and the presence of toxic solvent residues in the final extract are considered to be some of the serious concerns following conventional extraction. Moreover, the high-temperature operation during the conventional extraction process may damage the quality of heat sensitive active compounds in the extract [1]. With proper isolation, numerous cellular components of microorganisms and plants could fulfill the human nutritional and functional needs. For example, polysaccharides, such as pectin from fruits and vegetables are used in a wider range of foods. With a suitable chemical modification of pectin structure, it could be for anti-colon cancer activity, cardiovascular health enhancer, cholesterol reduction and for the prevention of diabetes [2]. Several investigations on cavitation-assisted extraction of natural products, such as polysaccharides, bioactive compounds, proteins, flavors, fragrances, essential oils, and fine chemicals (pigments and dyes) indicated its competence in achieving highest yield and better quality of extract from numerous matrices (food, plant, and microorganisms). Recovery of food components, such as aromatic compounds, pigments and antioxidants (anthocyanins, flavonols, or phenolic acids) are of particular interest, due to their usefulness in food industries and pharmaceuticals. The extraction can be focused on obtaining valuable products, such as polyphenols, natural additives or can be used to eliminate undesired components (certain aroma) in food [3].

In this context, CE provides advantages over the conventionally employed techniques that include faster and effective extraction with efficient utilization of energy but at low capital investment. We have extensively reviewed the application of CE for a range of natural products. This review comprises of discussion regarding the crucial mechanisms behind cavitational extraction and the role of essential parameters for achieving enhanced yield.

2. Principles of Cavitation-Based Extraction

If the cavitation event occurs, due to the passage of ultrasound waves in the liquid medium, then it is termed as acoustic cavitation, whereas if it occurs, due to the pressure variations in the flowing liquid concerning the change in the geometry of constriction, then it is called as hydrodynamic cavitation (HC). Introduction of ultrasonic waves of certain frequencies (20-1000 kHz) can create bubbles followed by the collapse events [4]. In case of HC, when the liquid passes through the constriction, the velocity of the liquid increases at the expense of local pressure and the pressure around the point of vena contracta falls below the threshold pressure (usually the vapor pressure of the medium at the operating temperature), resulting in the formation of cavities. At the downstream of the constriction, as the liquid jet expands, the pressure recovers which results in the collapse of cavities [5]. NPC is also considered as a part of hydrodynamic cavitation, where the creation of negative pressure governs the cavitation phenomena via a vacuum pump and a continuous air-flow maintains the turbulence through the reactor. Figure 1 shows the types of cavitation-based extraction, where figure (a) represents the ultrasound-assisted extraction (UAE), figure (b) represents negative pressure cavitation (NPC) extraction and figure (c) demonstrates venturi type hydrodynamic cavitation (HC) extraction. Considering UAE reactor, an ultrasonic generator and a probe have been implemented to create cavitation phenomena. NPC device consists of an extraction pot, a collection pot, a heating system, a vacuum pump and a condenser, whereas the venturi type hydrodynamic cavitation (HC) reactor ideally consists of a feed tank, a plunger pump for circulating the solution through the reactor, a pressure gauge and the cavitation chamber consisting of an orifice or a venturi tube as the constriction to generate bubbles. The collapse of cavities can generate temperatures of up to 5000 K inside the bubble core along with the production of highly reactive free radicals owing to the homolytic cleavage of water molecules and dissolved gases, such as oxygen [6]. The cavitation events generate transient bubbles, and their successive collapse generates several physical effects, such as turbulence, shear forces, shock waves, and microjets. The overall mechanism behind the enhancements as observed in the extraction of natural products via cavitational effects can be summarized below:

(1) Increased mass transfer rate and enhanced solvent penetration into the cells, due to the temperature and pressure generated during bubble collapse events resulting in thinning of membranes and disruption of cells.
(2) Enhanced diffusion caused by microscopic level turbulence, intense inter-particle collision, and agitation in microporous particles of the matrix, due to the implosion of cavitating bubbles.
(3) Enhanced diffusion of solvent into the matrix, due to hydration and swelling of the matrix with the enlargement of pores.
(4) Generation of highly reactive free radicals and the associated radical driven cell disruption.
(5) The increased surface area of matrix following disintegration by shock waves and microjets.

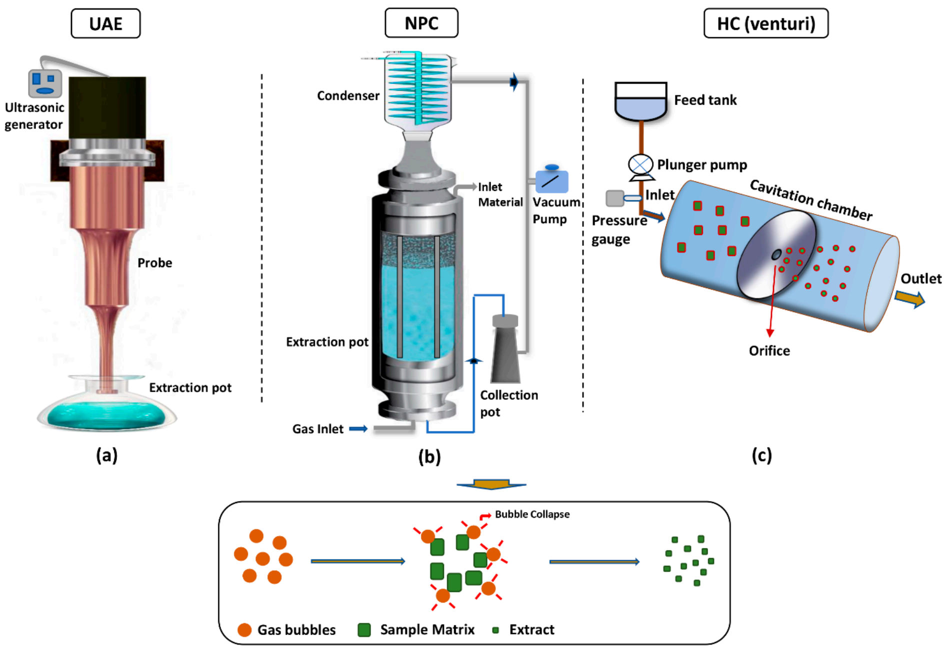

Figure 1. Types of cavitation reactor (**a**) UAE (ultrasound-assisted extraction); (**b**) NPC (negative pressure cavitation); (**c**) HC (hydrodynamic cavitation, venturi) and overall mechanism.

The already reported results indicated the formation of micro-fissures, microchannel and the generation of pores on the matrix surface leading to improved permeability. Enhanced accessibility of the solvent to the internal structure of cells facilitates the release of target compounds and their diffusion from the matrix to the solvent increases to manifold [7].

3. Extraction of Vital Products

CE has been employed for the extraction of different types of natural components, including proteins, natural dyes, pigments, essential oils, aromatic compounds, flavors, etc. which are useful in pharmaceutical, food and cosmetic industries for a range of applications. UAE is the most employed method for the extraction of natural products, including bioactive compounds, essential oils, lipids, protein, polyphenols etc.

3.1. Bioactive Compounds

Industrial interest for naturally occurring bioactive compounds are on a continuous rise and to meet the growing demand, CE methods can be the viable option. Phenolic compounds are of particular interest, due to their antioxidant properties, which could be effectively extracted from plants. Phenolic compounds are known to provide flavor, as well as distinct color to the wine. Phenolic compounds can be divided into three major groups, such as phenolic acids, flavonols, and anthocyanins. Antioxidants present in plants, vegetables, and fruits can prevent cardiovascular diseases, cancer, premature aging and hence making them as one of the valuable ingredients of extraction. As antioxidants can prevent the cell oxidation process, there is a high demand in cosmetic, pharmaceutical and food industries. The extraction of natural antioxidants can replace the application of synthetic substances, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), because of their health concerns. Looking into the usefulness of bioactive compounds, their effective extraction is vital, but, the conventional extraction methods, such as maceration and Soxhlet extraction are inefficient.

The root of *Salvia miltiorrhiza* contains bioactive phenolic compounds, such as salvianolic acid B, which has shown better antioxidant activity compared to vitamin E. However, previous reports indicated the drawbacks of conventional reflux extraction method, due to its immediate hydrolysis to tanshinol and degradation at high temperature. But, the implementation of UAE was successful in obtaining the highest yield of salvianolic acid B, which can be attributed to its low-temperature operation [8]. The recovery of resveratrol from functional foods (cookies and jams), via ultrasound assisted extraction has demonstrated the highest efficiency with an increase in the concentration of methanol compared to water, indicating its solvent dependent nature. Resveratrol is known for its antioxidant, anticancer and anti-aging activities. The yield increased significantly following a change in the concentration of methanol from 70 to 90% [9]. Gonzalez-Centeno et al. [10] reported a 3-fold increase in phenolic compounds from grape pomace via UAE as compared to conventional mechanical agitation. UAE was implemented for the extraction of phenolic compounds from microorganisms, such as *Nannochloropsis spp.* Microalgae [11], which demonstrated two times better yield than maceration. The extraction of phenolic compounds and anthocyanins from rice bran (*Oryza sativa L.*), indicated a significantly higher yield along with a noticeable reduction in the extraction time compared to conventional methods. HPLC analysis indicated α-tocopherol, cynanidin-3-glucoside, sinapic acid, and vanillic acid to be predominant compounds in rice extracts [12]. Moreover, UAE enhanced the extraction of polyphenols from *Picea abies* bark under optimized conditions, and seven polyphenolic compounds (catechin, gallic, vanillic, syringic, p-coumaric, ferulic, and sinapic acids) were identified by HPLC analysis [13]. Pan et al. [14] reported the extraction of antioxidants from pomegranate peel using UAE and maceration methods. UAE exhibited an enhanced yield within less time compared to maceration under optimized conditions, where the continuous mode of extraction improved the yield by 24% while reducing the extraction time by 90%. Hammi et al. [15] also reported the extraction of antioxidants from *Zizyphus lotus* fruit via UAE under optimum conditions.

Phenolic compounds were extracted from defatted oat (*Avena sativa L.*) bran via UAE, and the results showed a significant increase in the yield of free phenolics with a reduction in the extraction time as compared to conventional extraction. The total phenolic content (TPC) enhanced with a change in the extraction temperature from 20 to 70 °C, and the yield at 70 °C was measured to be two times higher than that obtained at 20 °C via conventional extraction. As phenolics present in whole grains are known for their antioxidant properties, the total antioxidant capacity (TAC) of the extract was evaluated. Five phenolic acids (gallic acid, caffeic acid, proto- catechuic acid, p-coumaric acid, ferulic acid) were identified via HPLC-DAD in oat bran [16]. Moreover, the extraction of anthocyanins and phenolics from Blueberry (*Vaccinium ashei*) wine pomace has shown superior efficiency compared to conventional solvent extraction (CSE). The TA (total anthocyanin) and TP (total phenolic) yield were 2.5 and 3.2-folds higher than CSE and considering the extraction time, CSE took 35 min to yield 5.08 mg/g of TP, while UAE took only 30 min to yield 16.41 mg/g (Table 1) [17]. Pomegranate and orange peel are a rich source of polyphenols, which could be effectively extracted via UAE. Kazemi et al. [18] successfully extracted phenolic compounds (punicalagin and hydroxybenzoic acids) from pomegranate peel (Malas variety) via a pulsed ultrasound-assisted technique. Better efficiency in the extraction of phenolics was achieved under an ultrasonic intensity of 105 W/cm^2 and by following a duty cycle of 50% for a short time (10 min). UAE under pulse mode delivered an extraction yield of 41.6% within just 10 min, as compared to 45.4% via continuous sonication within 30 min. Considering the extraction of polyphenols from orange (*Citrus sinensis L.*) peel, Khan et al. [19] effectively extracted flavanone glycosides via UAE, which are known for their antioxidant properties. Similarly, UAE has proved to be better than conventional maceration method for the extraction of phenolic compounds from mandarin (*Citrus reticulata Blanco cv. Sainampueng*) peel, with 1.77 times higher yield than maceration [20]. UAE has been effectively implemented during the extraction of polyphenols (anthocyanins, phenolic compounds) from mulberry (*Morus nigra*) pulp. Anthocyanins, such as cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, cyanidin-3-*O*-(6″-malonyl-glucoside) and cyanidin-3-*O*-(6″-dioxalyl-glucoside) were detected via UHPLC-MS analysis. Extraction temperature and solvent composition (methanol: water) were identified as vital factors influencing the yield of anthocyanins (48 °C and 76% methanol) and total phenolic compounds (64 °C and 61% methanol) from mulberry pulp [21]. Tian et al. [22] implemented NPC for the extraction of secoisolariciresinol diglucoside (SDG) from flaxseed. NPC achieved a higher extraction yield of SDG as compared to conventional methods, and the yield, as well as purity of the extract was comparable to UAE. NPC based method has been employed for the extraction of flavonoids biochanin A and genistein, from *Dalbergia odorifera* leaves, which possessed an excellent antioxidant activity. Under optimum conditions, an extraction yield of 1.583 and 0.933 mg/g DW was obtained for biochanin A and genistein respectively (Table 2) [23]. Pigeon pea [*Cajanus cajan (L.) Millsp.*] is one of the most examined food legumes, because of its antioxidant, anti-inflammatory, antispasmodic and antimicrobial activities. Cajaninstilbene acid (CSA) and pinostrobin were extracted from pigeon pea leaves, and under optimized conditions, the yield via NPC method was comparable to UAE [24]. Zhang et al. [25] investigated the extraction of genistein and genistin from pigeon pea roots while obtaining a maximum yield of 0.418 and 0.398 mg/g respectively under optimized conditions. Table 2 listed the vital products extracted by HC and NPC based methods.

Polysaccharides (PS) represent a vital category of bioactive compounds as they exhibit numerous medicinal properties and can be extracted from food to fungi. Polysaccharides have shown to exhibit antitumor, anticancer, anti-hepatitis B, and antioxidant activities. Medicinal fungi or mushrooms are widely used for functional foods and nutraceutical application, following their beneficial properties. Ultrasound has been employed for the extraction of polysaccharides from the dry mycelium of medicinal fungus (*Cordyceps sinensis, Cs-HK1*). The polysaccharides yield was seen to rise with an increase in ultrasound intensity and extraction temperature, thereby demonstrating a linear dependency [26]. UAE was employed for the extraction of polysaccharides from *Angelica sinensis* and under optimum conditions a maximum yield of 6.96% was obtained. To verify the antioxidant activity of A. sinensis polysaccharides (ASP), experiments were conducted over rats, and it has been concluded that ASP can reduce cell oxidative damage caused by exhaustive exercises [27]. Zhu et al. [28] utilized UAE for the recovery of polysaccharides from *Polygonum multiflorum* roots and they were further purified to obtain neutral, as well as an acidic fraction, which demonstrated inhibition activity on HepG-2 and BGC-823 cell proliferation *in vitro*. The outcomes suggested the applicability of polysaccharides as a natural antitumor agent. Pectin is one of the vital polysaccharides which finds its broad applications in food industries and is believed to exhibit lipase inhibition, wound healing, anti-ulcer and to control cholesterol and thus suitable for applications in pharmaceutical industries. The extraction of pectin from passion fruit peel has indicated the role of ultrasound which demonstrated a higher yield (12.67%) during UAE as compared to conventional heating extraction (7.95%) [29]. Polysaccharides extracted from *Lentinus edodes* have been evaluated for their anti-hepatitis B activity, where a 1.62-fold increase in their yield was achieved via UAE as compared to conventional hot water extraction [30]. Table 1 demonstrates the application of UAE for the extraction of antioxidants from the various matrix.

Although numerous traditional medicinal plants are adopted worldwide from ancient times, the beneficial compounds present in them need to be extracted effectively. Andrographolide, a bitter compound extracted from *Andrographis paniculata*, is known for its anti-inflammatory, anticancer and hepatoprotective activities along with others. *Andrographis paniculata* has been used as a traditional Ayurvedic remedy for cold, flu, digestive and respiratory issues. UAE has been implemented for the extraction of Andrographolide, and while using optimum parameters, a yield of 29.97 mg/g was obtained within just 10 min of sonication [31]. Saponins are drawing the current attention of research, due to the increasing evidence of their antitumor, antibacterial, antifungal, anti-inflammatory and antiviral activities. To extract saponins from edible seeds (quinoa, soybean, red lentil, fenugreek, and lupin), UAE was implemented successfully. Fenugreek showed the highest total saponin (TSC) yield (12.90 g/100g), whereas soybean displayed the lowest yield (4.08 g/100g) [32]. Licorice plant herbs are well known for their applications in traditional Chinese medicines and have been used for thousands of years. Several reports indicated their antidotal, antiulcer and antiallergic properties. Ultrasound has been effectively used to extract glycyrrhizic acid from licorice and under optimum conditions, and a yield of 3.414% was achieved [33]. The application of HC in biotechnology has drawn growing interest, which is evident during the extraction of phycocyanin from Spirulina platensis as reported by Maria [34]. Phycocyanin is a pigment-protein complex which could be a potential drug for cancer treatment.

3.2. Oils

Numerous oleaginous plant and fruit seeds (nuts, almonds, papaya seeds, rapeseed, sunflower, soybean, flaxseed) are a rich source of essential oils. Though conventional extraction methods (solvent extraction, hot or cold press) were utilized widely for the above purpose, novel techniques are required to extract maximum oil contents from a matrix containing more than 30% of oil, such as rapeseed. Numerous types of essential oils can be extracted directly from plants or waste raw materials, which find their dominant applications in cosmetics, soap, perfumes, food flavoring and medicinal use. The necessity of organic solvents, such as hexane, isopropanol, and ethanol for the extraction of edible oil has raised serious environmental concerns, whereas ultrasound combined with other green solvents can be a viable solution. Outcomes on grape seed oil extraction via both UAE and Soxhlet demonstrated similar yield, but in terms of time, it was just 30 min of ultrasound extraction as compared to 6 h of the Soxhlet method. Also, only 15 min of ultrasound extraction was required in case of extraction of oil and phenolic compounds compared to 12 h of maceration [35]. Similarly, the extraction of oils from chickpea [36] indicated the role of ultrasound in cell wall disruption, thereby enhancing the extraction yield. Moreover, the degradation of heat sensitive natural products can be avoided via UAE, which was well demonstrated in the case of extraction of olive oil [37]. The ultrasound extraction of essential oils from peanut has exhibited its superior efficiency while minimizing the degradation of heat sensitive molecules and providing better yield [38]. Khoei et al. [39] implemented UAE for the extraction of rice bran oil and compared its efficiency with conventional Soxhlet extraction and indicated that the oil yield by ultrasound-assisted aqueous extraction was comparable to hexane Soxhlet extraction. Furthermore, during the US assisted extraction of oil from rapeseed, Sicaire et al. [40] reported to obtain better efficiency than the conventional maceration method.

3.3. Lipids

Oleaginous microorganisms are a vital source of lipids mostly as neutral lipids, phospholipids, glycolipids and free fatty acids (FFA), which can be effectively recovered via UAE. Solvent-free UAE was reported by Adam et al. [41] for the extraction of lipid from fresh *Nannochloropsis oculata* microalgae. Piasecka et al. [42] utilized UAE for extraction of lipid from *Chlorella protothecoides* microalgae where the yield was improved by 42%. Microorganisms, such as oleaginous yeast *Trichosporon oleaginosisus* (ATCC20509), oleaginous fungus (SkF-5), were also subjected to UAE for lipid recovery, which resulted in a substantial reduction in the duration of extraction (12 h to just 15 min) as compared to conventional methods [43]. Venturi-type hydrodynamic cavitation (HC) reactor can also be an ideal possibility to be deployed for the extraction of lipid from microalgae. High extraction yield of lipids (25.9–99%) from microalgae (*Nannochloropsis salina*) was obtained via HC extraction as compared to ultrasound-assisted extraction (5.4–26.9%). Under optimum conditions, HC recovered maximum lipid content from wet microalgae, even though the extracted lipid from wet biomass was tough compared to the dry form [44]. HC has also demonstrated high lipid extraction efficiency from dry *Nannochloropsis sp.* microalgae, which is vital for biodiesel production [45].

3.4. Proteins

CE can effectively extract bioactive peptides along with proteins from plants. Natural products, such as soybean and wheat germ are protein rich, which can be effectively extracted by cavitation-based techniques. Though numerous extraction methods, such as traditional solvent extraction, were opted to recover maximum protein contents, the insoluble defatted flakes containing a considerable amount of protein will remain in the solvent. Karki et al. [46] and Zhu et al. [47] combined ultrasound with conventional solvent extraction and reverse micelles method for the extraction of soy protein and wheat germ protein respectively. The combination of ultrasound was seen to enhance the extraction of soy protein to nearly 10-folds when it was operated at high amplitude, and the extraction of defatted wheat germ protein reached up to 45.6%. The reason behind obtaining the enhanced yield could be attributed to the structural disruption of flakes. Extraction of soy protein via hydrodynamic cavitation has been demonstrated to give better yield (82 vs. 70%) as compared to US extraction [48].

3.5. Dyes and Pigments

Dyes/colorants derived from natural products are of high demand, because of their non-toxic, biodegradable and environmentally friendly nature. More importantly, finding a replacement of synthetic dyes is essential, due to their applications in food, hair coloring, and textiles, etc. which are known for their adverse health concerns. UAE of carotenoids from tomato [49] and natural colors from plant materials [50], have been reported to enhance the yield by 143% and 13–100% respectively, as compared to conventional maceration and heating methods. The extraction of natural melanin from *Auricularia auricula* was seen to be enhanced significantly with an increase in ultrasound power from 100 to 250 W [51]. The extraction of pigments via UAE has also been demonstrated a better recovery as compared to conventional extraction methods. Pasquet et al. [52] investigated the extraction of microalgal pigment from *Dunaliella terti-olecta (chlorophyte)* and *Cylindrotheca closterium (bacillariophyte)*, using ultrasound, microwave and other conventional methods (cold and hot soaking). A relative comparison among all the methods demonstrated ultrasound to be a superior method of extraction. Carotenoids and chlorophyll can be extracted from microorganisms via UAE, which has been demonstrated by Cardoso et al. [53]. Better yield of carotenoids and chlorophylls was obtained after opting DMF (N,N-dimethylformamide) as the solvent during the extraction of *Dunaliella salina*. The extraction of carotenoids and fatty acids from *Synechococcus sp.* via both ultrasound and supercritical extraction indicated that β-carotene yield was higher for UAE, whereas the recovery of astaxanthin was better with supercritical fluid extraction.

3.6. Aromas and Flavors

Herbs and spices are a vital source of aromas and flavors, which can be extracted via UAE efficiently rather than utilizing the conventional hydro-distillation technique [54]. Thyme is widely used for food and flavoring across Mediterranean regions. Mnayer et al. [55] utilized UAE and sunflower oil as a green solvent for the extraction of green absolute from thyme (*Thymus vulgaris*), which could be a better option for food industries as compared to toxic solvent-based extraction. A good selectivity was also observed during the extraction with higher recovery of thymol and carvacrol (86.2%), which were free from waxy components. Following the application of sunflower oil as a green solvent, a significant enhancement in the extraction yield of up to 47% was obtained as compared to hexane assisted extraction. A detailed application of UAE for different matrix has been outlined in Table 1, which demonstrates the optimum conditions and the extent of extraction etc.

Table 1. Ultrasound-assisted extraction of vital products.

Category	Vital Products	Matrix	Conditions	Yield	Ref.
Bioactive compounds	Phenolic compounds	Defatted oat	f (kHz): 40; P (W): 200-600; T (°C): 70; ED (min): 25	184.16 mg/g	[16]
		Blueberry wine pomace	P (W): 400; T (°C): 61.03; ED (min): 23.67; L/S: 21.70:1	16.41 mg/g	[17]
		Pomegranate peel	f (kHz): 24; I (W/cm^2): 105; ED (min): 10; L/S: 70:1	320.26 mg/g	[18]
		Mandarin peel	f (kHz): 38.5; P (W): 56.71; T (°C): 48; ED (min): 40	26.51%	[20]
		Mulberry pulp	f (kHz): 24; P (W): 200; T (°C): 64; ED (min): 10; L/S: 11:1.5; pH: 7	1.21 mg/g	[21]
	Polysaccharides	Fungus	f (kHz): 20; I (W/cm^2): 44.1; T (°C): 70; ED (min): 40; L/S: 70:1	0.180 ± 0.028 g/g	[26]
		Angelica sinensis	P (W): 180; T (°C): 90; ED (min): 45; L/S: 7:1	6.96%	[27]
		Polygonum multiflorum	P (W): 140; T (°C): 62; ED (min): 80; L/S: 20:1	5.49%	[28]
		Passion fruit	f (kHz): 20; I (W/cm^2): 664; T (°C): 85; ED (min): 10; L/S: 30:1; pH: 2	12.67%	[29]
		Lentinus edodes	P (W): 290; T (°C): 45; ED (min): 21; L/S: 20:1	9.75%	[30]
Traditional medicine	Andrographolide	*Andrographis paniculata*	f (kHz): 22; P (W): 134; T (°C): 40; ED (min): 10; L/S: 40:1	29.97 mg/g	[31]
	Saponin	Edible seeds (quinoa, lentil, fenugreek, soybean, lupin)	-	5.51 ± 1.18, 10.63 ± 1.86, 12.90 ± 0.91, 4.08 ± 0.7, 4.55 ± 0.36 g/100g	[32]
	Glycyrrhizic acid	Licorice	f (kHz): 44; P (W): 250; T (°C): 69; Extraction time (min): 34	3.414%	[33]
Oil	Olive		f (kHz): 40 and 585; P (W): 242; T (°C): 29; ED (min): 50	-	[37]
	Peanut		f (kHz): 40; Power density (W/L): 115; ED (min): 60; L/S: 6:1	-	[38]
	Rice bran		f (kHz): 60; T (°C): 45; ED (min): 70; pH: 12	-	[39]
Protein	Defatted soy flakes		f (kHz): 20; P (W): 1280; ED (min): 2; pH: 8.5	78%	[46]
	Defatted wheat germ		f (kHz): 20; P (W): 363; ED (min): 24	57%	[47]
Dyes and pigments	Carotenoids	Tomato waste	f (kHz): 20; T (°C): 45; ED (min): 6	13.59 ± 1.06 mg/g	[49]
	Dyes	Plants (*Acacia decurrens*, *Tagetes erecta*, *Punica granatum*, *Mirabilis jalpa*, *Celosia cristata*)	f (kHz): 20; P (W): 80; T (°C): 45; ED (h): 3	4.5, 26, 20, 26, 16 %	[50]
	Melanin	*Auricularia auricula* fruit bodies	f (kHz): 40; P (W): 250; T (°C): 63; ED (min): 36; L/S: 43:1; pH:12	120.05 mg/100 g	[51]
	Pigments: Fucoxanthin, Chlorophyll	Marine microalgae	P (W): 12.2; T (°C): 8.5; ED (min): 15	4.49 ± 0.08, 4.95 ± 0.27 µg/mg	[52]
Aroma and Flavor	Green absolute	Thyme	f (kHz): 20; P (W): 98; T (°C): 50; ED (min): 22; L/S: 10:1	5.92 g/100 g	[55]

f: frequency; P: Power; I: Intensity; T: Temperature; ED: Extraction duration; L/S: Liquid to solid ratio.

Table 2. HC and NPC assisted extraction of vital products.

HC Reactor	Extract	Matrix	Conditions	Yield	Ref.
Venturi	lipids	Microalgae *Nannochloropsis salina* (wet)	Cv: 1.17; ED (min): 25.05	25.9–99%	[44]
		Microalgae *Nannochloropsis sp.* (dry)	Cv: 0.126; T (°C): 42; ED (h): 2	93%	[45]
	Protein	Soybean	Inlet pressure (MPa): 100	82%	[48]
	Phycocyanin	*Spirulina Platensis*	-	-	[34]
NPC	Secoisolariciresinol diglucoside	Flaxseed cakes	NP (MPa): −0.04; T (°C): 35; ED (min): 35; L/S: 13.16:1	16.25 mg/g	[22]
	Flavonoids: genistin, genistein	Pigeon pea roots	NP (MPa): −0.05; Room temp.; ED (min): 45; L/S: 44:1	0.418, 0.398 mg/g	[25]
	Cajaninstilbene acid, Pinostrobin	Pigeon pea leaves	NP (MPa): −0.075; T (°C): 45; ED (min): 30; L/S: 30:1	5.675 ± 0.127, 0.538 ± 0.014 mg/g	[24]
	Baicalin, Wogonoside, Baicalein, Wogonin	*Radix Scutellariae*	NP (MPa): −0.07; Room temp.; ED (min): 60; L/S: 40:1	128.89 ± 2.32, 25.07 ± 1.42, 28.28 ± 1.71, 7.55 ± 0.80 mg/g	[56]
	Baicalein, Wogonin	*Radix Scutellariae*	NP (MPa): −0.07; T (°C): 50; ED (min): 60; L/S: 20:1	95.8 ± 1.67, 70.65 ± 0.67 mg/g	[57]
	Biochanin A, Genistein	*Dalbergia odorifera T. Chen* leaves	NP (MPa): −0.05; Room temp.; ED (min): 20; L/S: 24:1	1.583, 0.933 mg/g	[23]
	Alkaloids (vindoline, catharanthine, vincristine, vinblastine)	*Catharanthus roseus* leaves	NP (MPa): −0.075; ED (min): 30; L/S: 20:1	0.5783, 0.2843, 0.018, 0.126 mg/g	[58]
NPC/Enzyme	Alkaloids (vindoline, catharanthine, vincristine, vinblastine, anhydravinblastine)	*Catharanthus roseus* leaves	**NPC:** NP (MPa): −0.075; ED (min): 30; L/S: 20:1. **Enzyme:** Incubation T (°C): 35.87; Incubation time (h): 8.62; pH: 4.73	4.940 ± 0.215, 6.283 ± 0.307, 0.049 ± 0.002, 0.066 ± 0.003, 0.038 ± 0.001 mg/g	[59]
	Flavonoids: genistein, apigenin	Pigeon pea roots	**NPC:** NP (MPa): −0.04; T (°C): 30; ED (min): 20; L/S: 40:1. **Enzyme:** Incubation time (h): 6; pH: 5	0.628, 0.359 mg/g	[60]
	Astragalosides III, Astragalosides IV	*Radix Astragali (Astragalus)*	NP (MPa): −0.08; Incubation T (°C): 45; ED (min): 30; L/S: 50:1	0.103, 0.325 mg/g	[61]
	Isoflavonoids (Calycosin, Formononetin)	*Radix Astragali (Astragalus)*	**NPC:** NP (MPa): −0.080; ED (min): 30; L/S: 25:1. **Enzyme:** Incubation T (°C): 35; Time (min): 60; pH: 4	0.650 ± 0.015, 0.307 ± 0.013 mg/g	[62]
NPC/IL	Flavonoids: genistin, genistein, apigenin	Pigeon pea roots	NP (MPa): −0.07; T (°C): 74; ED (min): 15; L/S: 20:1	0.482 ± 0.008, 0.496 ± 0.017, 0.291 ± 0.015 mg/g	[63]
NPC/DES	Flavonoids: (9 type)	*Equisetum palustre L.*	NP (MPa): −0.07; T (°C): 60; ED (min): 20; L/S ratio: 25:1	57.14–89.25%	[64]
NPC/Homogenate	Polysaccharides	*Radix Astragali (Astragalus)*	Homogenate time (s): 70; NP (MPa): −0.068; T (°C): 64.8; ED (min): 53; L/S: 13.4	16.74%	[65]
NPC/MW	hyperin, 2′-*O*-galloylhyperin, chimaphilin	*Pyrola (P. incarnata Fisch)*	Microwave power (W): 700; NP (MPa): −0.05; T (°C): 50; ED (min): 12; L/S: 30:1	1.339 ± 0.029, 4.831 ± 0.117, 0.329 ± 0.011 mg/g	[66]
NPC/Homogenate			Homogenate time (s): 120; NP (MPa): −0.05; T (°C): 50; ED (min): 25; L/S: 30:1	1.205 ± 0.054, 4.961 ± 0.108, 0.291 ± 0.016 mg/g	[67]
NPC/MW	Phenolic compounds	*Pyrola*	Microwave power (W): 700; NP (MPa): −0.07; T (°C): 40; ED (min): 15; L/S: 20:1	0.406–5.977 mg/g	[68]
NPC/US	Total Phenols, flavonoids, procyanidins	Blueberry leaves	NP (MPa): −0.07; T (°C): 50; ED (min): 15; L/S: 30:1	352.12 ± 12.8, 111 ± 4.11, 211±7.81 mg/g	[69]

Cv: Cavitation number; NP: Negative pressure; T: Temperature; ED: Extraction duration; L/S: Liquid to solid ratio; IL: Ionic liquid; DES: Deep eutectic solvent; MW: Microwave; US: Ultrasound.

4. Effect of Essential Factors on CE

The efficacy of CE can be significantly affected by several factors, such as the type of ultrasonic reactor, sonication frequency, ultrasonic power density, solvent characteristics, and temperature. The extent of extraction is also dependent on intrinsic factors, such as the properties of the matrix. Discussion considering all vital factors necessary for cavitation-based extraction are included below.

4.1. Solvent Characteristics

Selecting an appropriate solvent to the property of the employed sample is the preliminary step in the extraction process. Solvent properties play an essential role in facilitating the cavitation energy to the matrix. The cavitational phenomena can be affected via viscosity, surface tension, polarity and vapor pressure of the liquid medium. While water is preferred over organic solvents (ethanol, methanol, acetone, isopropanol) and other inorganic solvents, but water may not effectively extract all the desired components. Reported data indicated the simultaneous application of two organic solvents (methanol/ethanol) during capsaicinoid extraction from dedo de moça pepper (*Capsicum baccatum L.*) [70].

Ultrasound extraction also paves the way for using green solvents other than toxic organic solvents. Alternatives for organic solvents, such as edible oils are prevalent for the extraction of antioxidants [71]. Li et al. [72] reported the use of sunflower oil in place of hexane for the extraction of carotenoids from carrot. A recent report on UAE of carotenoids from pomegranate peels demonstrated using vegetable oils as the solvent, and the highest extraction efficacy was noticed for sunflower oil under optimum conditions [73]. The presence of ultrasound during extraction improved the diffusivity of carotenoids and the resultant extraction yield while overcoming the major limitation related to the high viscosity of vegetable oil. The selection of an appropriate solvent is dependent on the identification of the functional group of matrices and its suitability. While, organic solvents, such as alcohols, acetone, and ether were preferred for the extraction of bioactive, as well as non-polar compounds, such as aromatics, water is used for polar constituents, such as amino acids, carbohydrates and glycosides. Other than solubility, the integrity of the cell walls should also be considered.

4.2. Reactor Type and Its Design

Reactor type and its design are vital factors during the process of extraction. UAE can be operated either via bath or probe type unit, where the bath type unit is the most commonly adopted. The lack of uniformity in the distribution of ultrasound energy limits the reproducibility of bath type UAE process, while the probe type sonication can be advantageous following its more intense cavitation, which can be focused on specific sample zone for better yield. Jerman et al. [74] reported probe type ultrasound to be favorable for the extraction of phenolic compounds in lab-based investigations. UAE of antioxidants from numerous plants via probe type units indicated better extraction yield and higher antioxidant capacity of extracts as compared to the bath type system [75]. Overall, the extraction efficiency via probe-type sonicator was better than the bath-type reactor, whereas care should be taken for the extraction of heat sensitive materials as probe type sonication may lead to degradation of compounds following intense cavitation during the process.

4.3. Temperature

A change in the solution temperature during cavitation affects the cavitation intensity owing to variations in the physiochemical properties of the liquid medium [76]. Due to the cavitation effect, the rising temperature during the extraction process needs to be controlled via external methods, such as by circulating cold water or by using a chiller. Reported data indicate that the extraction temperature varies between 10 to 80 °C depending on the type of solvent and ultrasonic intensity. The diffusion rate enhances at higher solvent temperature, thereby assisting in breaking the solute-matrix interaction. The mass transfer, in general, enhances with an increase in the extraction temperature, but the extraction yield and quality could vary for every individual extract depending on its property. The extraction yield of phenolic compounds from defatted oat increased with an increase in temperature. The solubility of phenolic compounds, as well as their diffusivity, might get improved at high temperature, resulting in higher yield [16], whereas, during the extraction of phenolic compounds from blueberry wine pomace, an increase in temperature from 61.03 to 70 °C resulted in a decline in the yield [17]. Varying the temperature of the solution affects the cavitational intensity and thereby affecting the penetration capability of solvent into the cells. An increase in the solution temperature is associated with less intense bubble collapse. Moreover, an increase in the extraction temperature beyond threshold value can also affect the extraction yield. Considering the correlation between the operational parameters and the rise in extraction temperature, it is advisable to consider the boiling point of the solvent, power density, etc. to establish the optimum extraction temperature for better outcomes. An overview of the previous reports indicated that UAE could be effectively operated at lower operating temperature compared to conventional methods, which makes it ideal for the extraction of heat sensitive materials.

While a temperature range of 10–70 °C was reported for the extraction of phenolics and anthocyanins from mulberry pulp [21], a range of 40–70 °C was opted for the extraction of polysaccharides from fungus during UAE [26]. The operating temperature was 25–45 °C for the extraction of carotenoids from tomato waste [49], whereas for aromas it was reported to be in the range of 10–50 °C [55]. While an increase in temperature from 20 to 70 °C [1] has shown a favorable effect for the extraction of natural products, Esclapez et al. [77] suggested low temperature (below 30 °C) for better outcomes in the extraction of natural products. From these observations, it can be concluded that a substantial extent of extraction can be achieved using UAE within the temperature range of 30-40 °C only.

4.4. Intensity and Pressure

The generation of a number of active cavitation bubbles can be significantly altered depending on the extent of applied ultrasound intensity. The ultrasound intensity can be calculated from the following Equation (1).

$$I = P/S \tag{1}$$

where "I" is the intensity (W/cm^2), "P" is the ultrasound power and "S" is the surface area of the transducer.

The correlation between sonochemical reactions and the applied power can be illustrated as follows: (1) The rate and the generation of number of active bubbles increase with an increase in intensity, (2) an increase in the size of individual bubbles with an increase in intensity, resulting into higher collapse temperatures because of the conversion of higher available potential energy into heat, (3) an increase in the mixing capability of solution results with an increase in the intensity because of the turbulence produced from cavitational effects.

By increasing the power, the energy of cavitation enhanced following a more violent implosion. The optimum power dissipation for effective extraction is dependent on the configuration of the reactor and the product employed for extraction. Cavitation events could be affected or reduced marginally beyond the optimum power intensity, because of the excessive production of heat during sonication, which leads to a less violent bubble collapse [78].

Generally, the extraction yield increases linearly with an increase in power density, but in some instances, it may be an exception depending on the properties of target molecules. Nipornram et al. [20] observed a linear enhancement in the yield of mandarin peel extract (MPE) with an increase in power level from 30.34 to 59.36 W. Zhu et al. [28] indicated a decline in the extraction of polysaccharides from *Polygonum multiflorum* with a rise in power beyond 140 W. Therefore, the intensity can affect both the total amount of extracts to be recovered, as well as the proportion of final products. Freitas de Oliveira et al. [29] reported the existence of an optimum intensity for the extraction of pectin from passion fruit. Hence, the optimum intensity needs to be decided following the properties of individual compounds. Higher amplitude sonication can opt for high viscous solvents, but the optimization of intensity is necessary for the type of matrix to avoid the degradation of extracted compounds.

In the case of hydrodynamic cavitation (HC), the variation in the inlet pressure or negative pressure can alter the cavitational phenomena. In the case of venturi type HC, deciding the value of cavitation number (Cv), can be beneficial while selecting the optimum inlet pressure for extraction. The cavitation number can be estimated based on the following Equation (2).

$$(C_v) = \frac{P_2 - P_v}{\frac{1}{2}\rho v_0^2} \quad (2)$$

where P_2 is the fully recovered downstream pressure, P_v is the saturated vapor pressure of the liquid, ρ is the density of liquid and v_0 is the average velocity of liquid at the constriction of the orifice. With an increase in inlet pressure and a decrease in cavitation number below 1, the intensity of cavity collapse increases with the generation of a larger quantum of active radicals. However, beyond the optimum inlet pressure, indicating supercavitation, where indiscriminate and rapid growth of bubbles takes place at the downstream of orifice constriction which leads to choked cavitation [79].

4.5. Frequency

A wide range of ultrasonic frequencies was implemented during the extraction of natural products depending on the matrix type. The extent of structural damage of cell surface was observed to be the highest for frequencies under 100 kHz. The capillary effect is frequency dependent, as the rigid structures require high frequency ($\leq$ 500 kHz), whereas low frequency (20–40 kHz) is suitable for flexible materials (vegetable matter, algae, etc.). The mechanism behind the capillary effect can be attributed to the peristaltic action of ultrasound waves resulting in expansion and contraction of capillary channels. However, in the case of high-intensity low-frequency sonication, the capillary effect is attributed to reciprocating pumping action at the open ends of capillary rather than peristaltic action.

Low-frequency sonication is known to generate extreme cavitational conditions as compared to high frequency, which could be favorable for better extraction yield under optimum conditions. As low-frequency ultrasound exhibits a stronger sonophysical effect compared to high frequency, the reported data indicated an enhancement in substrate porosity and better mass transfer rate for the frequency range of 20–100 kHz. Dong et al. [8] observed a better yield of salvianolic acid B from *Salvia miltiorrhiza* root under 28 and 45 kHz frequency as compared to 100 kHz. González- Centeno et al. [80] suggested 40 kHz be the most effective during the extraction of phenolics from grape pomace as compared to 80 and 120 kHz. Comparatively better extraction yield was reported for the frequency range of 20–40 kHz. Overall, even though low frequency has demonstrated better extract yield, but the specific frequency is substrate dependent. Hence, the effect of cavitation on the extraction efficiency depends upon numerous intrinsic characteristics, such as ultrasound frequency, intensity, temperature, HC pressure and the properties of mediums, such as viscosity.

5. Novel Combined Extraction Techniques

The combination of novel extraction technologies has been observed to bring synergistic extraction yield compared to employing individual processes. Considering ultrasound, it can be suitably coupled with microwave (MW), supercritical fluid or enzymes to assist extraction in order to enhance the process efficiency.

5.1. Cavitation and Microwave Assisted Extraction

Two novel promising techniques, such as a microwave (MW) and ultrasound (US) can be combined for better extraction yield and energy efficiency. Microwaves can only be beneficial for selective materials corresponding to the presence of polar components, but the introduction of ultrasound can generate intense agitation and overall modification of the matrix surface.

Both extraction techniques can be either operated as single reactor configuration or via two separately connected reactors, which can be operated simultaneously or one by one. The combined US-MW extraction of pectin from Pomelo peels [81], resulted in a 38% recovery within just 33.94 min as compared to 14.25% during only US extraction. Highest pectin yield was obtained for the sequential order of US-MW rather than MW-US treatment, and among the optimized parameters, pH played a significant role in deciding better yield. US-MW extraction has demonstrated to enhance the yield of oligosaccharides by 76.59%, 17.47% and 27.21%, respectively, as well as a substantial decline in the extraction time by 12.18, 8.92, and 1.16 times, respectively, compared to hot water extraction, UAE and MW [82]. Lu et al. [83] reported ionic liquid-based US-MW extraction of anthraquinones from rhubarb, which demonstrated better efficiency as compared to employing individual techniques (ultrasound, microwave, and heat-reflux extraction). The combined US-MW approach exhibited higher efficiency (18.90–24.40%) and shorter extraction time (6 h to 2 min) than individually employing them. Table 3 lists UAE based combined methods for natural products extraction.

Combined NPC-MW was used for the extraction of phenolic compounds (arbutin, hyperin, catechin, epicatechin, chimaphilin) from *Pyrola (P. calliantha)*, following the selection of 1-butyl-3-methylimidazolium tetrafluoroborate as an appropriate extraction solvent [68]. The coupled technique showed higher extraction yield within a shorter duration than MW or NPC alone. Another report on NPC/MW coupled method for the extraction of hyperin and chimaphilin from *Pyrola (Pyrola incarnata Fisch.)* demonstrated 1.43 and 1.28-folds higher extraction yield than NPC and MW methods respectively [66].

5.2. Cavitation and Enzyme Assisted Extraction

Enzymatic treatment of plant cells is prevalent, due to their capability to enhance hydrolysis, as well as degradation of impenetrable cell walls, thereby facilitating the release of intracellular contents, such as bioactive compounds. However, the combination of enzyme and CE could bring better outcomes in the extraction. The extraction yield of polysaccharides was reported to enhance via the application of US, combined with enzymes. The enzymatic reaction with the substrate is said to be increased via the introduction of ultrasound that could enhance the collision frequency between the enzyme and the matrix. Wu et al. [84] reported an enhancement in the recovery of polysaccharide from pumpkin (*Cucurbita moschata*) via combined US/enzyme extraction as compared to SLE or US alone. Evaluation of the properties of polysaccharides extracted from pumpkin suggested their potential application in food and medicinal industries as a natural antioxidant because of their radical scavenging activity and reducing power. Tchabo [85] reported an increase in the yield of phytochemical compounds from mulberry (*Morus nigra*) must via enzyme assisted ultrasound extraction. The process has considerably enhanced the extraction of phytochemicals (phenol, flavonoid, and anthocyanin). The combined effect of US/enzyme on pectin extraction from sisal waste was evaluated by Yang et al. [86]. Both sequential, as well as combined, treatment of enzyme (Celluclast 1.5 L) and ultrasound resulted in appreciable higher pectin yield (31.1%) than any of the individual processes (9.4%). Moreover, the recovered pectin via US/enzyme extraction demonstrated higher galacturonic acid content and a higher extent of esterification than conventional acidic extraction. Zhang et al. [87] successfully utilized polyethylene glycol (PEG) as the environment friendly solvent for the US/enzyme-based extraction of polysaccharides from Gingko biloba leaves (GBLP) and have demonstrated that the combined method is far better than the traditional hot water extraction. During the extraction of oil from Pomegranate seed, the low extraction yield using water as a solvent was successfully mitigated by combining enzyme (*Peclyve V*) with US, which reduced the extraction time by 91.7% as compared to individual methods [88]. The low extraction yield during aqueous cavitation-based extraction of oils could be attributed to the resultant stable emulsion obtained from the combination of water and oil, which is either difficult to break apart or laborious to isolate the oil fraction from the solution.

Table 3. UAE based combined methods.

Type	Extract	Matrix	Conditions	Yield	Ref.
US/MW	Pectin	Pomelo peels	**MW:** P (W): 643.44; Irradiation time (min): 6.40. **US:** *f* (kHz): 40; Sonication time (min): 27.52. Solvent: water; pH: 1.80	38%	[81]
	Oligosaccharides	lotus seeds	**MW:** P (W): 250 **US:** *f* (kHz): 25; P (W): 300.46; ED (min): 5.42; L/S: 10:1; Solvent: water	11.009 ± 0.019%	[82]
	Anthraquinones	Rhubarb	**MW:** P (W): 500. **US:** P (W): 300; ED (min): 2; L/S: 15:1	28 mg/g	[83]
US/Enzyme	Polysaccharides	Pumpkin	**US:** *f* (kHz): 20; P (W): 440; T (°C): 51.5; ED (min): 20; L/S: 5.70:1; pH: 5; Solvent: water	4.33 ± 0.15%	[84]
	Phytochemical: Total phenolics, Total flavonoids, Total anthocyanins	Mulberry must	**US:** *f* (kHz): 34; P (W): 60 W; T (°C): 20; Solvent: water. **Enzyme:** Enzyme concentration: 0.010% (v/w); ED (min): 12	298.06; 379.24; 55.14 (mg/100 mL)	[85]
	Pectin	Sisal waste	**US:** *f* (kHz): 20; P: 450 W. **Enzyme:** Enzyme loading: 88 U/g; T (°C): 50; ED (h): 20; L/S: 15:1; pH: 4	31.1%	[86]
	Polysaccharides	Gingko biloba leaves	Solvent: Polyethylene glycol; T (°C): 51.88; ED (min): 37.13; pH: 4.34	7.29 ± 0.21%	[87]
	Oil	Pomegranate Seeds	**US:** *f* (kHz): 20; P (W): 130; T (°C): 55. **Enzyme:** Enzyme loading: 2% w/w; ED (min): 10; pH: 5. L/S: 6:1; Solvent: Water.	95.8%	[88]
SFE-US	Bioactive compounds	Dedo de moça pepper	Solvent flow rate: 1.7569×10^{-4} kg/s; Pressure (MPa): 20. **US:** P (W): 800; T (°C): 40; ED (min): 60	45%	[89]
	Antioxidants	Oregano	Solvent flow rate: 1 ± 0.1 kg/h; Pressure (MPa): 35. **US:** *f* (kHz): 30; Power density (W/L): 150; T (°C): 35; ED (min): 60	26.4 ± 1.1 µmol TE/g	[90]
	Antioxidants	Blackberry bagasse	Solvent flow rate: 2.77×10^{-4} kg/s; Pressure (MPa): 25. **US:** P (W): 400; T (°C): 50; ED (min): 120; L/S: 400	9.87 ± 0.40%	[91]
	Capsaicinoids	Malagueta pepper	Solvent flow rate: 1.673×10^{-4} kg/s; Pressure (MPa): 15. **US:** *f* (kHz): 20; P (W): 360; T (°C): 40; ED (min): 60; L/S: 600 ± 2	75.3%	[92]
	Oil	Almond	Solvent flow rate: 15 kg/h; Pressure (MPa): 33. **US:** *f* (kHz): 20; P (W): 75; T (°C): 45; ED (h): 5; L/S: 50	18%	[93]

P: Power; *f*: Frequency; ED: Extraction duration; L/S: Liquid to solid ratio; MW: Microwave; US: Ultrasound.

Application of combined NPC and enzyme extraction has been reported by Zhao et al. [62], for the extraction of isoflavonoids (calycosin, formononetin) from *Radix astragali*, which is a well-known medicinal plant. Under optimum conditions, a higher extraction yield of 94.67% for calycosin was obtained compared to non-enzymatic pre-treated extraction. Zhang et al. [60] also used the coupled method for the extraction of genistein and apigenin from pigeon pea roots, which demonstrated an increase in the extraction yield up to 44.70% and 53.05% respectively, compared to only NPC method.

5.3. Ultrasound and Supercritical Fluid Assisted Extraction

Supercritical fluid extraction (SFE) of natural products has drawn particular interest in recent years, due to its low critical constant, non-toxic and non-flammable properties. For SFE, carbon dioxide (CO_2) is the most commonly employed solvent for the extraction of bioactive and antioxidant compounds from vegetal materials, following its moderate operating temperature, low-cost, non-flammable and environmentally friendly nature. Combination of US with CO_2 resulted into an increase in the extraction yield, which could be associated with enhanced mass transfer rate. Better stability of CO_2, due to its inert nature and process operation at low temperature leads to minimal damage to vital components of the extract. Bioactive compounds were obtained with high purity from red pepper (*Capsicum baccatum L. var. pendulum*) via CO_2 based supercritical fluid extraction assisted by ultrasound (SFE-US) [89]. Santos-Zea et al. [90] obtained 9-38% and 10-86% enhanced yield of phenolics, as well as antioxidants respectively from dry oregano via introducing a multiple circular sonotrode type ultrasound reactors, which were operating along with CO_2. The process demonstrated the importance of reactor configuration for obtaining better extraction yield. For the extraction of antioxidant compounds from blackberry bagasse, Reátegui et al. [91] adopted SFE-US method, which indicated the effect of ultrasound on SFE for enhancing the global yield and the quality of extract. SFE-US extraction has also been used for the extraction of capsaicinoids from malagueta pepper (*Capsicum frutescens L.*) [92] and oil from almonds [93]. The yield of SFE was enhanced up to 77% following the introduction of ultrasound during capsaicinoids extraction while considering same parameters for all type of extractions and four major capsaicinoids (capsaicin, dihydrocapsaicin, nordihydrocapsaicin, and homodihydrocapsaicin) were quantified successfully. During the extraction of oils from almond, the yield also enhanced up to 20% than treatments without ultrasound. The introduction of ultrasound reduces pressure, temperature, the flow rate of CO_2 and the overall extraction time as well. An enhancement in yield can be attributed to both the mechanical and thermal effects of ultrasound.

6. Advantages and Disadvantages of CE

The advantages of cavitation-based extraction compared to conventional methods are listed as below:

(1) Effective mixing capability;
(2) Operation at a lower temperature;
(3) Easy operation and the elimination of multiple process steps;
(4) Selective extraction and enhanced yield.

While cavitation-assisted extractions have great potential to improve and revolutionize extraction technology, there is immediate concern regarding the degradation of extract and the efficiency of the technique during large-scale application. The drawbacks of UAE are (1) attenuation of ultrasound waves for highly concentrated dispersed phase, (2) lack of uniformity for dispersed extract materials following the decline in the transmission of ultrasound waves away from the vicinity of the generator, (3) higher energy consumption as compared to NPC. Therefore, negative pressure cavitation (NPC) extraction technique can be useful in the future. As NPC extraction is operated at room temperature, the degradation of heat sensitive compounds can be prevented. NPC has already been effectively employed either alone or in combination with other extraction methods for the extraction of numerous natural products. Several reports indicated that NPC had achieved better extraction yield and purity of bioactive compounds within a shorter interval of extraction as compared to UAE.

7. Future Perspectives

To obtain the highest extraction efficiency under cavitation-based methods, optimum values of solution temperature, ultrasound intensity, sonication frequency, and HC pressure should be decided. Future investigations should also focus on the implementation of negative pressure cavitation extraction for a wide range of products. Intensification in the generation of bubbles during cavitation-based methods via innovative reactor design and uniform distribution of cavitational energy throughout the extraction solution should also be explored. Implementation of the cavitation-based extraction method could lead to a promising novel greener extraction technique for the recovery of useful natural products. Most of the reported data indicated the use of a simple reactor configuration, which may not be feasible for large-scale applications. With innovative design, CE can be made efficient and sustainable for industrial applications. Following essential factors are to be considered for large-scale implementation of CE.

(1) Use of multi-frequency and multiple transducer sonoreactor.
(2) Developing a continuous flow cell reactor, while introducing ultrasonic transducers in periodic spaces.
(3) Eliminating erosion of transducer material via suitable building materials.

8. Conclusions

This review showed that the rate of extraction of CE is enhanced with combined methods (US-MW, US-supercritical fluid, US-enzyme) and the extraction efficiency reached a maximum after considering optimum operational parameters, such as ultrasonic intensity, sonication frequency, solution temperature, and HC pressure. Furthermore, the application of a proper solvent and selecting a suitable reactor type, played a vital role in deciding the extraction efficiency, which was found to be matrix dependent. The introduction of cavitation during the combined process provides additional reactive radicals while facilitating the damage of cell structure for better release of cellular contents. Though UAE is mostly adopted for the recovery of a wide range of natural products, the application of HC based extraction is emerging as a suitable alternative. From the reported results, NPC extraction proved to be more effective in the extraction of heat-sensitive compounds than UAE. Overall, cavitation-based extraction methods demonstrated the successful and rapid extraction of natural products and are expected to provide an efficient solution in large-scale operations. Overall, the CE method performed more effectively compared to traditional methods of extraction. This new greener extraction approach has great promise and capacity as an innovative tool for the recovery of natural products within a shorter time interval and with less energy input.

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