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Novel Bioactive Extraction and Nano-Encapsulation

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Definition: An extraction technology works on the principle of two consecutive steps that involves mixture of solute with solvent and the movement of soluble compounds from the cell into the solvent and its consequent diffusion and extraction. The conventional extraction techniques are mostly based on the use of mild/high temperatures (50–90 °C) that can cause thermal degradation, are dependent on the mass transfer rate, being reflected on long extraction times, high costs, low extraction efficiency, with consequent low extraction yields. Due to these disadvantages, it is of interest to develop non-thermal extraction methods, such as microwave, ultrasounds, supercritical fluids (mostly using carbon dioxide, SC-CO_2), and high hydrostatic pressure-assisted extractions which works on the phenomena of minimum heat exposure with reduced processing time, thereby minimizing the loss of bioactive compounds during extraction. Further, to improve the stability of these extracted compounds, nano-encapsulation is required. Nano-encapsulation is a process which forms a thin layer of protection against environmental degradation and retains the nutritional and functional qualities of bioactive compounds in nano-scale level capsules by employing fats, starches, dextrins, alginates, protein and lipid materials as encapsulation materials.

Keywords: non-thermal extraction; bioactive compounds; nanoencapsulation; ultrasound; cold plasma; high-pressure processing; supercritical extraction; pulse electric field

Citation: Noore, S.; Rastogi, N.K.; O'Donnell, C.; Tiwari, B. Novel Bioactive Extraction and Nano-Encapsulation. *Encyclopedia* **2021**, *1*, 632–664. https://doi.org/10.3390/encyclopedia1030052

Academic Editors: Raffaele Barretta, Ramesh Agarwal, Krzysztof Kamil Żur and Giuseppe Ruta

Received: 11 June 2021
Accepted: 20 July 2021
Published: 26 July 2021

1. Introduction

Bioactive compounds also known as secondary metabolites are widely present in plant matrix and over the past few decades, several in vitro and in vivo reports including epidemiological, and cohort studies provide evidence that consumption of plant-based food provides protection against several diseases. These bioactive extracts are also capable of treating chronic diseases including cancer, cardiovascular and diabetes mellitus (DM). Nutraceutical and pharmaceutical sectors use these extracts to develop functional food- and plant-based medicines, which have a potential to cure and deliver health benefits. According to the World Health Organization (WHO), about 80% of the global population depends on natural medicines. The initial steps followed to use these active compounds from plant matrix are extraction followed by pharmacological testing, isolation, characterization and clinical evaluation. Figure 1 represents a detailed flow chart of bioactive compound extraction from plant matrix.

The quality and yield of the bioactive compounds depend on two important factors: (a) the method opted for its extraction, (b) its extraction parameters including plant matrix type, solvent used, time and temperature. The most conventional method employed for bioactive extraction is Soxhlet extraction, maceration and hydro-distillation. Although, these techniques are commercially employed, but excessive use of solvents and longer processing times are the downsides of these technologies. Presently, demand for sustainable, chemical-free, advanced extraction processes with enhanced overall yield

of bioactive compounds, also known as "green techniques", which include ultrasound-assisted, enzyme-assisted, microwave-assisted, pulsed electric field-assisted, high-pressure processing, supercritical fluid and pressurized liquid extraction processes are gaining attention. Treating the plant matrix with these green technologies helps in breaking the cell structure, which allows the bioactive compound to leach or rinse out from the cell wall through solvents; as a result, it enhanced extraction yield. Further, purification of the extracted bioactive poses another technological challenge as each of these compounds has a unique molecular structure depending on their type, source and biological activity. The extracted compounds can be further purified, employing super critical CO_2 isolation, by addition of a co-solvent including ethanol, water to isolate the respective bioactive compound efficiently at an optimized temperature and pressure [1]. In addition, it is essential to protect the extracted bioactive compound post extraction and purification, as these compounds are highly sensitive to environment exposure including moisture and high temperature (sensitive under heat, light, oxygen). Therefore, protection techniques such as nanoencapsulation are used to ensure that biological activity of these compounds is preserved until they reach and perform their function at the targeted location in the human body.

Encapsulation plays a vital role in protecting the bioactive compounds from getting degraded. At present, there are two kinds of encapsulation including microencapsulation and nanoencapsulation. The reason why nanoencapsulation is preferred over microencapsulation is due to its nano-scale size, as the smaller the size of the capsules, the higher their bioavailability and their release can be modified and controlled in a better way comparatively. Nanoencapsulation provides a protective shield around bioactive compounds. It is a system where a suitable nano-carrier, resistant to enzymatic degradation especially in gastrointestinal tract including chitosan, zein, and alginate, are widely used to encapsulate bioactive compounds employing several delivery methods including association colloids, nano-particles, nano-emulsions, nano-fibers/nano-tubes, nano-laminates. The selection encapsulation method is based on two main factors: (a) nature of the core material; (b) nature of wall material including wall material size, thickness, solubility, permeability and its rate of delivery. Basically, these techniques are classified into three main genres including chemical (emulsion and interfacial polymerization), physical–chemical (emulsification and coacervation) and physical–mechanical methods (spray-drying/spray-cooling/spray-congealing/prilling, freeze-drying, electrodynamic methods and extrusion) [2]. However, in certain cases, combinations of these techniques are practiced as in the case of emulsification; first using homogenization, the emulsions are prepared and later converted to dry powder state using spray-drying and/or freeze-drying techniques [3]. Reports indicate that about 80–90% of flavor encapsulation is done using spray-drying, while 5–10% by spray-chilling, 2–3% by melt extrusion and ~2% by melt injection [4]. Castro et al. [5] reported electro-spinning encapsulation as a heat-free technique to encapsulate fragrance and flavor, which is extremely promising for heat-sensitive compounds.

To recapitulate, this chapter provides a comprehensive summary on several aspects of bioactive extraction using non-thermal technologies and its nanoencapsulation. A brief description on nano-carriers employed for encapsulation is also discussed along with the detailed description of their application in food systems. Various opportunities and future challenges are also outlined.

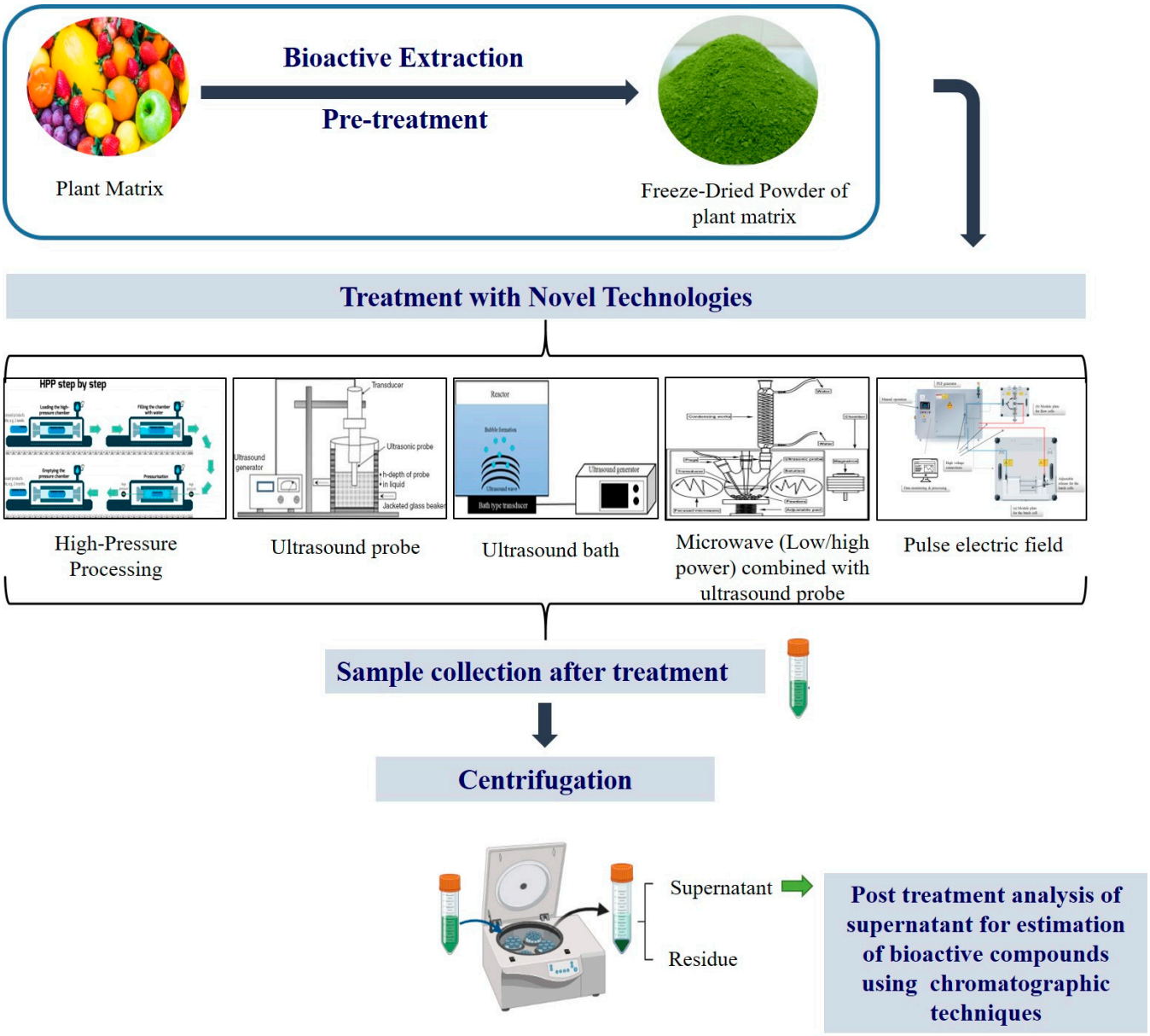

Figure 1. Illustration for the extraction of bioactive compound using novel strategies.

2. Bioactive Compounds from Plant Materials

Ever since the beginning of human existence, plants have always been a boon for living a healthy life, as they not only provide a healthy environment to live, but most importantly, they provide food and bioactive compounds for medicinal use. In the beginning, plants and plant-related foods were used as a source of food and nutrition; later, their medicinal properties were discovered, which were able to cure diseases. Vinatoru et al. [6] reported that Egyptian papyruses extracted oil from coriander and caster and used it in several applications including medicine, cosmetics and as preservatives. Further, Paulsen et al. [7] reported that, during the Roman and Greek era, herbal plants were used by several therapeutics. According to literature [8], bioactive compounds comprise three different categories including terpenes/terpenoids, alkaloids and phenolics. Basically, the chemical structure of these three categories differs, as shown in Figure 2, and maximum bioactive compounds extracted from plant matrix belong to the terpenoids family.

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

2.1. Glycosides

Glycosides are generally bonded by a mono/oligosaccharide or uronic acids. The part that is bonded with saccharide is called glycone and the other part is termed as aglycone, which consists of pentacyclic triterpenoids/tetracyclic steroids. The major subgroups of glycosides include cardiac glycosides, saponins, anthraquinone, glucosinolates and cyanogenics. Moreover, flavonoids commonly exist as glycosides. These glycosides are broken down in colon post ingestion; however, hydrophobic glycosides tend to get absorbed by the muscle cells. Cardiac glycosides are generally found in plants such as the *Scrophulariaceae* family, specifically in *Digitalis purpura* and in *Convallaria majalis* from *Convallariaceae* family. Additionally, cyanogenic glycosides can be found in the *Prunus* spp. of *Rosaceae* family as well as saponin, a bitter-tasting compound is found in glycosides. These saponin glycosides, found widely in the *Liliaceas* family (*Narthesium ossifragum*), is comprised of bigger molecules attached to hydrophilic glycone as well as hydrophobic aglycone, which creates forming quality, and thus it is used in the production of soap/detergent. Saponins also play an important role in modulating immune system and reducing blood sugar level. Besides, anthraquinone glycosids found in the *Rumex crispus* and *Rheum* spp. of polygonaceae family help in electrolyte secretion as well as induction of water and peristalisis in colon. Moreover, flavonoids are comprised of tri-ring at the center of the structure and proanthocyanidin is an oligomer in flavonoids. These two groups of compounds can also exist as glycosides. These are responsible for liberating antioxidant properties, inflammation and anti-carcinogenic activities. They are also responsible for the pigments in a wide range of plants. In addition, isoflavones are considered as a nutritional supplement type of bioactive molecules produced almost exclusively by the Fabaceae (Leguminosae or bean) family. They are basically a precise group of molecules, popularly known as phytochemicals, natively found in legumes and spices such as red clove. They are also considered as antioxidant molecules, as they help in the reduction of damage caused by oxygen in the body. Additionally, it plays a vital role in fighting against cancer cells.

2.2. Tannins

Tannins are widely found in plants, especially in the *Fagaceae* and *Polygonaseae* family. They are basically divided into two types, including condensed and hydrolysable tannins. Condensed groups of tannins are comprised of bigger polymers of flavonoids, while hydrolysable groups of tannins are clusters of monosaccharide (glucose) bonded with various derivatives of catechin. Tannin molecules tend to indiscriminately bind with protein molecules. Larger groups of tannins are used as medicine for treating skin bleeding, diarrhea and transudates.

2.3. Mono/Sesqui-Terpenoids and Phenylpropanoids

Synthesis of terpenoids takes place by a penta-carbon isoprene. In case of monoterpenoids, two units of isoprene are found, while in sespui-terpenoids there are three units of isoprene. They are popularly known for their low molecular weight and wide range of categories (more than 25,000). However, phenylpropanoids comprises group of molecules where the basic carbon skeleton starts from nine and more, with strong odor, flavors and are volatile in nature. Generally, these compounds are commonly called volatile oils, widely found in the *Lamiaceae* family. It is used as an herbal medication including antineoplastic, antiviral and antibacterial effects. Besides, it also helps in gastrointestinal stimulation. In addition, diterpenoids are lipophilic non-volatile (odorless) compound and is a cluster of 4 units of isoprene with a strong flavor. It is widely found in various plants including *Coffee arabica* and popularly known for its antioxidant qualities.

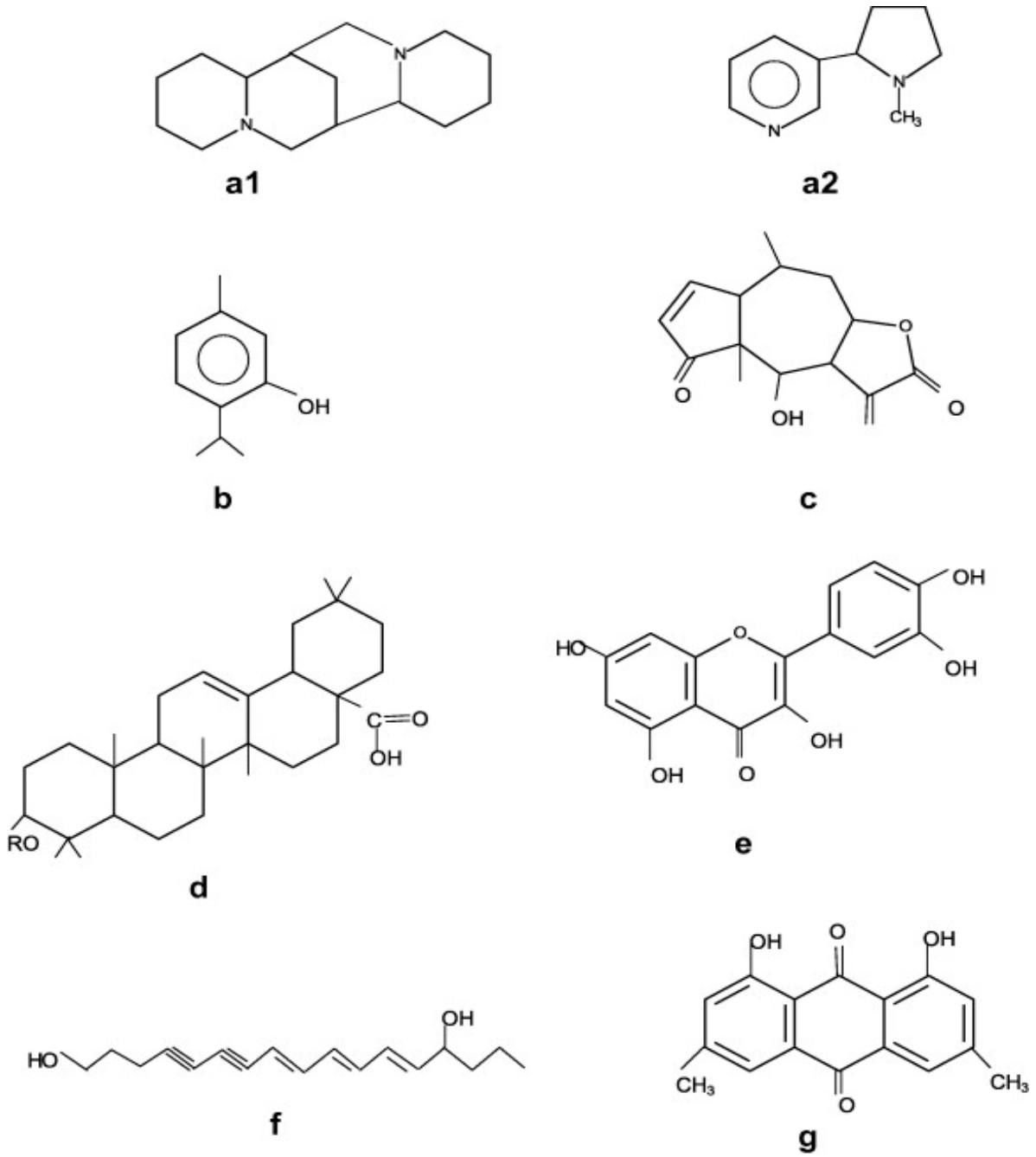

Figure 2. Basic structures of plant bioactive compounds alkaloids (**a1**,**a2**), monoterpenes (**b**), sesqueterpenes (**c**), triterpenes, saponins, steroids (**d**), flavonoids (**e**), polyacetylenes (**f**), polyketides (**g**) (Adopted with permission from Wink et al. [9].

2.4. Resins

Resins are composite mixtures which comprise both volatile as well as non-volatile attribute compounds; as well, they are comprised of a lipid soluble group of compounds. Non-volatile resins consist of diterpenoid and triterpenoid compounds, while volatile resins are equipped with mono/sesquiterpenoids. These resins are broadly found in herbaceous plants and are popularly known for their wound healing and antimicrobial properties.

2.5. Alkaloids

Alkaloids, a bitter-tasting and nitrogen-holding compound is a heterocyclic with limited spread in the plant kingdom. The *Solanaceae* family, including *Atropa belladonna*,

Datura spp as well as *Hyoscyamus niger*, consists of tropane alkaloids with anticholinergic properties. It is widely used for reducing muscle pain. Besides, pyrrolizidine alkaloids belong to the *Asteraceae* and *Boraginaceae* family, especially in *Senecio* spp. It comprises of a wide range of application including treating cancer cells, stimulating bone marrow leucocytes and myocardial contractility. In addition, methylxanthine alkaloids are distributed in *Coffee arabia* as well as *Theobroma cacao*.

2.6. Proteins

Plant proteins have gained significant popularity in the field of food and medicinal sectors as they are a major source of nutrient for humans and animals. The *Euphorbiaceae* family as well as *Fabaceae* and lentils are known to contain a high content of protein.

3. Novel Strategies for the Extraction of Bioactive Compounds from Plant Matrix

3.1. Individual Strategies

3.1.1. Ultrasound-Assisted Extraction (UAE)

Bioactive extraction from plant matrix using ultrasound has been widely employed over the past few decades [10]. It works on the principal of mechanical wave with a frequency ranging from 20 kHz to 100 MHz, which passes through a medium at a cycle of expansion and compression. In the case of liquid medium, cavitation bubbles are formed, at high acoustic pressure [11]. This phenomenon is known as "acoustic cavitation" as it enhances the extraction yield as the high shear force is induced by the cavitation, which leads to mass transfer of bioactive compounds by turbulent mixing and acoustic flow [12,13]. Ultrasound (US) extraction works on four basic parameters including ultrasound power, ultrasonic intensity, mode of working (e.g., non-pulsed/pulsed) and acoustic energy density [14]. In addition, it is divided into two different set-ups such as the US-bath and US-probe systems. In the case of an ultrasound bath system, the ultrasonic transducer array is placed below at the bottom of the extraction bath, which can also be attached at the side walls of the US-bath or inside the bath as a transducer array box. The transducer array box can be placed at any direction as per the requirement based on sample matrix. Whereas, in the case of the US-probe system, the probe is bonded with the transducer, which is submersed in liquid medium, enabling direct distribution of US waves, hence resulting in minimum loss of US energy. In addition, US intensity is an important factor affecting the yield of bioactive extraction, hence, it is important to consider the type of US employed, especially the probe diameter and the design of transducer employed as per the requirement [15].

Over the past few years, US has evolved, as from the fixed US power system, now it is possible to adjust the acoustic power. Most probe-type US devices usually control the amplitude of the probe vibration, and some of them can apply busters to increase its maximum amplitude. Alexandru et al. [16] developed a continuous US system for scale-up extraction to industrial level. In this system, a huge capacity of samples can be extracted continuously by feeding into a relatively small tank with multi-horn ultrasonic reactor. Elevated amplitude/intensity can enhance the sonochemistry but it leads to degradation of the transducer, which leads to increased agitation and reduced cavitation level. Hence, high amplitude/intensity is not essential to improve the extraction efficiency of cavitation level. However, the sample with high viscosity needs high amplitude as the high viscous samples tend to decrease the effect of sonication or cavitation [17]. Therefore, to achieve the required level of cavitation, it is necessary to enhance the level of amplitude [18]. Further, enhanced US frequency results in reduction in cavitation level. US develops cavitation bubbles, which take time to be initiated after the compression–rarefaction cycles. At high frequencies, it is challenging to produce acoustic cavitation, as the cycles of compression–rarefaction are too short to allow the growth of the cavitation bubbles. Therefore, higher amplitude and intensity of ultrasonic devices are needed to produce acoustic cavitation at high frequency [19]. Apart from physical properties, chemical properties including solubility and stability of the target compound in selected solvent also play an essential

role in the extraction yield and efficiency of bioactive compounds from plant matric using US. Parameters like time and temperature are also considered to influence the level of extraction [20,21].

Several bioactive compounds have been effectively extracted using US from a plant-based matrix (fruits, vegetables/their by-products) [22–24]. Pan et al. [25] extracted bioactive compounds from pomegranate peel using conventional and US extraction techniques. The results indicate that a continuous US-pulsed system enhanced the level of antioxidant extraction to 22–24% and reduced the extraction time to 90%. Due to the enhanced extraction yield and reduced time as well as energy consumption, US is considered as an alternate and green technology for the extraction of bioactive compounds. Apart from fruits and vegetables, US is also employed to extracted bioactive compounds from medicinal herbs, spices and oleaginous seeds [26–29].

3.1.2. Microwave-Assisted Extraction (MAE)

Over the past few years, microwave (MW) has gained popularity in the extraction of bioactive compounds from plant-based matrix [30–33]. It works on the principal of electromagnetic waves and frequencies, mostly 915 MHz and 2450 MHz frequencies employed for industrial and domestic applications. The mechanism behind this technique is that MW works on heating effect, which results in higher extraction temperature, causing faster mass transfer [34]. MW has the tendency to penetrate inside the sample matrix causing interaction in polar components, thus causing direct/bulk heating effect to the solvent and the sample matrix [12]. Further, this direct/bulk heating by MW also helps in the reduction of time and solvent used especially in industrial level extraction. Moreover, in MW extraction, the direct heating enters inside the matrix and increases local temperature and pressure, leaching out the target bioactive compounds from the sample matrix to the solvent solution. Two different setups are available for MW extraction: (a) open system, (b) closed system, where the pressure can be adjusted, e.g., increase or set at atmospheric level, respectively. The closed system MW extraction is carried out in a sealed vessel with constant MW heating, at controlled pressure and temperature. This closed system helps in reaching higher temperatures than the open system, as the amplified pressure in the closed vessel increases the boiling point of the extraction solvent [35]. Although high temperature and pressure lead to efficient, high and fast extraction yield with less solvent consumption, they also escalate the safety risks (Figure 3). In addition, this particular system is limited to certain bioactive compounds as maximum compounds are heat-sensitive and tends to degrade at elevated temperature, thus, the open system is promoted widely [36].

MW extraction depends on several ranges of factors including microwave power, frequency, exposure time, moisture content, particle size of sample matrix, type and composition of solvent, dilution ratio, extraction temperature, extraction pressure and the number of extraction cycles. The detailed description of these factors has been reported by some reviews. The most critical factor is selection of extraction solvents as its solubility with sample matrix, its dielectric constant and dissipation plays a major role in extraction process. Solvents with higher dielectric constant like water and polar solvents can store more microwave energy than nonpolar solvents, thus water and polar solvents are reported to be better for MW extraction [37]. Besides, the dissipation factor, which converts electromagnetic energy into heat, is considered a significant factor for MW extraction. Ajila et al. [38] reported that solvents including ethanol and methanol, which contain a higher dissipation factor, are better solvents than water in the extraction of phenolics. Although, water possesses a high dielectric constant as compared to ethanol and methanol, but due to its low dissipation factor, it fails to heat up the sample matrix in depth. Therefore, for this reason, combination of solvents (water with ethanol or methanol), which contains high dielectric constant as well as a high dissipation factor, can be used to enhance the extraction efficiency.

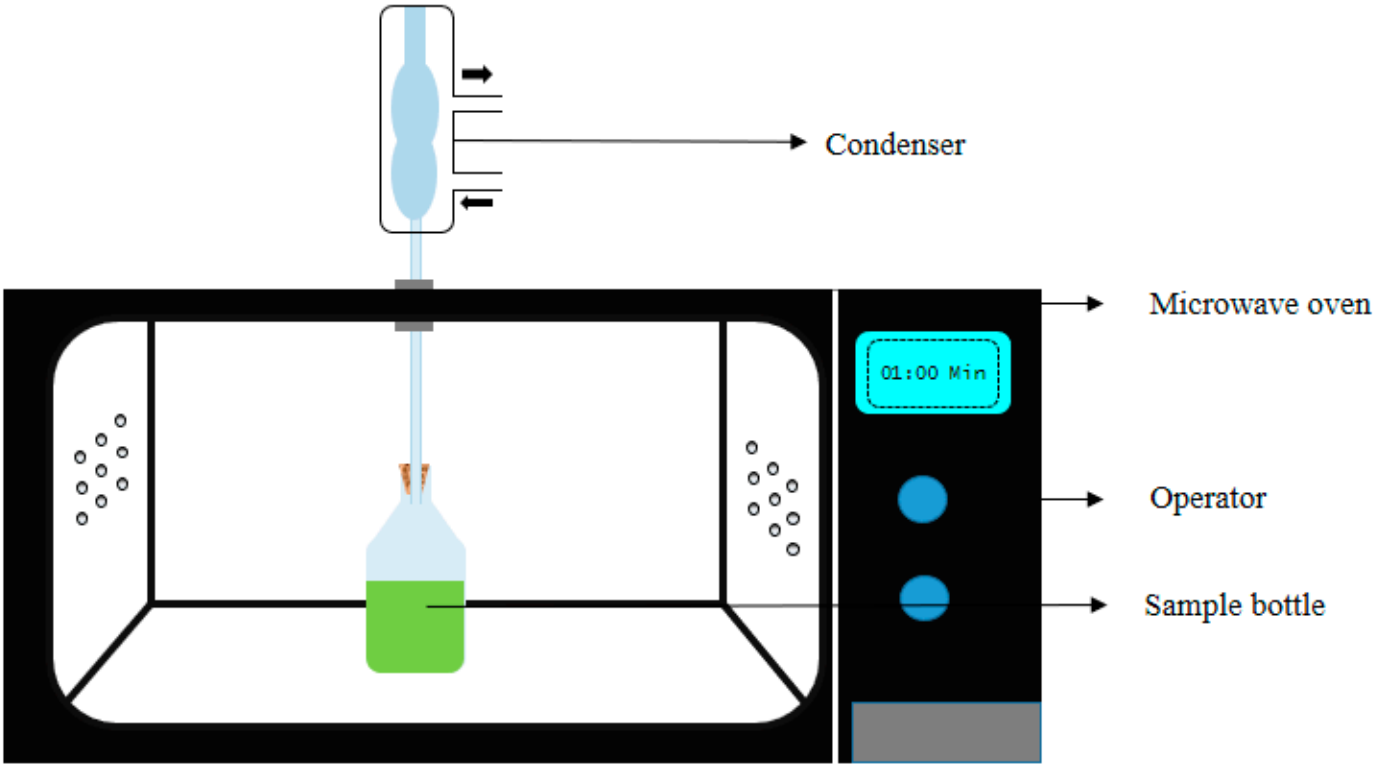

Figure 3. Schematic representation of the microwave-assisted extraction apparatus.

MW extraction comprises a wide range of advantages over conventional extraction techniques including reduction in extraction time, solvent used and extraction cost with a significant level of enhancement in extracted compounds. Shu et al. [39] extracted ginsenosides from ginseng root using MW extraction techniques for 15 min and resulted in a higher yield compared to conventional extraction, which took 10 h to complete. Dhobi et al. [40] extracted flavolignin and silybinin from Silybum marianum employing MW extraction and results revealed that the extraction efficiency was enhanced to 60% compared with the conventional solvent extraction methods. Similarly, Asghari et al. [41] extracted cinnamaldehyde and tannin from some medicinal Asian plants and their results reflected in a quicker and easier technique compared with conventional extraction techniques.

3.1.3. Enzyme-Assisted Extraction (EAE)

EAE is considered as one of the most efficient, eco-friendly, and non-thermal extraction strategies over conventional extraction techniques. It has been employed by several food industries for the extraction of various bioactive compounds saponin, carotenoid, anthocyanin and many more [41]. Incorporation of certain enzymes including pectinases, cellulases and hemicellulases during extraction can significantly enhance extraction efficiency/yield of bioactive compounds by the principal of degradation in cell wall and membrane interiority [42,43]. In this technique, adequate knowledge about the catalytic specificity and its mode of action is necessary to acquire as well as to know its optimum conditions suitable for the enzymes to act on the plant matrixes. In order to use enzymes efficiently for EAE, it is essential to understand their catalytic specificity and mode of action, as well as investigate optimal conditions and which enzyme or enzyme combination is more suitable for the raw materials [44]. Several significant factors including enzyme composition and concentration, type of extraction solvent, solid-to-liquid ratio, enzyme/substrate ratio, pH, extraction temperature and time play a vital role in activation of enzyme reaction and extraction of bioactive compounds [12,45].

Temperature is one of the important factors influencing the rate of extraction, but excessive increase of temperature may also inactivate enzymes. Moreover, a wide range of compounds are heat-sensitive, and therefore require mild temperature throughout the extraction process [46]. Furthermore, pH is one of the major reaction conditions where the enzyme gets activated and stated to degrade the cells of the sample matrix. The optimum pH for each enzyme has already been reported; however, it may vary depending upon the matrix used and reaction conditions applied [19,47]. Enhancement in ratio between enzyme/substrate tends to improve catalytic reaction rate, but due to this amount of enzyme used, increases, which results in increased extraction cost. Further, the solvent used for the extraction may not be suitable for the enzymes used in the extraction process, for instance, several enzymes used for extraction of bioactive compounds from plant matrix are active in water, which may be not be active at higher concentrations of solvents including methanol and ethanol. Many bioactive compounds are highly soluble in concentrated methanol and ethanol; therefore, in such cases, major concern needs to be given to the selection of enzyme and its reaction conditions to achieve the desired extraction yield.

EAE is broadly employed for the extraction of bioactive components from a wide range of plant matrix including flavonoid from the peel of citrus, fructans from Dasylirion wheeleri, curcumin from turmeric, anthocyanin from beetroot, total phenolics from pomegranate peels and Cassia fistula pods, polysaccharide from seaweed and Cedrela sinensis, lycopene from tomato tissues and fatty acids from microalgae [48–53].

3.1.4. Pulse Electric Field-Assisted Extraction (PEF)

Over the years, PEF has become one of the most promising non-thermal and cost-effective bioactive extraction techniques to extract compounds used by the nutraceutical and pharmaceutical sector. The concept of PEF began in 1999 by a researcher named Ganeva and co-workers. They treated beer yeast with 2.75 kV/cm pulse electric power and kept it for macerating for 5 h for the extraction of protein. Further, they found that, after treating the sample with PEF, the dissolution enhanced, which was reflected in a significant increment in protein extraction. This gave a light of hope to the other researchers, as PEF has the ability to improve the mass transfer rate through cell membrane. Based on this belief, many researchers carried out several experiments for the extraction of bioactive compounds employing PEF and found that this non-thermal technology, when compared with several other extraction techniques, indicated shorter treatment time (some microseconds) with higher extraction yield [54]. In addition, this technique can easily be employed at the industrial level for continuous flow of extraction. The system is equipped with a high-voltage pulse generator, a sample holding chamber and a controller. The treatment chamber contains two electrodes with a gap. One of the electrodes is connected to the pulse generator and the other is earthed (Figure 4). Before treating the sample, it is subjected to fine powder, followed by agitation in the selected solvent. After agitation, the sample is pooled in the treatment chamber, led by the treatment parameter settings such as pulse number or pulse width (μs), electrode voltage (24 kV), energy input (kJ), frequency (Hz). Usually, at high electric voltage, the extraction is higher, but in the case of some compounds such as polysaccharides, it tends to decompose, which results in low extraction yield [54]. Hence, it is important to decide the parameters of the extraction based on the targeted compounds. In addition to this factor, including solvent conductivity, polarity, solubility with the target compounds also plays a vital role in the extraction process. Generally, conductivity, solubility of the solvent and dilution ratio of solvent to solute as well as pulse duration/width is directly propositioning to the extraction yield. However, if we further increase these conditions beyond the requirement, then it tends to reflect negative results as when a high amount of electric pulse is applied, the targeted compound may also start to degrade, which can reduce the extraction yield and thus selection of the correct solvent, and operation factors are extremely significant [55]. Bioactive compounds including protein, saccharides, calcium and others are easily extracted using PEF.

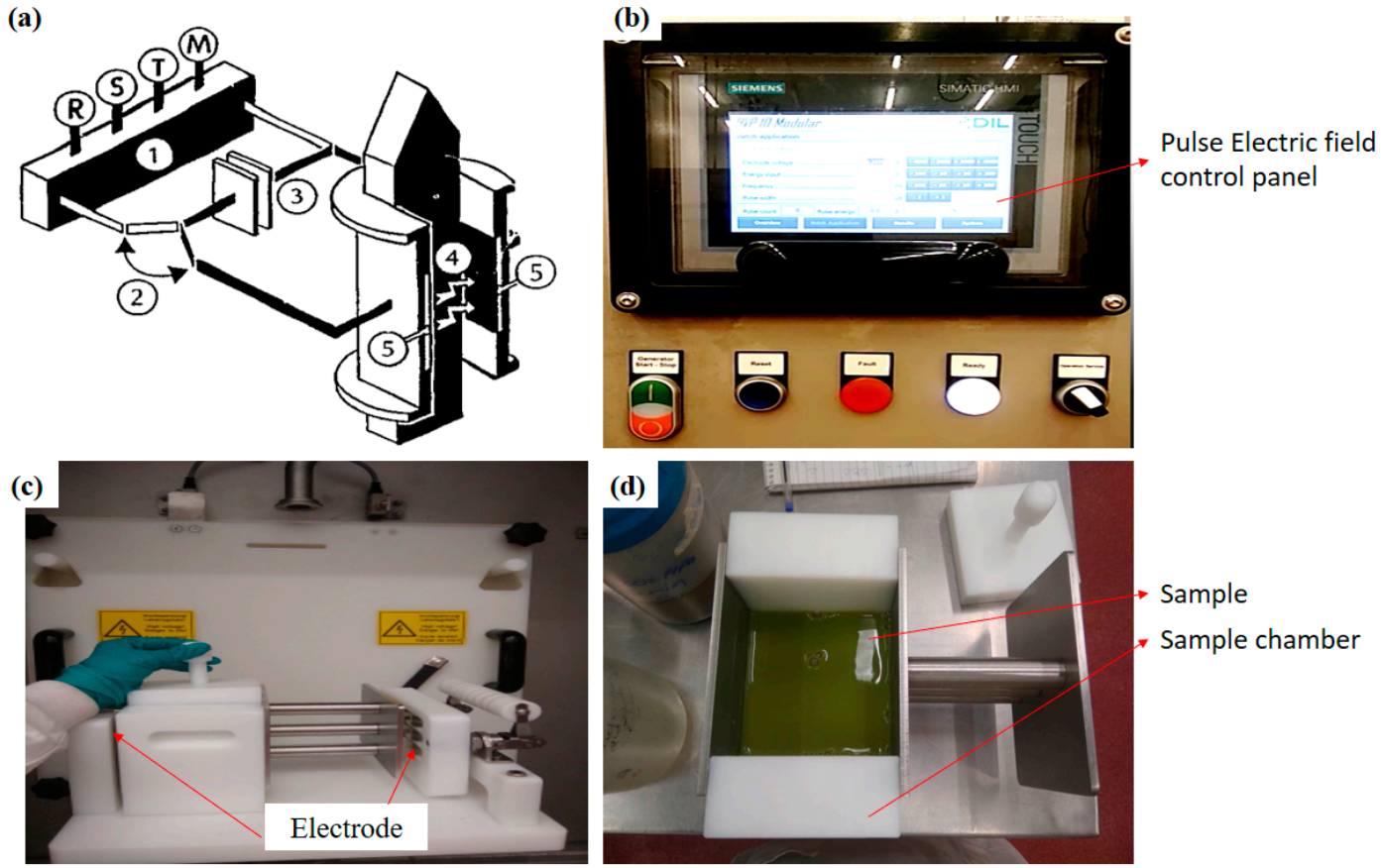

Figure 4. Simplified schematic diagram of PEF (**a**) 1. High-voltage generator; 2. Switch; 3. Capacitor; 4. Medium; 5. Electrodes: and R, S, T, M, connector points for the main supply; (**b**) control panel of PEF; (**c**) Pulse electric field electrodes and treatment chamber; (**d**) sample chamber with sample. (Modified and adopted with permission from Knorr et al. [56].

3.1.5. Moderate Pressure Application

Supercritical-Assisted Extraction (SFE)

Supercritical fluid extraction is employed over the conventional extraction method, as the solvents used in this technique differ in physicochemical properties including density, diffusivity, viscosity and dielectric constant. In addition, these properties play a critical role in the extraction process, as these supercritical fluids are low viscous and high in diffusivity, thus movement of solvent through the plant matrix becomes easy and results in a faster rate of exchange. There are a wide range of compounds/solvents including carbon dioxide, ethane, ethane, methanol, nitrous oxide, n-butene, n-pentane, sulphur hexafluoride and water used as supercritical fluid. However, carbon dioxide is considered the most promising fluid for the extraction of bioactive compounds due to few reasons, such as, it is harmless to the environment and human health, its favorable critical temperature (31.2 °C) which helps to extract heat-sensitive compounds easily and the extracted compounds are preserved from oxidation when exposed in air [57]. As carbon dioxide is at room temperature in its gaseous state of matter, it is easily eliminated after the extraction is completed, and the achieved compounds are left as solvent-free extraction.

Basically, the SFE process of extraction is divided into two main categories: (a) solubilization of bioactive compounds in the extraction fluid; (b) its separation into the fluid of supercritical. Throughout the extraction, the fluid passed through the cells of plant matrix, solubilizing the compounds present in cell membrane, thereby resulting in the extraction chamber with the solubilized target compound. Further, by release of pressure and change in temperature, the fluid becomes separated from the compound and, as a result, the pure form of the compound is extracted. Brunner et al. [58] reported that the initial step of

extraction (solubilization) takes place in several stages. In the beginning, the plant matrix absorbs the supercritical fluid, which leads to swelling of its cellular membrane followed by expansion in intracellular passages, which results in mass transfer, and thus the solubilized compounds moved from inner cell membrane to outer surface, and lastly, it is separated from the fluid. In order to optimize the treatment conditions of the SCFE technique, intense knowledge in thermodynamic (solubility and selectivity) and kinetic data (mass transfer coefficients) is essential. The kinetic illustration of SFE is achieved by extraction curve graph, illustrated in Figure 5, which educates about the extraction yield subjected to extraction time (t). Overall extraction curve (OEC) is divided into three different time phases of mass transfer, (a) constant extraction rate (CER) and the phase is called tCER, wherein the compound is packed inside the solute, therefore leading to convection mass transfer; (b) falling extraction rate (FER) and the phase is called tFER, wherein convection is combined with diffusion mechanism as the external lipid layer of the cell membrane fails to remain intact; (c) diffusion control (DC) and the phase is called tDC. In tDC, the lipid layer is completely corroded and the diffusion starts inside the plant matrix; hence, maximum extraction is achieved [59–61]. Moreover, the evaluation of the extraction curve was carried out using spline model, where the extraction takes place from constant phase of extraction to falling extraction rate and then finally to diffusion rate [62]. In addition, tCER tFER and tDC (in min) indicate the time span of CER, FER and DC respectively. As the sample passes through these phases, the bioactive compounds are extracted with the increase in time at a specific pressure and temperature. At higher temperature with low pressure (approximately 20 MPa), extraction yield is amplified. However, the rise in temperature reduced the characteristics of compounds extracted.

Due to the promising outcome of SFE techniques, it provides a wide range of application in the food, cosmetics and pharmaceutical sectors, as it helps in the extraction of flavors, analgesics and anti-inflammatory drugs. It is also helpful for the development of drugs for the treatment of chronic diseases such as stroke, cancer and Alzheimer [63,64].

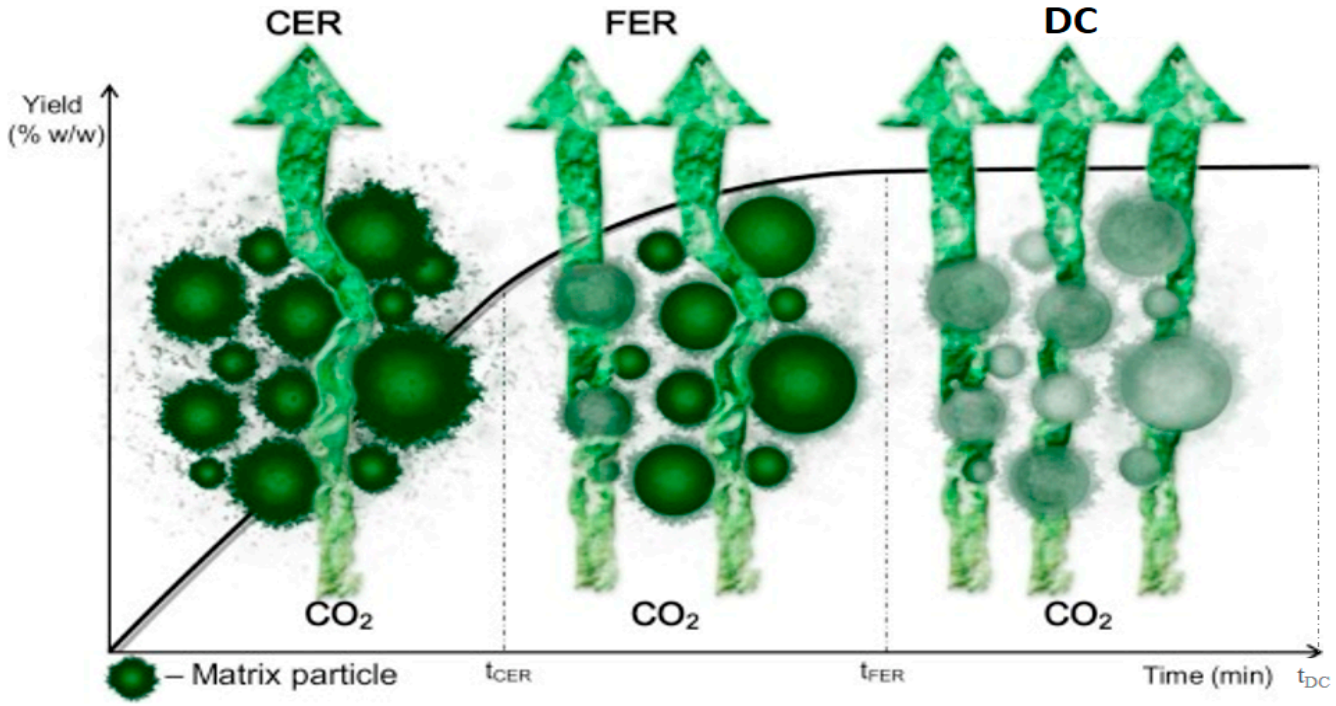

Figure 5. Graphical representation of mass transfer of bioactive compounds from cell membrane to solvent (modified and adopted with permission from Rui et al. [62]).

3.1.6. High-Pressure Application

High Hydrostatic Pressure-Assisted Extraction (HHPAE)

This novel extraction technique works on the principle of combination of pressure (100 to 500 MPa) and temperature (20–50 °C) which results in enhancements to mass transfer rate. According to the US Food and Drug Administration, this technique possesses environmentally friendly attributes, and hence has gained popularity in a wide range of food and nutraceutical sectors [65]. The mild temperature employed in HHPAE has positively reflected promising results for the extraction of heat-sensitive bioactive compounds [65–67]. HHPAE improved the rate of extraction by enhancing mass transfer rate by rupturing the cell membrane and organelles at minimum consumption of solvent and time [68–71]. HHPAE was first reported by a German researcher, Knorr et al., 1999 [72], for the extraction of caffeine from coffee seeds. Further, in 2004, Sanchez-Moreno et al. [73] stabilized a protocol for the extraction of carotenoid from tomato at 100–400 MPa. Over the last few years, HHPAE has evolved rapidly for the extraction of these bioactive compounds. Firstly, the plant matrix is dried and milled followed by sieving (40–60 mesh) to secure an even particle size of sample for the extraction. Secondly, an appropriate solvent is selected based on the solubility of the target bioactive compound in that solvent. Lastly, fine plant powder is incorporated in solvent in a sterile polyethylene bag. The bag is further vacuum-sealed and kept inside the pressure vessels equipped with a pressure and temperature regulator (thermocouple) attached at the top and bottom of the vessel to maintain the desired temperature (Figure 6). Further, the pressure vessel is filled with water to create a pressure by a pressure pump attached to the vessel. Post extraction, the mixture is filtered and the solid particles are removed. The filtered extract is further centrifuged at 4000 to 8000 rpm for 10–15 min. Post centrifugation, the supernatant is collected and passed through a 0.45 µm membrane for characterization and quantification analysis of the targeted compound [74,75]. Liu et al. [76] studied the effect of high-pressure treatment on cell membrane of ginseng roots using scanning electron microscopy (SEM), and the results reveal that the damaged/ruptured cell membrane was clearly identified in the high-pressure-treated sample compared to untreated samples, and therefore it is concluded that HHPAE enhances the extraction efficiency of bioactive compounds in plant matrix. The efficiency of the extractions is based on a few important parameters including pressure applied, time/temperature combination, dilution ratio of solvent and solute, particle size of solute and polarity of the solvent used [77]. Solvents with similar polarity to the targeted compounds significantly give better extraction yield.

HHPAE has been proven to be promising for enhancing the diffusion capacity of the solvent inside the plant matrix by rupturing the cell membrane, which results in improved permeability, hence increased extraction yield [78]. It also breaks the hydrophobic bonds and denatures the protein molecules, thereby making the extraction better [79,80]. Moreover, based on dissolution mass transfer theory (mass transfer rate = pressure/resistance of mass transfer), the dissolution is higher in HHPAE [81]. The more the pressure/temperature (30 °C, 50 °C, 70 °C) is applied, the more is the solvent dissolution to cell, which enables the compounds to leach out the membrane. In addition, pressure-holding time helps in maintaining the equilibrium of solvent between inside and outside of the cell membrane. However, long pressure-holding time may damage the biological activities of the plant matrix; therefore, it is necessary to maintain a suitable time according to the target compound. If the dry sample has to be given high-pressure treatment, it will facilitate cell enlargement, leading to swelling and opening of pores in the cell membrane [82–85].

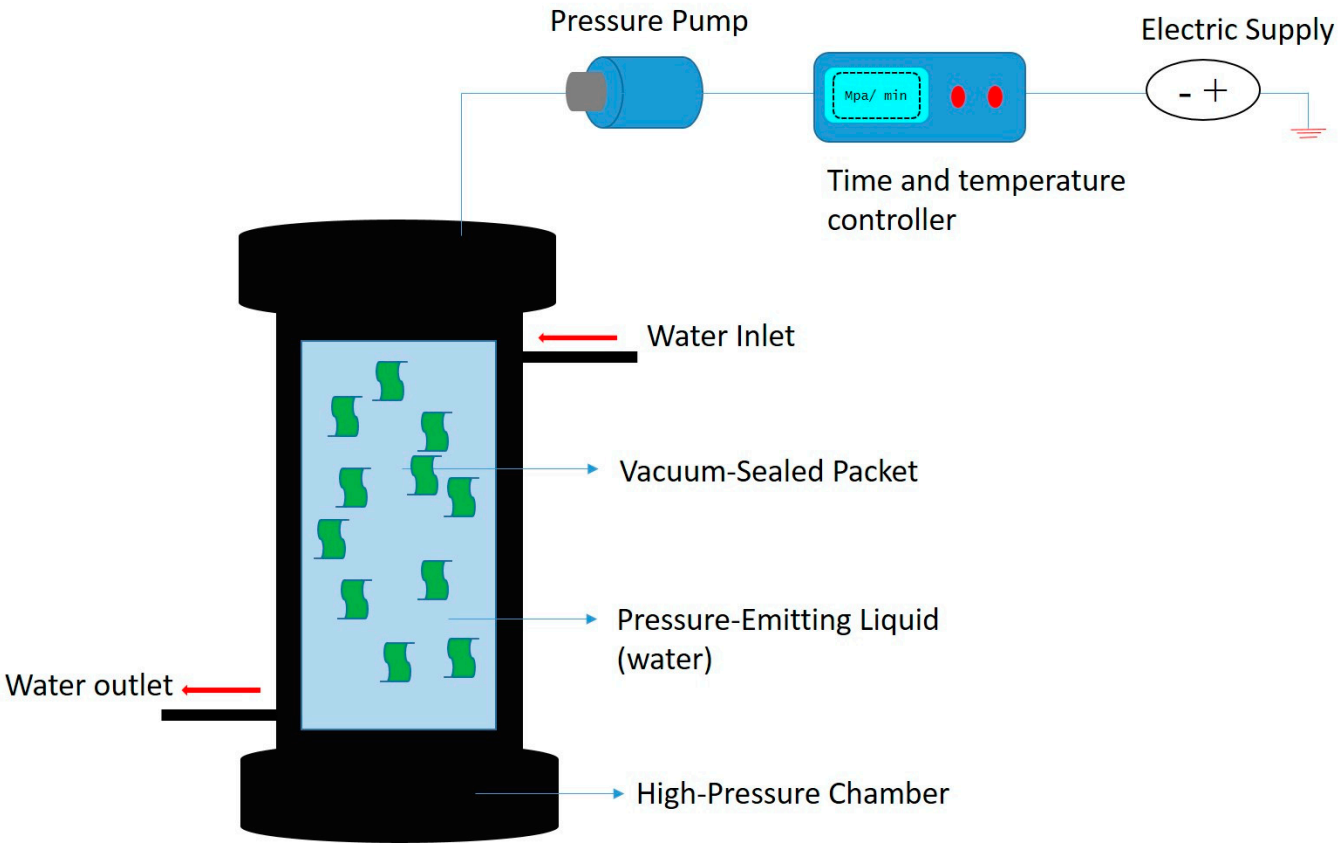

Figure 6. Schematic representation of high-pressure processing.

3.2. Combination of Novel Stategies

In the past few decades, researchers have been trying to enhance the extraction yield of bioactive compounds using novel technologies, but in order to further increase and purify the yield, combination strategies have been implemented, which mainly includes ultrasound-enzyme-assisted extraction, ultrasound-microwave-assisted extraction, microwave-enzyme-assisted extraction, ultrasound/microwave-enzyme-assisted extraction, pulse electric field enzyme-assisted extraction, supercritical fluid enzyme-assisted extraction and high-pressure enzyme-assisted extraction [86–89]. Each individual technique, such as ultrasound when applied on plant matrix, tends to enhance its mass transfer rate by rupturing the cell membrane; however, some portion of the cell membrane is still hindering the path, which can be removed by hydrolysis of the sample using enzyme treatment. Therefore, the combination treatment gained popularity and gave promising results. Table 1 illustrates extraction of bioactive compound saponin from several novel treatments individually, as well as in various combinations.

Table 1. Novel extraction strategies for the extraction of bioactive compounds.

Strategies	Bioactive Compounds	Matrix	Solvent	Dilution Ratio	Extraction Parameters	Time/Temp	Yield	Ref.
Individual Strategies								
Ultrasound-assisted Extraction	Saponins	*Zizyphus jujuba*	Ethanol 50%	1:36	38 W	50 min	15.54%	[90]
		Quinoa	Ethanol	1:10	60% A	15 min	5.51 g/100 g	[91]
		Lentil					10.63 g/100 g	
		Fenugreek					12.90 g/100 g	
		Soyaben					4.08 g/100 g	
		Lupin					4.55 g/100 g	
		Alfalfa (*Medicago sativa*)	Ethanol 78.2%	1:11.4	112.0 W	2.84 h/76.8 °C	1.61%	[92]
		Eclipta prostrasta L.	Ethanol 50%	1:14	100 W	3 h/70 °C	2.096%	[93]
	Total phenolic compounds	pomegranate (*Punica granatum* L.) peel	Distilled water	1:4	400 W/60% A	10 min	69 mg/g	[94]
	Total phenolic compounds	Tamarillo fruit *(Solanum betaceum)*	Acetone 80 %	1:50	50% A	12 min	23.96 mg/g	[95]
	Flavonoids	*Lycium barbarum* L. fruits	Mixture of choline chloride and p-toluene sulfonic acid	1:2 M	60% A	1.5 h	Myricetin (57.2 mg/g)Morin (12.7 mg/g)Rutin (9.1 mg/g)	[96]
	Flavonoids and phenolic compounds	*Ocimum tenuiflorum* leaves	Ethanol 55. 34%	1:40	50 W/0.26 W/cm^3	11.71 min	Gallic acid (6.81 µg/mL) Vanillic acid (8.52 µg/mL) Rutin (14.21 µg/mL) Sinapic acid (11.37 µg/mL) Quercetin (3.49 µg/mL) Luteolin (1.76 µg/mL) Apigenin (8.66 µg/mL)	[97]
	Total flavonoids (TF) and total phenolic (TP) compounds	wild garlic (*Allium ursinum* L.)	Ethanol 50%	1:5	28.8 W/L	80 min/80 °C	TP 1.61 g GAE/100 DW; TF 0.41 g CE/100 g DW	[98]

Table 1. *Cont.*

Strategies	Bioactive Compounds	Matrix	Solvent	Dilution Ratio	Extraction Parameters	Time/Temp	Yield	Ref.
	Total phenolic compounds	Peaches and Pumpkins	Ethanol 100%	1:10	44.60% A	27.86 min/ 41.45 °C	Gallic acid 55 mg/100 g	[99]
	Phenolic compounds	Sparganii rhizoma	Ethanol 80%	1:22.74	300 W	33.54 min	ρ-Hydroxybenzaldehyde (2.12 μg/g) Vanillic acid (21.66 μg/g) ρ-Coumaric acid (4.32 μg/g) Ferulic acid (2.08 μg/g) Rutin (10.06 μg/g) Kaempferol (106.35 μg/g)	[100]
	Flavonoids	Olive (Olea europaea) Leaves	Distilled water	1:41	270 W	50 °C/50 min	74.95 mg RE/g dm	[101]
	Flavonoids	Grapefruit (*Citrus paradisi* L.)	Ethanol	1:8	100 W	25 °C/3 min	75 mg gallic acid equivalents/g dw	[102]
Microwave-assisted Extraction	*Saponins*	*Furcraeaselloa var. marginata*	Water	23.54 mL/g	2.45 GHz/1000 W	9 min/90 °C	5.77%	[103]
		Physalis alkekengi L. *var. franchetii (Mast.) Makino*	Ethanol 80 %	1:32	300 W	29 min	6.41 mg/g	[104]
		starfish *Echinaster sepositus*	Ethanol 50 %	1:40	200 W	3 min	60.3 mg/g	[105]
		Phyllanthus amarus	Methanol 100%	1:50	360 W/4 s/Min Irradiation time	50 min	227.9 mg/g	[106]
		Aralia elata (Miq.)	Ethanol 100%	1:20	560 W/3 cycles	50 min/40 °C	1.22 mg/g	[107]
		Gac (Momordica cochinchinensis Spreng.) Seeds	Ethanol 100%	1:30	360 W/Irradiation cycle 10 s on 15 s off/cycle/3 cycles	75 S	26 mg/100 g	[108]
		Ganoderma atrum	Ethanol 95%	1:25	33 kHz	5 min/90 °C	0.968%	[109]
		P. ginseng	Ethanol 45%	1:20	88 W	180 s/83.7 °C	1.31%	[110]
		Cacao pod husk	Methanol 85%	1:50	600 W 6 s/min irradiation time	40 min	69.9 mg EE/g (Escin Equivalant)	[111]
		Paramignya trimera root	Methanol 100%	1:100	360 W/5 s/2 min Irradiation time	40 min	520.5 mg escin equivalents (EE)/g	[112]

Table 1. *Cont.*

Strategies	Bioactive Compounds	Matrix	Solvent	Dilution Ratio	Extraction Parameters	Time/Temp	Yield	Ref.
	Anthocyanin	Blueberry powder	Ethanol 55.5%	1:34	7 min Irradiation time	47 °C	73.73 %	[113]
	Anthocyanins	Purple corn (*Zea mays* L.) cob	1.5 M HCl–95% Ethanol	1:20	555 W/19 min	55 °C	185.1 mg/100 g	[114]
	Rutin and Quercetin	Stalks of *Euonymus alatus* (Thunb.) Sieb	Ethanol 50%	1:40	170 W/6 min	Room Temperature	Rutin 0.225 mg/g; Quercetin 0.012 mg/g	[115]
Enzyme-assisted Extraction	Saponins	*Gomphrena celosioides* Mart	Water	1:25	Cellulose 0.7% (*v*/*w*)	4 h/60 °C/5	1.550%	[116]
		Pseuderanthemum palatiferum (Nees) Radlk. Dry Leaf Powder	Water	1:7.5	Viscozyme 7.5%	75 min/55 °C	2.267 mg/g	[117]
	Flavonoids	Grape skins	Water	1:10	Lallzyme EX-V (10.52 mg/g) pH 2.0	3 h/45 °C	0.012 mg/g	[118]
	Total flavonoids and total phenolic compounds	Bay leaves (*Laurus nobilis* L.)	Methanol 100%	1:5	30 mg of the ternary enzyme mixture (cellulase: hemicellulase: xylanase; 1:1:1	1 h at 40 °C	TPC 5.87 mg GAE/g; TFC 5.18 mg QE/g	[119]
	Flavonoid compounds	*Stevia rebaudiana*	n-hexane	6:1	pectinases and β-glucanases	100 W/140 °C	Luteolin 0.657 mg/g	[120]
Pulse electric field-assisted extraction	*Saponins*	Acanthophyllum Roots	Water	1: 6	7 kV/60	-	9.1%	[121]
High-pressure processing extraction	*Saponins*	Bitter Melon	Ethanol 70%	1:45.3	423.1 MPa	7 min/30 °C	3.270 g Rg1 equivalents/100 g (Ginsenoside standard)	[122]

Table 1. *Cont.*

Strategies	Bioactive Compounds	Matrix	Solvent	Dilution Ratio	Extraction Parameters	Time/Temp	Yield	Ref.
Combine Techniques								
Ultrasound-assisted surfactant Extraction	*Saponins*	*Panax notoginseng*	ethanol	1:6.25	1% (*w*/*v*) of DTAB/SDS vesicle	20 min		[123]
Microwave-assisted surfactant extraction	*Saponins*	*Momordica charantia* L.	Water	1:12	400 W/SDS 0.05 concentration	5 min	4.69%	[124]
Pulse electric field-assisted enzyme extraction	*Saponins*	Panax ginseng	Water/β-glucosidase 2% (4.7 pH/50 °C)	1:50	15 kV/2 µs/10		38.15 mg/g	[125]
High-pressure-processing-assisted enzyme extraction	*Saponins*	Ginseng Root	Ethanol 70%/Cellulose 60 µL/30 mL	1:5	100 MPa	12 h/50 °C	40.02 mg/g	[126]
Conventional Extraction								
Reflux extraction	*Saponins*	Bitter Melon	Ethanol 70%	1:35	-	3 h	2.478 g/100 g	[127]
Solvent extraction		starfish *Echinaster sepositus*	Methanol 70%	1:50	Magnetic agitator	24 h/Room Temperature	7.7 mg/g	[105]
Maceration	Total Phenolics	Blackberry (*Rubus fruticosus* L.) residues	Ethanol 50%	1:40	-	80 °C	3.66 mg GAE/g FR	[102]

4. Nanoencapsulation of Bioactive Compounds

Over the past few years, nanoencapsulation has gained popularity in the field of food science. It is a process of encapsulation whereby a bioactive compound as a core matrix is captured inside a wall matrix which can withstand the environmental and enzymatic degradation. Employing a significant wall matrix/nano-carrier provides protection against bioactive compounds, which are extremely sensitive to heat and digestive enzymes present in the stomach and gastrointestinal tract of the human body. Besides, these wall materials help in maintaining nutritional activity of the compound as well as helping in masking the undesirable taste of some of compounds [128]. Liposomes or lipid bilayer shells are considered best for encapsulation and delivery of bioactive compounds as they protect the compounds for a longer duration of time compared to other types of nano-carriers. In addition to this, casein micelles are considered promising to encapsulate minerals such as calcium and phosphate [129]. Nano-capsules generally range from 1 to 100 nm in particle size. Apart from the food industry, nanoencapsulation is also practiced by the packaging industry for packaging of meat and fruits to extend their shelf life with retained nutritional qualities [130].

Several nano-carriers including protein, casein, chitosan, gelatin, zein, polyethylene glycol, arabinogalactan, poly-D, L-lactide-co glycolide, poly L-lysine and polyaniline are used for encapsulation. According to literature, chitosan-based glycolipid nano-carriers have the tendency to enhance the anticancer activity of fucoxanthin by 25.8-fold, as they help to keep the compound active for a longer period of time [131]. In different studies, rutin was encapsulated using poly (lactic-co-glycolic acid) and zein as a wall matrix, which resulted in a slow delivery rate (25% after 60 h) of rutin at the targeted location in the human body [132]. Presently, one of the researchers used chitosan and alginate to encapsulate bioactive compounds from the waste of grapes, in which, interestingly, the bioactivity of the targeted compound was enhanced and the encapsulation protected the compound from degradation in the gastrointestinal tract [133]. Besides, compounds including peptides are encapsulated using lipid-based nano-carriers or liposomes, which are comprised of double-layer protection of surfactant molecules and aqueous fluid [134]. Furthermore, nano-carriers of hybrid structure (combination of liposome and chitosan) are also in practice to encapsulate compounds like caffeine to enhance the encapsulation efficiency [135].

The techniques employed to encapsulate these compounds are divided into categories based on power consumed for encapsulating, such as top-down and bottom-down techniques as well as their combined treatment [136]. In the case of the top-down method of encapsulation, high power consumption takes place as it is equipped with instruments like spray-drying, ultra-sonication, homogenizer and many more, while the bottom-down method is practiced in minimum consumption of energy; for example, precipitation, micro-emulsification, conjugation, interchange of atoms, etc. Major factors which play a vital role in selecting a particular technique for nanoencapsulation are delivery motive, delivery rate of release, solubility and stability of the nano-carrier, as well as cost of production [131].

4.1. Encapsulating Carriers for Bioactive Compounds

4.1.1. Polymeric Nano-Carriers

Polymeric nano-carriers are considered to be extremely suitable material for encapsulation and delivery of bioactive compounds. Presently, natural-based nano-carriers including casein, starch, chitosan, whey protein and albumin are maximum used. In 2018, Ravi et al. [132] used chitosan as a wall material to encapsulate marine carotenoid fucoxanthin. It resulted in enhanced anticancer activity of the bioactive compound and increased the caspase-3 activity 25.8-fold. Further, Gagliardi et al. [133] carried out a comparative study using synthetic and natural-based nanoparticles, namely, poly (lactic-co-glycolic acid) and zein for the encapsulation of rutin. The results indicated that zein loaded with 0.8% rutin concentration reflected slower release (25%) after 60 h as compared to poly

(lactic-co-glycolic acid) (100%). Further, in 2021, Portugal researcher Costa et al. [134] encapsulated bioactive grape pomace extract using chitosan and alginate nanoparticles, which protected the bioactive compounds from hydrolysis in the gastrointestinal tract as well as enhanced its bioactivity.

4.1.2. Lipid-Based Nano-Carriers

Lipid-based nano-carriers, known as vesicular carriers, include nano-liposomes, niosomes and particulate carriers (solid lipid nanoparticles and nano-structured lipid carriers). It is a spherical bilayer developed by the reaction between surfactant molecule and aqueous fluid. It is used to encapsulate various bioactive compounds including peptide. Solid lipid nanoparticles are fabricated by mixing solid lipid in internal phase, whereas nano-lipid particles are developed by mixing liquid and solid lipid together [137]. Chaudhari et al. [138] encapsulated piperine and quercetin using Compritol as a solid lipid, while squalene as liquid lipid and span 80 as well as tween 80 as emulsifiers and co-emulsifier. These encapsulated bioactive compounds reflected slower release due to slower erosion of lipid wall matrix (12 h). Another study conducted by Abd-Elhakeem et al. [139] illustrated about improving the bioavailability and oral target delivery of eplerenone by using lipid-based nanoencapsulation. Eplerenone-loaded nano-lipid capsules reflected in improved permeability up to two folds higher compared to conventional aqueous drug in rabbit intestine after the period of 24 h.

4.1.3. Hybrid Nano-Carriers

Hybrid nano-carriers consist of two main networks including internal (metallic materials and polymers) and external (single/multi-lipid layer) networks. The outer layer of this nano-particle acts as a protection against deterioration and water diffusion. These organic–inorganic and lipid-polymer carriers are basically developed for the treatment of cancer cells with controlled release of bioactive compounds. Seyedabadi et al. [136] developed a slow-release encapsulated caffeine using chitosan coated in nano-liposomes as compared to nano-liposome without chitosan covering; hence, combination of chitosome proved better for the encapsulation of caffeine.

4.2. Nanoencapsulation Techniques for Encapsulation of Bioactive Compounds

Nanoencapsulation of bioactive compounds is significantly more complex as compared to the micro-encapsulation process. It is divided into three main categories, which consist of top-down, bottom-down and a blend of both [131]. Top-down techniques require high-energy-efficiency instruments including spray-drying, ultra-sonication, high-pressure homogenization, etc., while the bottom-down technique is limited to low-energy-consumption techniques, such as precipitation, micro-emulsification, conjugation, layer-wise accumulation, interchange of atoms and molecular into nano-size level, etc. [137]. Several factors influence the choice of a particular technique for tailoring nano-capsules, which include delivery motive, delivery rate of release, solubility and stability of the nano-carrier, as well as cost of production.

In the present review, several encapsulation techniques including ultra-sonication, high-pressure homogenization, microfluidization, nano-fluidics, nano-spray-drying, electrospinning, electro-spraying, milling and vortex fluidic have been discussed.

4.2.1. Electrospinning

In electrospinning, fluids with electric charges are processed by passing high-voltage electricity to polymeric fluid, which results in the development of dry micro- and nano-structures. Basically, the instrument comprises three major parts including a syringe pump, stainless steel electrified needle, and the collector plate inside a chamber. The feed fluid is pushed with a definite flow-rate inside the nozzle/needle, which is subjected to high-voltage electricity. The experiments are carried out at ambient

temperature and after the nano-fibers are collected on the electric collector plate, they are kept in a desiccator prior to packaging [140]. The principal element responsible for the characteristic of nano-fiber includes operating conditions such as spinning fluid properties, polymer attributes and mechanical parameters of the instrument with its several nozzle setups [141]. The diameter of nano-fibers ranges from 1 µm to numerous nano-meters. These nano-fibers are in demand as a reinforced material in food packaging, drug delivery, and biosensing due to its substantial surface area, flexibility to develop into several structures and magnified porosity [142]. There are five different types of electrospinning strategies including blend electrospinning, coaxial electrospinning, emulsion electrospinning, high-throughput electrospinning and polymer-free electrospinning. In the blend and emulsion electrospinning method, the core (bioactive compound) and the wall (polymeric) solutions are blended together for electrospinning using single-nozzle, which works efficiently in controlling the release of bioactive compounds. Hydrophilic and hydrophobic molecules can be easily encapsulated using this technique [143]. On the contrary, in the case of a coaxial electrospinning setup, the component consists of a syringe with a twin-compartment, where two different nozzles are attached to one syringe outlet pump for electrospinning the core and wall solution together, which results in achieving encapsulated fibers [144]. However, high-throughput electrospinning is a needless technique applicable for the fabrication of ultrathin fibers via emulsions subjected to centrifugal pressure of polymeric fluid. In 2018, Kutzli produced glycoconjugates using high-throughput electrospinning. Apart from all these techniques, polymer-free electrospinning is an enhanced version of electrospinning, wherein the polymeric fluid with high molar mass is injected through a pump on the surface to achieve higher yield than the conventional techniques [145]. Xiao et al. [146] indicated that this technique was able to fabricate nano-fibers of a diameter ranging from 87 to 57 nm, whereas other reports by Moreira et al. [147] indicated that polymer-free electrospinning is useful for the food industry to improve the uniformity of nano-fibers derived from spirulina. Further, Poornima et al. [148] used electrospinning to encapsulate resveratrol with poly(ε-caprolactone) and poly (lactic) acid and the results proved to be effective in controlled drug release delivery, while another recent study by Leena and Anandharamakrishnan et al. [149] achieved the highest encapsulation efficiency (96.9%) of resveratrol using Zein. Researchers also indicated that these nano-fibers are useful as edible nano-films for oral delivery.

4.2.2. Electrospraying

Elcetrospraying, popularly known as electro-hydro-dynamic atomization (EHDA), is an alternate solution for the drying-encapsulation technique. It runs on high-voltage electric current at ambient temperature. The primarily principle for both the techniques (electrospinning and the electrospraying) is similar, the unique difference between these technologies lies in intermolecular cohesion of polymeric fluid which is remarkably low in the case of electrospraying, and thus results in breakage of jet into fine droplets. The jet particles, when exposed in air, gain a spherical shape in view of the surface tension. A report by Bhushani and Anandharamakrishnan [140] revealed that electrospraying helps to enhance the permeability and bioactive releasing attributes in catechins from green tea with the help of zein as a wall material. Later in 2019, Jayan and Anandharamakrishnan also revealed that resveratrol, when nanoencapsulated using the same wall material, results in 68% encapsulation efficiency [150].

4.2.3. Nano-Spray Dryer

The nano-spray-drying technique is quite similar to that of conventional spray-drying, where the fluid is subjected to droplet formation and further dried by the heated drying gas to form dry particles. In the case of nano-spray, the little modification has been made which includes a particular nozzle, which fabricates nano-droplets using a constant flow of drying gas used from laminar. Further, the nano-droplets are subjected to vibrating mesh of 4.0,

5.5, and 7.0 µm size holes. The fragment size of the spray-dried sample totally depends on the concentration of the fluid, temperature of drying gas, spray velocity and the size of the droplets [151]. Adel et al. [152] encapsulated curcumin in hydroxypropyl beta-cyclodextrin using the nano-spray-drying technique for the pulmonary delivery of curcumin in lung tissues and the results indicated significant reduction of proinflammatory cytokines compared to the pure drug. Further, Mozaffar et al. [153] dried nano-structured lipid carriers of 3% palm oil and 3% tween 80 (60 g/L) mixed with sodium chloride. The results revealed that the presence of sodium chloride protected nano-structured lipid carriers from aggregation during the process of spray-drying and about 50% of lipid molecules were encapsulated in salt particles.

4.2.4. Micro-/Nano-Fluidics

The primary concept of micro-/nano-fluidics is based on interfacial interaction between the core and wall fluids. It helps in the formation of spherical drops and slows down the release of the bioactive compounds. In addition to this, it helps in the production of similar-size accurate nano-droplets [154]. It consists of components including a molded set of channels fabricated on a base of polydimethylsiloxane (PDMS) of glass. The fluid is passed through this channel as these are interconnects from all directions. Gas and liquid are injected from a syringe using hydrostatic pressure. Generally, this technique incorporated four types of emulsion devices including single-, double-, multi- and flow-focusing nano-/microfluidic devices. It is employed for the fabrication of nano-emulsions, nano-liposomes and nanoencapsules. Jafari et al. [155] developed an oil-in-water nano-emulsion using microfludization at an optimized condition of 42–63 MPa microfluidization pressures with 1–2 cycles. The results of the study indicated smaller droplets of fish oil in developed nano-emulsion. After a couple of years, Wang et al. [156] modified citrus pectin using microfluidation, and the results revealed that properties of nano-emulsion were enhanced, thereby protecting cholecalciferol from UV degradation as compared to the original pectin. In addition, the molecular weight and hydrodynamic diameter of modified pectin was also reduced to 237.69 kDa and 418 nm, respectively.

4.2.5. High-Pressure Homogenization

High-pressure homogenization refers to the production of nano-fragments of a homogenous size in a fluid under a specific high pressure. It comprises 10–15-fold higher pressure (100–400 MPa) than conventional homogenizer. According to the research, this technique is excessively utilized by the milk and milk products industries to upgrade its texture, taste, flavor, and improved shelf life characteristics with enhanced anti-microbial quality (in activation of Salmonella spp., Listeria monocytogenes, Staphylococcus aureus, and Escherichia coli). About 3 and 4 log cycles reduction was reported at 200 and 300 MPa homogenization pressure at 30 °C and 40 °C inlet temperature [157]. It also acts as a substitute against thermal processing, as it is significantly effective for the inactivation of enzymes and microbial activity [158]. Additionally, it also helps in the development of nano-emulsion, which is stable at ambient condition. Fernandez-Avila et al. [159] developed a soy protein isolate-stabilized emulsion employing high-pressure homogenization, and the results revealed that emulsion treated with 100 to 200 MPa with 20% soybean oil was most stable with its improved physical stability in terms of particle size and rheology.

4.2.6. Ultrasonication

"Ultrasound" is a cluster of sound waves beyond human hearing frequency (>16 kHz). Basically, it is divided into two streams, low- and high-intensity waved; low sound waves are generally used for the detection purpose (sonography), whereas high sound waves are used for the modification in molecules including its size reduction, it also helps in the development of emulsification and extensively utilized by the food industries [160]. In nano-

technology, it is basically utilized for the development of several genres of nano-structure. The components of ultrasound comprise an electric generator, piezoelectric transducer for transforming electrical energy into sound energy and a sound emitter of titanium horn shape for conveying the ultrasonic waves into the sample or medium [161]. Various ranges of nano-delivery techniques have been developed, incorporating lipid and surfactant molecules as a wall material for the fabrication of nano-emulsions, nano-liposomes, niosomes, etc., using ultrasound [162–164]. Nano-carriers such as biopolymeric and polymeric have also been developed for the encapsulation of various food bioactive compounds by the food industry.

4.2.7. Supercritical-Based Technologies

It is an alternate green method for the development of nano-particles [165]. Principally, the temperature of critical solvent is above its critical limit or at single phase irrespective of pressure. Carbon dioxide is commonly used as a supercritical fluid as it is nontoxic, low cost and non-flammable. In this process, a liquid solvent is employed, which could absolutely mix with the super critical fluid such as carbon dioxide so as to liquefy the solute subjected to micro-ionization. Now, due to the insolubility of solute in the super critical fluid, instant precipitation takes place, which further brings out the outcome of developed nano-particles [166]. Presently, methods including micronization via rapid expansion of supercritical (RESS) solution, supercritical antisolvent (SAS), supercritical melt micronization (ScMM), spray coation, supercritical CO_2 coating, etc. are employed for encapsulation of bioactive compounds using supercritical system. Several researchers indicate that this technology can be useful in various ways including development of encapsulated products depending upon properties of wall matric and the active ingredients. Based on the behavior of the core and wall material to be encapsulated, the processing technique using supercritical CO_2 is decided. For example, the interaction of CO_2 with the active material, wall material and the solvent used. In case of a biopolymer drug delivery system, the interface between the supercritical CO_2 and the polymer used plays a vital role in encapsulation process. Whereas polymer including polylactide (PLA) is good for SAS treatment, in the case of RESS, it is difficult to solubilize in supercritical CO_2 [167,168].

4.2.8. Polymerization

In this technique of nano- encapsulation, firstly, to form nano-particles, monomers of an aqueous fluid are polymerized then the bioactive compound is mixed in it. Further, when the encapsulation takes place, the nano-particles are purified by removing extra stabilizer and surfactant settled on the surface of the nano-particles. This technique is generally incorporated for developing poly butylcyanoacrylate nano-particles [169,170].

4.2.9. Coacervation or Ionic Gelation

A technique with wide range of hydrophilic compounds (gelatin, sodium alginate and chitosan) was incorporated for the development of nano-particles. Two kinds of aqueous phase fluids are prepared using chitosan polymer (propylene oxide) and polyanion sodium tripolyphosphate. A nano-size coacervation is formed when the tripolyphosphate (negative charged) reacts with chitosan (positively charged) and, due to the reaction of ions, liquid is converted into gel [171].

5. Physicochemical Properties of Encapsulated Bioactive Compounds

5.1. Particle Size

The foremost properties of nano-particles are the size of its particle and its distribution. These properties are responsible for overall quality including its delivery ability, stability, viscosity, etc. [172]. Due to the relative mobility and significantly tiny size, the intracellular holding capacity is relatively higher in nano-particles than micro-particles. Reports reveal

that nano-particles of 100 nm reflected 2.5 times higher holding capacity compared to 1 µm micro particles [173].

Several types of microscopes are used to detect the size and structure of the nano-particles. Optical properties of nano-particles including single/double/multi-emulsions and micro/nano-capsules capsule are measured by scanning electron microscope/laser diffraction based on its properties (wet/dry). To determine the number of pores, surface study is required which needs extremely strong analyzers such as transmission electron microscopy. Several compound locations can be detected using confocal or fluorescence microscopy by mixing fluorophores to dye the bioactive compound. Dynamin light scattering, also known as photon correlation spectroscopy, is extensively utilized to detect size of the nano-particles, which are in the range of 1000 nm. It helps in finding the range of particle size along with its concentration in the given matrix [174]. It is operated to identify the charge attributes of the nano-particles. It indicates the electrical capacity of the nano-particles, which can further be modified by changing the composition of compounds mixed in the aqueous fluid. Zeta potential more than (+/−) 30 mV of a nano-particle is known to be stable. Interestingly, with the help of the Zeta potential test, it can be identified whether the wall material has been encapsulated inside the nano-capsule or covering its outside structure [175]. Desai et al. [176] reported that nano-particles can diffuse through the submucosal layers in rats while a micro-particle is only limited till the epithelial lining.

5.2. Stability of Encapsulated Bioactive Compound

"Stability of nano-particles" refers to the strength and balance needed by nano-particles to remain intact inside the wall matrix until the desired time and place of release. Nano-emulsions have better stability due to their morphological structure of tiny droplets. Additionally, the strength of bioactive compound to remain stable can be examined by placing them in a modified environment including high/low temperature, different ionic charge fluids and different pH range [177].

5.3. Encapsulation Efficiency and Loading Capacity

It is defined as the amount of bioactive compound encapsulated inside the wall matrix. The amount of compound encapsulated can be quantified by using techniques including high-performance liquid chromatography, UV-Vis spectroscopy and UV-Vis spectroscopy [178]. A perfect nano-particle is the one which has maximum compound loading capacity with minimum quantity of wall material. Loading of bioactive compounds can be carried out using two methods including incorporation and absorption methods. The capacity of entrapment is basically dependent on solubility of the compound encapsulated in the wall material, specifically the interaction in the molecules of bioactive compound-polymer, molecular weight and the availability of functional groups [179]. Proteins and macromolecules at isoelectric degree are reported to possess maximum holding capacity. Moreover, in the case of smaller molecules, the ionic reactions between compound and polymer can help in increasing the holding capacity of the matrix.

5.4. Control Release

The release of the bioactive compounds encapsulated in a particular matrix depends on several aspects including compound solubility, surface bound/adsorption, and diffusion from the matrix, matrix degradation and combination of both diffusion and degradation. Nano-spheres with even distribution of bioactive compounds tend to release by erosion of wall material. The process of release is totally controlled by diffusion if degradation of wall material takes place at a slow rate. The quick release of the compound results in poor wall material or low bounding capacity of the compound [180]. It was reported that the mixing method practiced plays a vital role on release profile of nano-capsules as it will slow the release of compounds [181]. In contrast

to this, if the compound is protected by the polymer coating, then the release takes place by the diffusion method from inside to matrix outside. Further, there are several techniques including ultra-filtration, reverse dialysis bag, dialysis bag and diffusion of cell with synthetic of artificial membrane that is practiced for the compound release in vitro.

6. Application of Nanoencapsulation in Food Industries

Application of nanoencapsulation in several industries including nutraceutical, pharmaceutical, food, packaging and preservation has exponentially expanded in the last few years. It is extremely promising for the fragrance and flavor industries as the volatile compounds tend to evaporate during processing time. Besides, these compounds undergo chemical changes due to oxidation at atmospheric condition, which results in degradation of the compounds, thus encapsulation helps to stabilize as well as retain the natural color, flavor and fragrance while enhancing the shelf life of the compound. An excellent example is retaining the fresh aroma of brewed coffee through microencapsulation of flavor compounds such as ketones, pyrazines, furans, pyridines, etc., using food starch derived from waxy maize as encapsulating material. Nanoencapsulation of tea compounds (caffeine, theanine and catechins) using various proteins, lipids and carbohydrates have been reported to increase the effectiveness of their health imparting properties such as anticancer, antidiabetic and anti-inflammatory [182–184].

It has been researched and reported that during gastrointestinal digestion, encapsulated catechin showed improved retention of its biological properties as compared to free catechin [185]. Rojas-Graü et al. [186] revealed that the nanoencapsulation technique can be utilized as an anti-browning technique for food industries. Nanoencapsulated plant-based compounds are tagged as anti-browning compounds. Tyrosinase enzyme, also known as catalase B, accelerates the unwanted chemical reaction during food processing including enzymatic browning of fruits, vegetables and beverages that causes adverse effects on its organoleptic characteristics (Polyphenol Oxidase + O_2 $\rightarrow$ Melanin). Zheng et al. [187] isolated tyrosinase inhibitors from Artocarpus heterophyllus to retard browning reacting in fresh-cut-apple slices. The results revealed that apple slices treated with Artocarpus heterophyllus extract along with 0.5% ascorbic acid reflected no browning reaction after 24 h.

Further, nanoencapsulation is popularly appreciated for improving the water stability, solubility and bio-accessibility of hydrophobic bioactive compounds including curcumin by binding it with naturally existing proteins (legume oligomeric globulins, ferritin and casein micelles) by a hydrophobic interactions bond which acts as a nanocarrier for hydrophobic nutraceuticals in drug delivery [188]. Human Serum Albumin-curcumin nano-particles can be used for cancer treatment as they reflect effective antioxidant activity with enhanced antitumor properties [189]. Luo and co-workers [190] carried out ex vivo and in vivo adhesion experiments employing Tannic acid/IR780-nano-particles, which were tailored with anti-ulcerative colitis properties (encapsulated Curcumin). Reports reveal that tannic acid-loaded curcumin nano-particles can be utilized for drug delivery to treat ulcerative colitis as tannic acid possesses degradable adhesive properties which can accumulate on the surface of inflamed mucosa. In Figure 4, ulcerative colitis mice were orally ingested with three different solutions including free IR780, IR780 nano-particles and tannic acid/IR780- nano-particles. A gradual decrease in adherence level was noticed in all the three samples at different time intervals (3 h, 6 h, 12 h, and 24 h). Mice with tannic acid/IR780-nano-particles reflected the maximum adherence towards inflamed mucosa. Additionally, nanoencapsulation is also considered as an effective technique for encapsulating antidiabetic synthetic compound insulin. In 2021, Hadiya et al. [191] encapsulated insulin using chitosan to 170–800 nm size of spherical shape and about 15–52% of delivery efficiency was achieved.

Nanoencapsulation is also useful in active packaging, which helps to prolong shelf life and preserve quality of the food products. It is employed to retain and enhance the nutritional and organoleptic attributes of the product with extended shelf life [192]. Encapsulated bioactive compounds rich in antioxidants and antimicrobials including vitamin C, Vitamin E, carotenoids, etc., are incorporated to edible films as active compounds during the fabrication as it helps in maintaining the level of freshness of the products. The organoleptic attributes of the coated product can be maintained by incorporating additional flavor, colors and sweeteners. Nano-fibers of cinnamon EO encapsulated in polyvinyl alcohol/β-cyclodextrin are obtained to use as a film for coating the packaging box. The film coating (1.5 cinnamon EO-β-cyclodextrin) acts as an antimicrobial barrier to suppress bacterial and fungal spoilage of the food sample while extending its shelf life by 5 d at 10 ± 0.5 °C [193]. Adel et al. [194] prepared a bio-composite using β-cyclodextrin citrate (50%), and oxidized nano-cellulose (7%) in chitosan solution. The prepared film reflected in reduced water vapor permeability 2.09 ± 0.08 (10–11 g m^{-1} s^{-1} Pa^{-1}). In addition, the film was fortified with clove EO nano-particles, which resulted in higher activity of Gram-negative bacteria than Gram-positive. Further, Xiao et al. [195] developed a nano-composite film by encapsulating pesticide/insecticide (iprodione) using poly (ethylene glycol)-poly (ε-caprolactone and chitosan. The encapsulation of iprodione reflected in its improved efficacy by 2-fold along with its reduced dosage.

7. Conclusions and Prospects

At present, due to the tremendous growth of deadly diseases, it has become necessary for humankind to build up a strong immune system and this could be only possible though ingestion of bioactive compounds extracted from plant sources. This scenario has encouraged researchers to search for the conventional and sustainable extraction method for collection of bioactive compounds from plant matrixes. Nevertheless, application of these novel extraction techniques still remains a challenge due to its working principal as it works on several parameters; therefore, in-depth knowledge is required to follow this technique on the larger scale at the industrial level to achieve a promising output. However, due to the evolution of these novel techniques, the extraction has become easy and the extraction yield has been significantly enhanced in maximum bioactive compounds. Novel technologies have helped in enhancing the extraction of bioactive compounds without significant degradation. Moreover, encapsulation techniques offered to deliver the bioactive compounds at the site where it is needed. The combination of these two techniques offers a synergistic effect for extraction as well as targeted delivery.

Author Contributions: S.N., writing—original draft preparation; N.K.R., writing—review and editing; C.O., writing—review and editing; and B.T., writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: The authors and their work were supported by the Irish Department of Agriculture, Food and the Marine, under the Food Institutional Research Measure to the U-Protein project under grant No. 2019PROG702.

Conflicts of Interest: The authors declare no conflict of interest.

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