Liquefied Dimethyl Ether Extraction Technology for Microalgae

Subjects: Engineering, Chemical

Contributor: Tao Wang, Li Zhu, Li Mei, Hideki Kanda

Microalgae are a sustainable source for the production of biofuels and bioactive compounds. Dimethyl ether (DME), which is characterized by its low boiling point and safety as an organic solvent, exhibits remarkable properties that enable high extraction rates of various active compounds, including lipids and bioactive compounds, from high-water-content microalgae without the need for drying.

Keywords: microalgae ; green solvent ; dimethyl ether ; extraction ; natural products

1. Introduction

Plants contain a wide variety of naturally occurring organic compounds that are produced and metabolized in their bodies. These compounds include waxes, terpenoids, lipids, phenolic compounds, polar glucosides, alkaloids, sugars, peptides, and various other substances [1]. The most important physiologically active plant compounds include phenolic compounds (including flavonoids), saponins, and cyclins, which play key roles as dietary supplements [2]. Natural phytonutrients are widely distributed and contain a diverse range of compounds with low to high molecular weights [3][4][5]. Compounds with strong physiological activities against living organisms have attracted considerable attention from researchers, leading to the exploration of new natural products and structural modifications, particularly in fields such as medicine, pharmaceuticals, and nutraceuticals [3][4][5][6][7][8].

Organic compounds obtained from nature serve as dietary supplements that help improve health, delay aging, prevent chronic disease, prolong life, and support the structure and function of the body [9][10][11]. The market for dietary supplements was estimated to be approximately USD 353 billion in 2019 and it is growing steadily [12].

Substances such as antibiotics, chemical preservatives, and alkaloids have been used in the formulation and extraction of bioactive compounds in various food industries, including sugarcane [13], tea [14], coffee [15], and plant extracts [16][17]. The preparation of natural material samples involves several critical steps: The initial phase includes preliminary washing of plant materials, drying or lyophilization, and grinding for homogenization. The next steps include extraction and qualitative/quantitative analyses [18]. The production of natural materials is expensive and has the drawback of reduced nutrient concentrations in the raw material itself; this poses a significant obstacle for the natural materials industry [19][20]. Consequently, several natural ingredients require solvent-based extraction and purification to produce dietary supplements [21][22].

2. Disadvantages of Conventional Extraction Techniques

2.1. Disadvantages of Traditional Solvent Extraction

Conventional extraction methods for natural organic compounds have historically relied on various solid–liquid extraction techniques using organic solvents, such as the Soxhlet extraction method, immersion method, and steam distillation [23]. Commonly used solvents in these methods include acetone, acetic acid, chloroform, dichloromethane, diethyl ether, ethanol, and hexane. The quantitative and qualitative performance of the extraction depends heavily on the polarity of the solvent used. This necessitates the selection of a solvent appropriate for the polarity of the target component, without a predefined method or solvent [24]. Despite their simplicity, conventional extraction methods suffer from low selectivity, low recovery and extraction rates, labor intensiveness, time consumption, and the use of large amounts of often toxic organic solvents, leading to potential trace residues in the extracts [25].

Traditionally, organic solvents such as chloroform, hexane, methanol, and dichloromethane have been used to extract lipids and other functional compounds [26][27] (**Figure 1**). However, owing to significant waste generation and risks to the

environment and human health, the demand for sustainable, nontoxic extraction methods has increased. Conventional extraction processes require dried algal starting materials and consume considerable time and energy [28]. For lipid extraction from microalgae, 90% of process energy consumption is attributed to lipid extraction [29]. Wet extraction, which accounts for 70% of total energy consumption, appears to be promising.

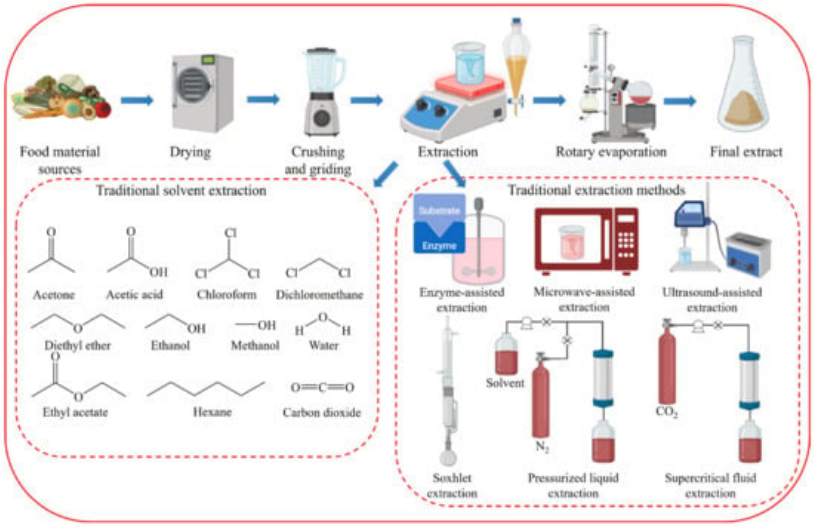

Figure 1. Conventional organic solvent extraction of phytochemicals.

Ethanol is a low molecular weight organic compound that exhibits both hydrophilic and lipophilic properties, making it suitable for the extraction of bioactive compounds such as phenolic acids, flavonoids, and phenolic acid esters [30]. However, the use of ethanol in food processing is prohibited in certain regions and cultures, necessitating the use of alternative solvents. When ethanol is used to extract highly aqueous samples, the addition of benzene to the ethanol–water mixture is required to increase water volatility and prevent water contamination via co-boiling, thereby preserving the non-polar components [31]. Considering the effect of ethanol on human health, dietary supplements should either avoid its use or maintain its concentration as low as possible [32][33].

Supercritical carbon dioxide ($scCO_2$) exhibits an intermediate state between gas and liquid when maintained at high temperatures and pressures above the critical point (31.3 °C, 7.38 MPa) [34]. The use of $scCO_2$ remarkably improves the extraction efficiency of functional components, enabling selective extraction via temperature or pressure control [35][36][37]. The extraction of functional components using $scCO_2$ has been applied to various natural food sources, such as essential oils [38], γ-oryzanol [39], chamomile seed oil [40], and hops [41], as well as for caffeine removal [42] and oil extraction from microalgae [43][44][45]. However, the extraction of functional components from highly aqueous samples using supercritical methods is challenging [46]. This is because of the non-polar nature of $scCO_2$, which often requires the addition of entrainer solvents such as methanol [47][48], ethanol [49], and acetone [50] to facilitate extraction [51].

2.2. Disadvantages of Traditional Extraction Methods

Pre-drying is essential for moisture-containing natural products because moisture content inhibits solvent extraction [52]. For example, coffee hulls have a high moisture content, ranging from 18% to 80% *w/w*, which includes bound water trapped in the fine structure of solid particles. Therefore, most solvent extraction techniques require dried samples [53]. Historically, drying natural materials under natural conditions has been the primary method of preservation. However, this method is now being abandoned owing to its lengthy process and the inability to adjust the drying parameters.

The production of instant coffee requires high thermal energy (21.10 and 8.50 MJ/kg product) for spray drying and extraction, accounting for three-quarters of the total process [54]. Spray drying is the most commonly used method for this purpose and requires 10–20 times more energy per kilogram of evaporated water than drying using an evaporator. To reduce energy consumption, researchers use evaporators to preconcentrate coffee samples before drying [55]. Heat-sensitive substances require extraction at room temperature or cold solvent removal, such as via lyophilization. High extraction temperatures result in solvent loss and component degradation. Anthocyanins, which are valuable, colored bioactive compounds, are increasingly extracted worldwide, but their functionality is limited by their decomposition at 50–60 °C, indicating limited temperature stability [56].

The extraction of natural compounds requires a series of complex operations, such as sample drying, pulverization, extraction, and solvent removal [57] (**Figure 1**). The extraction process begins with solvent selection and involves the use of extraction techniques with higher extraction rates [58]. Traditional extraction techniques such as maceration, Soxhlet

extraction, and decoction have significant drawbacks, including long extraction times, poor selectivity, expensive solvents, and the need for significant solvent evaporation [59].

Maceration involves coarsely grinding the raw material, placing it in a container, pouring the solvent to completely cover the material, and extracting it while stirring until the soluble substances dissolve [60]. However, this method typically takes several days to weeks due to its long soaking time [61].

Soxhlet extraction, a model extraction technique traditionally used to extract compounds, particularly lipids, from solid or semi-solid matrices, has several drawbacks, such as long extraction times (12–24 h), high solvent volumes, high energy consumption, and issues regarding selectivity and efficiency [62][63][64].

Decoction is used to extract thermally stable bioactive compounds by boiling the raw materials in water [65]. However, this limits the extraction of water-soluble components, increases the solvent-to-solid ratio, and introduces numerous water-soluble impurities into the extract [66].

3. Advantages of Liquefied DME as an Extractant

3.1. Physical Properties of DME

DME is a simple ether with the chemical formula CH_3–O–CH_3 and lacks a direct C–C bond. DME has a high oxygen content (34.8%) and low carbon-to-hydrogen ratio (C:H) [67]. The two methyl groups in DME form two polarized bonds oriented at an angle of 111.8 ± 0.2°, resulting in a bent V-shaped molecular geometry around the central oxygen atom [68]. DME contains two types of bonds (C–O and C–H). Although there is a 0.4-unit electronegativity difference between C–H bonds, which results in weak polarity, C–O bonds have a 1-unit electronegativity difference, indicating a higher polarity [69]. Because of the uneven distribution of charged electron clouds throughout the molecule, DME exhibits a dipole moment of 1.3 D, making it a polar substance [70].

DME is a gas under standard conditions and has a boiling point of −24.8 °C [71]. This gaseous state results in minimal residue in the extracted materials [72]. Although denser than dry air, DME exists as a vapor at 0.1 MPa and 25 °C. Moreover, it transitions from the vapor to the liquid phase above a saturated vapor pressure of 0.59 MPa at 25 °C [73][74]. The density of liquid DME at 25 °C is 668 kg/m^3 [75].

The dielectric constant (ε) of liquid DME at 30.5 °C and 6.3 MPa is 5.34 [76]. In comparison, the dielectric constant (ε) of water (30 °C, 25 MPa) is 80 [77]. This suggests that the polarity of DME is suitable for dissolving non-polar to moderately polar substances [78]. DME can bind to both polar and non-polar compounds via the oxygen atom at its molecular center. It forms hydrogen bonds with the hydrogen atoms of other molecules, thereby increasing extractability [79][80].

3.2. Cell Destruction and Drying-Free Extraction Techniques

Plant cells are surrounded by a cell wall, which is mainly composed of cellulose. For example, microalgae such as *Chlorella* species possess a robust cell wall approximately 88 nm in thickness [81]. Consequently, the extraction of active components, such as lipids, from cells requires long processing times, hydrophobic extraction solvents, and energy-intensive mechanical disruption methods [82]. Because phospholipids in cell membranes are amphiphilic molecules, they require a mixture of polar and non-polar organic solvents for extraction. Liquid DME is well-known for extracting neutral and complex lipids from dairy products [83]. Liquid DME is used to extract compounds from various wet and dry biomasses containing lipid-rich compounds without cell disruption [84][85][86][87][88] (**Figure 2**).

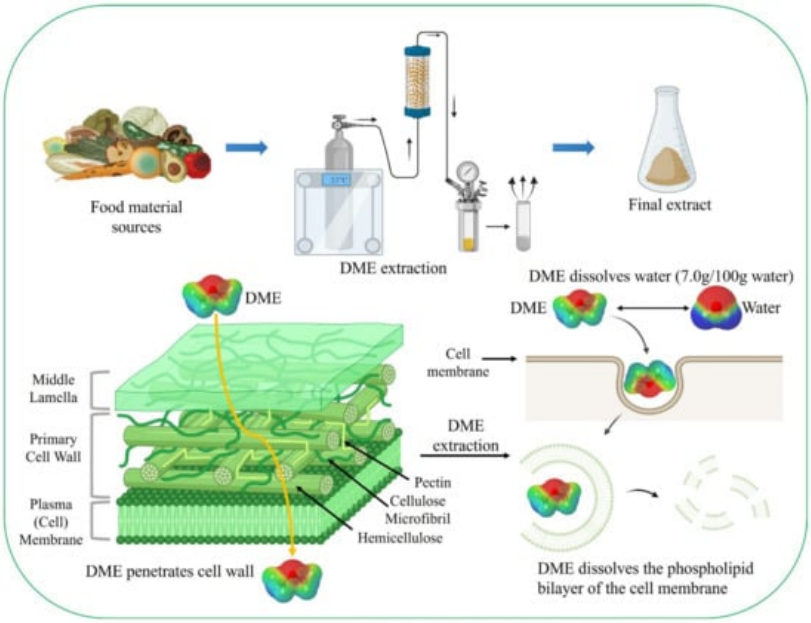

Figure 2. Extraction process using liquefied DME; liquefied DME dissolves the phospholipid bilayer of the cell membrane and water.

3.3. Safety of Liquefied DME as an Extraction Solvent

DME, a recognized organic solvent with a low boiling point that is safe for human use, has significant potential for the extraction of various active ingredients. It has been approved for use as an extraction solvent in the food industries of the United States, Europe, and other regions. The European Food Safety Authority (EFSA), in its assessment of the safety of DME as an extraction solvent for the removal of fats from animal protein sources, stated that residual levels of up to 9 µg/kg in extracted animal protein do not pose a significant safety concern [89]. Food Standards Australia New Zealand (FSANZ) approved the use of DME as an extraction solvent processing aid for all dairy ingredients and products [90].

In experiments with rats exposed to DME, DME residues in the bodies of the rats were in the range of 14–19 ppm when the airborne concentration of DME reached 1000 ppm. These concentrations were equivalent to 1/61 of the airborne concentrations accumulated in the body. After inhalation for 60 min, the rats' various organs showed DME concentrations that decreased to less than 4 ppm within 90 min [91][92].

3.4. Environmental Issues Caused by Liquefied DME Extraction

The synthesis of DME from renewable sources, utilizing biomass-derived CO_2 and hydrogen generated via water electrolysis (powered by solar or wind energy), enables the production of DME from renewable feedstocks [93]. The lack of explosive peroxide formation in DME allows safe storage [94]. As it does not form peroxide aerosols, DME has attracted considerable attention as a propellant for household hairsprays [95]. Generally considered biodegradable, nontoxic, non-carcinogenic, and non-corrosive, DME has proven to be ideal for various everyday applications such as personal care products (hairsprays, shaving creams, foams, and antiperspirants), household products, paints, coatings, food, insect repellents, and animal products [96][97]. DME then undergoes photochemical reactions with OH radicals to produce CO_2 and H_2O [98]. Experimental modeling under ultraviolet radiation indicates that DME has a degradation half-life of 3–30 h, reaching approximately 100–150 h in the upper atmospheric regions up to an altitude of approximately 10 km. Although freon compounds may take several years or decades to degrade, DME degradation occurs in approximately 0.014 years (5.1 days) [98].

DME has similar physical properties to LPG and has been developed as a synthetic fuel. In China, it is used commercially as a substitute for LPG in city gas, often blended with 20% propane for consumer use [99]. It is also used as a fuel in automotive and industrial applications. However, pure DME has an explosive range of 3.427 vol% in air, which is a significant safety concern when used as an extraction solvent [99]. To address this issue, the blending of DME with CO_2 has been investigated. When the mole fraction of CO_2 exceeds 0.882, the mixture falls out of the explosive range and becomes non-flammable [99].

3.5. Liquefied DME Extraction

Figure 3 shows a schematic of a laboratory-scale liquefied DME extraction system [100]. This DME extraction system consists of a series of connections, including a metal tank containing liquefied DME (500 mL capacity), an extraction

column (10–100 mL capacity), and an extraction solution collection tank (96 mL capacity).

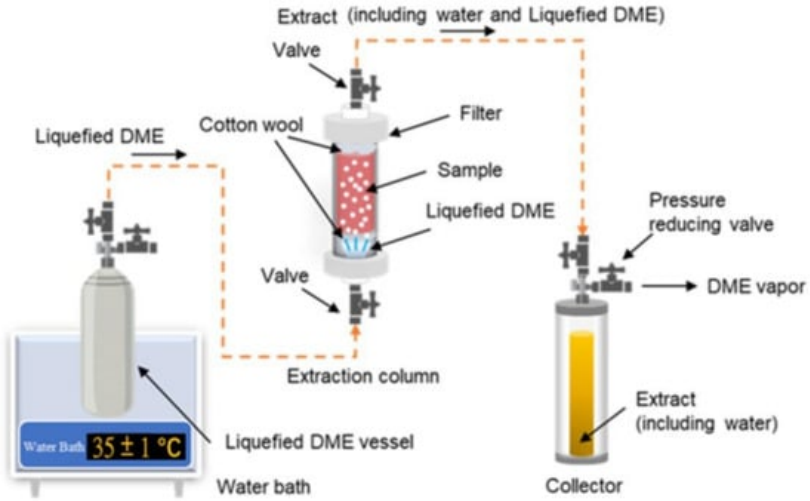

Figure 3. Schematic of a laboratory-scale extraction system using liquefied DME.

Kanda et al. pioneered the design and development of the first DME ambient-temperature drying and purification process prototype [101]. Using this prototype, ambient temperature dewatering and deodorization of high-moisture coal and sewage sludge were achieved [101]. Kanda et al. (2019) developed the largest microalgal oil extraction apparatus in the world (**Figure 4**a). This apparatus successfully extracts oil from high-moisture microalgae without drying [102]. In addition, they were able to limit CO_2 emissions during the extraction process to a level determined by the CO_2 captured from the oil. A centrifugal separator was used to recover microalgae from a 300-ton raceway cultivation tank at 1500–2100 G and at a processing rate of 3–7 tons per hour (**Figure 4**b).

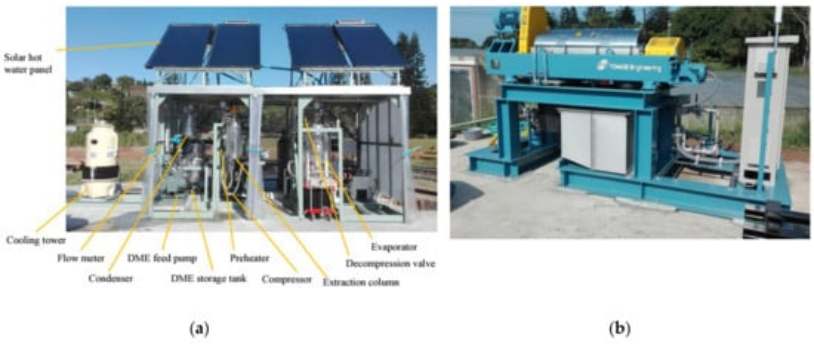

Figure 4. (**a**) Experimental setup of a microalgae oil extraction system using liquefied DME; (**b**) A microalgae recovery system [102].

4. Applications of Liquefied DME Extraction

4.1. Lipid Extraction from Microalgae

Microalgal biomass is a rich source of various nutrients, including fatty acids, carotenoids, proteins, minerals, and other essential nutrients that can be used as functional food ingredients [102][103][104][105][106][107][108][109][110]. Many species of microalgae grow well in saline water, such as seawater, thus avoiding the need for limited freshwater resources [111]. Some oleaginous species of microalgae overproduce lipids and fatty acids by modifying the physical and chemical properties of the culture medium [112]. The lipid content of some microalgae may reach 77%, exceeding the index of higher plants (such as soybeans) [113]. The protein content of *Arthrospira maxima* has been found to reach 71% [114].

Microalgal oils have recently been used as alternatives to fish and vegetable oils with low nutritional values [115]. Microalgal oils contain highly utilizable and nontoxic fatty acids, such as polyunsaturated fatty acids (PUFA), arachidonic acid (ARA), c-linolenic acid (GLA), eicosapentaenoic acid, and docosahexaenoic acid (DHA) [116]. Long-chain polyunsaturated fatty acids such as eicosapentaenoic acid (ω-3 C20:5) and DHA (ω-3 C22:6) obtained from microalgae are essential for humans due to their beneficial effects on health, including neurodevelopment and the prevention of chronic diseases [117].

4.2. Extraction of Functional Components from Natural Resources

In addition to lipids, liquefied DME has been used to extract bioactive compounds from various sources, including spices, green tea, algae, fruits, vegetables, grains, natural plants, and fish. In 2003, Catchpole et al. used liquefied DME to extract specific pungent compounds from ginger, black pepper, and chili powder [118]. Despite the significant extraction of water, liquefied DME showed similar efficacy as $scCO_2$ in isolating pungent compounds from spices. Complete extraction was achieved with minimal solvent consumption. At temperatures of 35, 40, 50, and 60 °C, liquefied DME showed nearly equivalent extraction rates. Subsequently, subcritical propane was suggested as a cost-effective alternative to CO_2 because of its lower operating pressure and reduced energy consumption during spice extraction, similar to liquefied DME. However, subcritical propane is the least effective at dissolving pungent components and is unsuitable for carotenoid extraction [118][119].

Liquefied DME has been previously used to decaffeinate green tea [120]. The main functional components of green tea are caffeine and catechins [121]. Excessive caffeine consumption can lead to health problems, such as dizziness, increased heart rate, tremors, and insomnia, owing to overstimulation of the central nervous system [122]. Liquefied DME enables catechin extraction while completely removing caffeine. Ciulla et al. also demonstrated higher extraction rates of caffeine from coffee beans and powder using liquefied DME rather than using $scCO_2$-based extraction methods [123].

Natural carotenoids exhibit several beneficial effects, including antioxidant, anti-inflammatory, antiproliferative, and antiapoptotic properties [124]. As antioxidants, carotenoids detoxify intracellular free radicals, thereby reducing the incidence of oxidative damage and associated diseases [125]. Carotenoids, which are widely distributed in nature, are biosynthesized by various organisms, including photosynthetic organisms such as algae, plants, fungi, and bacteria [125].

Using an enzyme-assisted DME and ethanol co-solvent extraction method, Billakanti et al. were able to extract almost all lipids, including polyunsaturated fatty acids and fucoxanthin, from the wet, brown seaweed *Undaria pinnatifida* [126]. *Undaria pinnatifida* contains a mixture of sulfated and branched chain polysaccharides that are tightly bound to the cell wall [127]. Therefore, extracting bioactive compounds from brown seaweed biomass is difficult because the cell wall is a major obstacle [128].

Microalgae have attracted widespread attention as natural sources of carotenoids because they grow faster than other higher plants. The Liquefied DME extraction method successfully extracted 7.70 mg/g of astaxanthin, a carotenoid, and 30.0% of its dry weight of lipids from microalgae (*Haematococcus pluvialis*) [129]. The extraction rate of astaxanthin was 1.82% lower than that achieved through acetone extraction using drying and cell disruption. Liquefied DME extraction removed 92% of the water from the microalgae and increased the carbon and hydrogen contents. Babadi et al. reported the extraction of total carotenoids (4.14 mg/g algal dry weight) and total chlorophyll (8.45 mg/g algal dry weight) from the microalgae *Chlorococcum humicola* using liquefied DME [130].

5. Theoretical Study of Liquefied DME

The use of Hansen solubility parameters (HSP) to evaluate the solubility of various analytes of natural origin has increased [131]. HSP is used to quantify molecular interactions and solubility [132][133].

HSP is based on three interaction forces: dispersion, dipole, and hydrogen bonding forces. The dispersion force (δd) indicates random interactions between molecules and represents the non-polar nature of the molecules. The dipole force (δp) indicates polar interactions between molecules and represents the polar nature of the molecule. The hydrogen bonding force (δh) represents hydrogen bonding interactions between molecules and their hydrogen bonding abilities [134]. These interaction forces can be summed to obtain the HSP. The solubility of a substance in a solvent is higher when its HSP is similar to that of the solvent.

HSPs are typically estimated using experimental data or molecular modeling techniques [135][136]. The HSP distance between two substances is expressed by the following equation [137]:

$$\mathrm{R_a} = \sqrt{4(\Delta\delta\mathrm{d})^2 + (\Delta\delta\mathrm{p})^2 + (\Delta\delta\mathrm{h})^2}. \quad (1)$$

The difference in the HSP R_a [$MPa^{1/2}$] can be obtained by taking the sum of the squares of the differences between the three parameters and determining their square roots [135]. The smaller the difference, the more similar the interactions between the substances and the higher the solubility and compatibility.

Based on the experimental data on solute–solvent interactions, plotting the solubility parameters of good and poor solvents for a solute in a three-dimensional diagram produces a Hansen solubility sphere, with regions of good solvents clustered together [131]. The spherical region indicates the extent to which the substance interacts with the solvent. The radius of the sphere represents the interaction radius R_0 [$MPa^{1/2}$]. The ratio of R_a to R_0 is the relative energy difference (RED), which can be calculated using Equation (2). Here, RED ≤ 1 indicates a good solvent and RED > 1 indicates a poor solvent. RED can be used as an indicator of solubility [131].

$$\mathrm{RED} = \frac{\mathrm{R_a}}{\mathrm{R_0}} \quad (2)$$

6. Bioactive Extraction to Biomedical Advances

Tuna are one of the most important marine fish species worldwide [138]. Tuna giblets are rich in bioactive compounds such as unsaturated fatty acids, vitamins, and proteins. These compounds have antioxidant properties and can be converted into value-added products [139]. However, the internal organs, particularly the livers, of tuna are difficult to process and are often discarded [140].

Fang et al. reported that liquefied DME can be used to extract lipids and vitamins from tuna liver [141]. Compared to the conventional $scCO_2$ method, liquefied DME extraction can prevent lipid oxidation and effectively reduce damage to omega-3 polyunsaturated fatty acids (n-3 PUFAs) and vitamins, thereby obtaining high-quality liver oil with excellent yield. The pressure used in liquefied DME extraction is much lower (0.8 MPa) than that used in $scCO_2$ extraction (35 MPa), and no freeze-drying pretreatment is required.

Lipids, water, and vitamins can be extracted from tuna liver using liquefied DME to precipitate high-quality proteins. Currently, pH shifts, including alkaline or acidic extraction, isoelectric precipitation, centrifugation, and lyophilization, are the best processing methods for obtaining proteins from tuna liver [142]. However, this method is complex and time-consuming, and the lyophilization process is time- and energy-intensive [143].

Kanda et al. crystallized glycine from an aqueous solution using liquefied DME as an antisolvent [144]. Liquefied DME can be operated at 20–25 °C, potentially reducing the energy consumption of drying or crystallization with ethanol. Kanda et al. also prepared liposomes by dissolving soy lecithin and cholesterol in liquefied DME and infusing them into warm water [145]. Transmission electron microscopy, dynamic light scattering for particle size distribution measurements, and zeta potential measurements revealed that the resulting liposomes ranged in size from approximately 60 to 300 nm, with a zeta potential of approximately −57 mV. This indicates that the liquefied DME injection method successfully produces liposomes similar to those produced using conventional diethyl ether at temperatures above 45 °C. The liquefied DME method does not require the residue of conventional diethyl ether in the final product of liposomes or the high-temperature and high-pressure conditions of $scCO_2$.

Organ transplantation is a treatment option for patients with severe organ failure. During organ transplantation, cells derived from the patient are grown on a three-dimensional scaffold to create an organ that will not be rejected. When porcine tissue is decellularized to create a scaffold, the porcine aorta is similar in structure to the human aorta, making it suitable for transplantation into humans [146]. The decellularization of tissues from different species involves three steps: extraction of lipids using sodium dodecyl sulfate (SDS), DNA fragmentation using DNase, and the removal of DNA fragments via washing with water and ethanol [147]. However, long processing times, inflammation caused by SDS at the contact site, and difficulty in completely removing the toxic surfactant from the tissue may cause certain problems. Liquefied DME was used to extract lipids, DNA, and cell nuclei from ostrich carotid tissue and porcine aorta [147][148][149][150]. Demonstrating that ostrich carotid tissue can be used as an alternative to porcine scaffolds, researchers can decellularize the porcine aorta after lipid extraction using DME, followed by DNase treatment and washing for at least five days. Furthermore, the introduction of liquefied DME into conventional decellularization eliminates the need for surfactants.

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