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An Overview of Recent Developments in Safron Nanoemulsion Encapsulation

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ABSTRACT

Saffron is a costly, bulbous, stemless herb whose various bioactive constituents, including crocins, crocetin, safranal, picrocrocin, and essential oils, have excellent nutritional and therapeutic characteristics. Saffron nanoencapsulation is a feasible technique for improving the bioactivity and bioavailability of its bioactive components and their storage stability. Owing to its antibacterial properties, saffron can be put into various food products to extend their shelf life. The recent publications revealed a unique nanoemulsion formulation of saffron extract and a preparation method using a high-speed homogenizer followed by ultrasonication. This technology offers new prospects for the food and pharmaceutical industry to preserve saffron's color, flavor, aroma, and medicinal ingredients in environmental and gastrointestinal conditions. Additional research and collaboration between research laboratories and the industry are needed. This literature review examined recent investigations on the manufacturing and application of saffron nanoemulsions. This research discusses the application of the ultrasonic nanoemulsification technique for saffron extraction, nanoencapsulation, and the possible antibacterial characteristics of saffron.

Keywords: Nanoemulsions; *Crocus Sativus*; Extraction; Encapsulation; Antimicrobial

Introduction

Structures between 1 to 100 nanometers (nm) in size are the focus of current nanotechnology study, development, and management [1]. Many macroscale features of food could be modified by applying nanotechnology in the food industry, including texture, flavor, other sensory attributes, coloring strength, processability, shelf-life stability, and variety [2]. Functional chemicals can also have their water solubility, thermal stability, and oral bioavailability enhanced via nanotechnology. It can be utilized in food manufacturing, processing, packaging, storage, and flavor and color enhancement. Nanoparticles boost the surface-to-volume ratio, hence enhancing the physical qualities of food. In this context, using nanoemulsions as carriers for lipophilic substances demonstrates the enormous potential of nanotechnology in the food business [3-6]. A nanoemulsion is a colloidal dispersion structure that consists of two immiscible liquids and an emulsifying agent (surfactant) to create a stable, thermodynamically stable colloidal system. Emulsifiers stabilize the interface of O/W nanoemulsions. The dispersed phase is also called the internal or discontinuous phase, while the outer phase is the dispersion medium, external phase, or continuous phase. The oil phase can load numerous lipophilic bioactive substances, including essential oils, lipo-soluble vitamins, and various lipophilic nutraceuticals [7,8]. In the food sector, vegetable oils (such as soybean, castor, sesame, coconut, sunflower, olive, and corn) are frequently used to create O/W nanoemulsions.

Emulsifiers are amphiphilic compounds added to emulsions to stabilize their kinetic stability by decreasing the interfacial tension between the two phases. The type of emulsifier utilized significantly affects the physical stability of nanoemulsions. The emulsifier may be ionic (anionic or cationic), nonionic, or zwitterionic. Most emulsifiers in food applications include phospholipids, proteins, and polysaccharides [9,10]. The spherical structures of oil/water nanoemulsions consist of an amphiphilic layer comprised of surface-active chemicals and a lipophilic core. Nanoemulsions are transparent, thermodynamically unstable, but kinetically stable, unlike turbid emulsions. Moreover, they resist gravitational separation and droplet aggregation. Hence, their potential for encapsulating lipophilic nutritional molecules in delivery systems is high. Nanoemulsions encapsulate four elementary classes of beneficial compounds: fatty acids, carotenoids, antioxidants, and phytosterols [11,12]. Two nanoemulsion fabrication processes exist in high-energy and low-energy techniques [13-15]. In high-energy techniques, the nanoemulsion droplet size is determined by two opposing forces, the droplet disruption force and the droplet coalescence force [16]. Only powerful mechanical devices, such as high-pressure valve homogenizers, ultrasonicators, and microfluidizers, can generate intense, disruptive forces and produce minute oil droplets in the aqueous phase [13]. Homogenizers with high-pressure valves can be used to make nanoemulsions with a diameter of 1 nm.

In these devices, the mixture of oil and water phases passes through a valve at a pressure ranging from 500 to 5000 psi, forming minute emulsion droplets [11]. The smaller the particles formed, the higher the pressure, the lower the interfacial tension, and the faster the material absorption. This approach is highly effective but energy-intensive and exothermic [17]. In ultrasonication, the mixture of aqueous and oil phases is subjected to high-frequency sound waves (greater than 20 kHz) to change big droplets into nanoemulsions [16]. In this approach, the droplet size is determined by the input energy, sonication period, emulsifier concentration, viscosity ratio of phases, and amplitude of the waves [18]. The smaller the diameter of the nanoemulsions produced, the higher the frequency, so that if frequencies in the MHz range are employed, the emulsifier is no longer required [16]. The notable aspect of the ultrasonication technique is that the nanoemulsions created by this technique can enhance the antibacterial capabilities of the packaging material. (Hashemi Gahruie, et al. [19]) investigated the bioactivity of Zataria multiflora essential oil nanoemulsions integrated into a basil seed gum-based film network. This study revealed that the antibacterial capabilities of nanoemulsion droplets generated by ultrasonic emulsification increase as their size decreases. Within the microfluidizer devices, the mixture of oil and water is pushed to flow through an interaction chamber at 500-20,000 psi of pressure. In the microfluidization technique, even if the temperature rises owing to high pressure, the size distribution of the particles produced is uniform [20].

Using the physicochemical features of emulsion components while applying a modest amount of energy is the fundamental premise of energy-efficient low-cost techniques. For the creation of nanoemulsions, numerous low-energy techniques, such as spontaneous emulsification, phase inversion temperature, phase inversion composition, membrane emulsification, solvent displacement, and emulsion inversion point method, are applied [21]. In the spontaneous approach, the physicochemical properties of the constituent chemicals are the primary factor in the creation of nanoemulsions. In fact, at a given temperature, the oil phase, the aqueous phase, and the emulsifier are combined gently, resulting in the spontaneous creation of nanoemulsion droplets [22]. Compared to high-energy approaches, the intuitive method has the disadvantage that the droplet size cannot be controlled. To stabilize nanoemulsions, however, substantial volumes of synthetic surfactants are necessary [23]. However, the ease and effectiveness of this technique have led to its widespread application in nanoemulsions containing fat-soluble vitamins and fish oils [13]. Phase inversion temperature and phase inversion composition are two ways to transform a W/O emulsion into an O/W emulsion by modifying the system's temperature and composition, respectively [17]. In the membrane emulsification method, an emulsifying device consisting of a specialized membrane with a particular hydrophobic property is utilized. The dispersed phase must flow through the membrane's pores into the immiscible continuous phase [24].

In the solvent displacement technique, which can be carried out spontaneously at room temperature, the oil phase is mixed with the water-miscible organic solvent before diffusing into the aqueous phase. The organic solvent is eliminated after nanoemulsion production [11]. When an emulsion of water/oil with a high oil-to-water ratio is converted into an emulsion of oil/water by reaching the catastrophic phase inversion point, the emulsion inversion point method can be applied [17]. Unique physicochemical properties of various nanoemulsions attract interest for use in the food industry. In the beverage industry, the optical properties of nanoemulsions, which depend on particle composition, concentration, size, and distribution, are crucial. Nanoemulsions have rheological properties and can enhance the texture of various foods. Over time, nanoemulsions experience physical and chemical instability due to gravitational separation, droplet aggregation, and Ostwald ripening, respectively. However, their smaller particle size makes them more resistant to aggregation and creaming than conventional emulsions [25]. There are numerous applications for nanoemulsions in the food industry. These include enhancing chemical stability, bioavailability, antimicrobial function, texture modification, flavor enhancement, nutrient enrichment, and colorant function. Due to their structural aldehydic, ketonic, or ester bonds, flavors and colorants are susceptible to oxidation; therefore, nanoemulsions are suitable carriers. Using nanoemulsions to encapsulate flavors and colorants improves their stability and shelf life [26].

Saffron (*Crocus sativus* L.) is a bioactive compound-rich herb used as a flavoring and coloring agent [27]. Additionally, saffron has pharmaceutical effects and functions as an anticancer, anti-inflammatory, and antidepressant agent [28]. When the bioactive compounds of saffron are adequately processed and delivered to the body while retaining their biological properties, they can serve a beneficial function. Various techniques, including microencapsulation and nanoencapsulation, have been used thus far to preserve the bioactive components of saffron. In recent years, nanoencapsulation has been regarded as a promising method for encapsulating bioactive saffron compounds by surrounding them with preservative materials. This article provides detailed information on the recent developments in saffron encapsulation techniques, emphasizing nanoemulsions.

Saffron (*Crocus Sativus* L.)

Saffron is a bulbous, stemless herb primarily cultivated in Iran, India, and Greece, with a worldwide production of 430, 22, and 7 tons in 2021 [29]. During drying, more than 80% of the saffron's moisture is removed, leaving a residual moisture content of only 7 to 10% (w/w) [30]. Saffron is a spice that possesses potent medicinal properties. In traditional Chinese medicine, saffron has been used as an antispasmodic, sedative, menstrual regulator, and abortifacient. This spice has therapeutic effects on the central and peripheral nervous systems (Figure 1). A study by (Ghaffari, et al. [31]) showed that saffron extract could reduce oxidative stress in the hippocampus and improve learning and memory impairment in an animal model of multiple sclerosis. Saffron contains several bioactive compounds, such as flavonoids, anthocyanins, and carotenoids [32]. Four major carotenoids, crocins, crocetin, picrocrocin, and safranal, have been identified in the chemical analysis of saffron's composition: crocins, crocetin, picrocrocin, and safranal (Figure 2). The plant's stigma contains a higher concentration of these four critical carotenoids responsible for saffron's color, aroma, and flavor [33]. Crocin is a hydrosoluble molecule with a negative partition coefficient value (log Poctanol/water = -2.5) [34] and characterized by its plasma half-life from 1.7 h to 2.4 h at 30°C [35]. It exhibits therapeutic properties against neurodegenerative diseases like Alzheimer's [36]. In a study by Ahmad and coworkers on hemiparkinsonian male Wistar rats, pre-treatment with crocetin (25, 50, and 75 µg/kg body weight) for seven days helped prevent Parkinsonism [37].

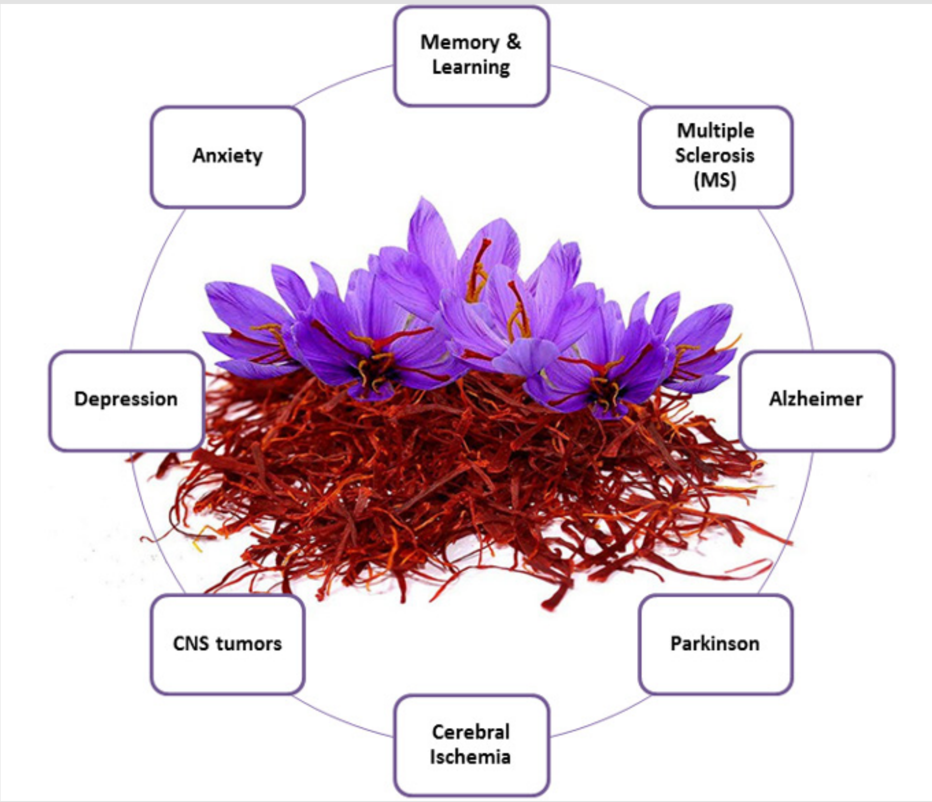

Figure 1: The saffron ′s pharmacological effects extend to the central and peripheral nervous systems.

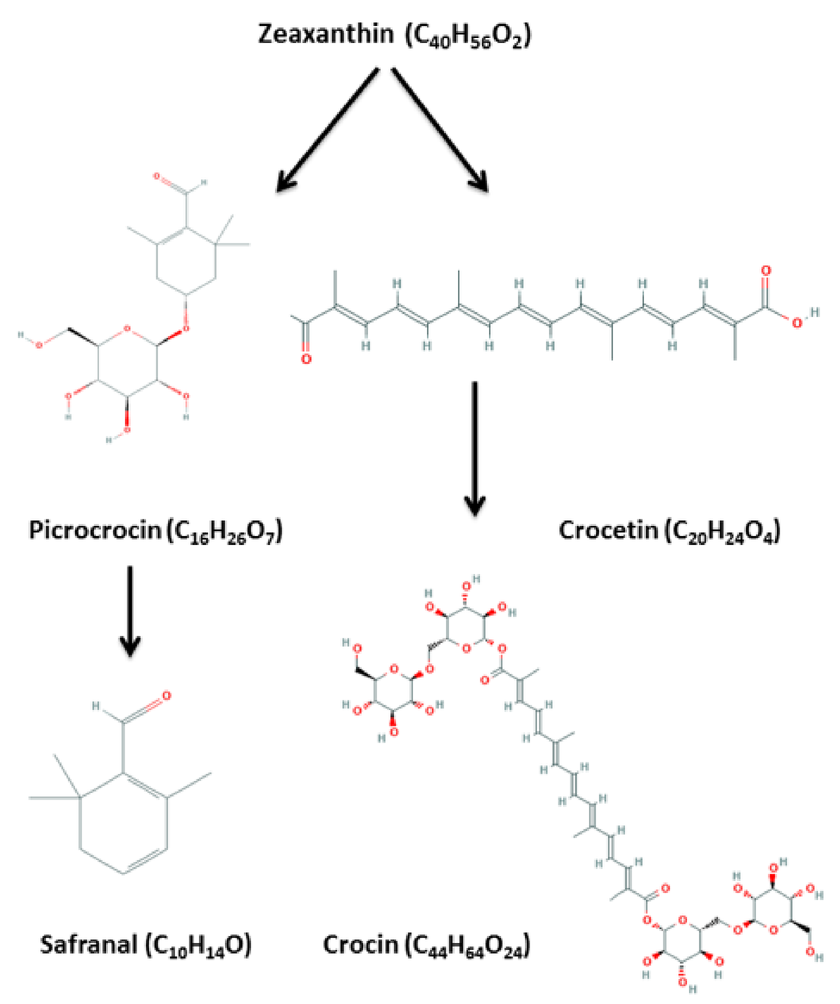

Figure 2: The chemical structure of the principal bioactive components of saffron. The bio-oxidative cleavage of zeaxanthin produces several chemicals.

The crocin in saffron may also be effective in preventing cerebral ischemia. Crocin can potentially protect a rat model of stroke against ischemia and cerebral edema, according to research by (Vakili, et al. [38]). Crocin's antioxidant property is even more significant than other well-studied natural antioxidants such as beta-carotene and lycopene [39]. The half maximal inhibitory concentration of crocin in the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radical scavenging assay is approximately 500 ppm in methanolic solution [40]. Crocetin is a pigment component found in dried saffron stigmas. It is a molecule with a positive partition coefficient that is highly liposoluble (log Poctanol/water = 4.72) [41] and characterized by its plasma half-life from 6.1 to 7.5 h at 30°C [32]. Numerous foods use crocetin's yellow hue as a natural coloring agent. Animal studies have demonstrated that crocetin has multiple pharmacological properties, including antioxidant activity [42], anti-inflammatory [43], anti-atherosclerotic [44], insulin resistance improvement and neuroprotection [45]. Trans-sodium crocetinate (TSC) has also been used in clinical trial studies involving cancer patients with resistant solid tumors, with encouraging results [46]. Picrocrocin imparts saffron's bitter flavor and has anticancer properties [47]. The molecule is slightly hydrosoluble and has a negative partition coefficient value (log Poctanol/water = -0.24) [48] and characterized by its plasma half-life of 174 h at 30°C [49].

Liposoluble safranal derived from picrocrocin with a positive partition coefficient (log Poctanol/water = 2.90) [50] and characterized by its plasma half-life from 1.2 to 2 h at 30°C [51]. It is responsible for the aroma of saffron and has antidepressant properties [52]. Also frequently reported are saffron's positive effects on depression treatment and anxiety reduction [53-55]. A recent meta-analysis study revealed that the effect of saffron on severe depression was significantly greater than placebo [56]. Clinical trials have indicated that saffron's effect on depression and anxiety is comparable to commercial antidepressants [57]. It can be concluded that saffron is primarily used as a food ingredient, but its constituents have pharmaceutical applications in treating various illnesses.

Emulsion Liquid Membrane for Extraction of Saffron Bioactive Compounds

In biomedical sciences, the emulsion liquid membrane (ELM), also known as artificial kidneys, is one of the most efficient methods for extracting metal ions, organic acids, and biochemical compounds. This method has many applications in the pharmaceutical, medical, and food industries. The ELM method utilizes double emulsions ($W_1/O/W_2$), which consist of an organic liquid (oil phase) placed between two aqueous phases. The inner aqueous phase (stripping phase W_1) comprises the extractable, while the outer aqueous phase (feed phase W_2) is the carrier phase enriched with the target compounds (Figure 3). The concentration gradient causes the transfer of target molecules from the outer aqueous phase to the inner phase through the membrane [58]. A successful ELM extraction is dependent on many variables, including organic phase composition, surfactant composition, external phase polarity, external feed phase pH, internal phase composition, treat ratio, phase ratio, emulsification speed, stirring speed, emulsification time, and temperature [59,58]. ELM requires four steps to extract saffron bioactives:

1. Preparation of water in oil emulsion (W_1/O),
2. Stirring of the W_1/O emulsion on the feed phase (aqueous saffron extract),
3. Separation of the external feed phase, and
4. Demulsification of W_1/O in order to obtain the enriched saffron bioactive extract.

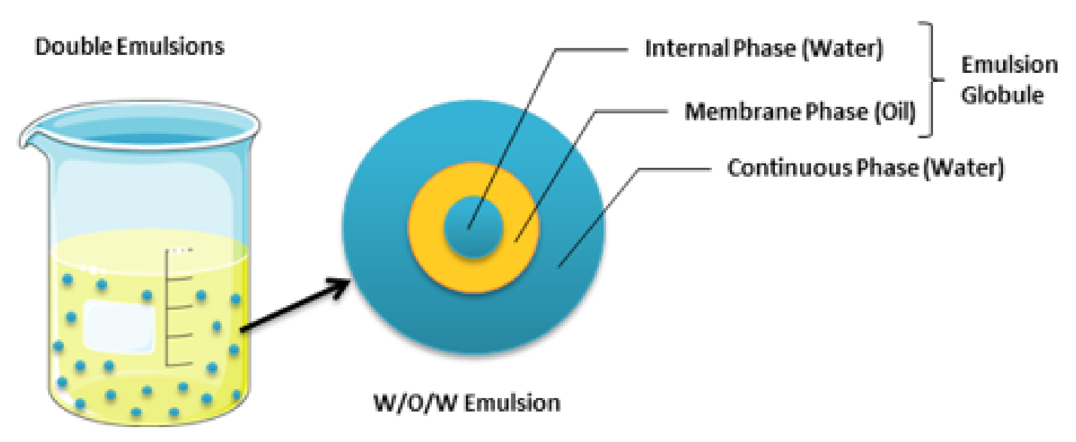

Figure 3: Diagram illustrating the creation of double emulsions. During the extraction procedure, the saffron extract resides in the continuous phase before being transported to the internal phase. Saffron extract is inserted in the internal phase and preserved by the membrane and continuous phases during encapsulation.

Bioactive compounds are transferred from the feed phase to the stripping phase during the most crucial extraction phase, the second step. Mokhtari, Pourabdollah [30] used the ELM method to extract saffron bioactive compounds. This study demonstrated that an ELM system containing Span 80 (2.5 wt%) as a surfactant, n-Decane as a membrane, a phase ratio of 0.8 (4:5), and a treat ratio of 0.3 at a stirring rate of 300 rpm could collect more than 90% of saffron bioactives in the inner aqueous phase of the designed ELM system. The phase ratio is the volume of the internal phase to the volume of the membrane, and the treat ratio is the volume of the emulsion phase to the volume of the external phase, according to this study [30]. The diameter of the emulsion is a crucial parameter for efficient extraction. The more stable emulsions are, the smaller their particle size. However, the size reduction of the emulsion makes demulsification challenging to perform. Therefore, preparing the ELM system and concentrating on various components is crucial for efficient extraction.

Nanoencapsulation of Bioactive Compounds from Saffron

Nanoencapsulation is a method for efficiently transporting bioactive compounds in nanoscale capsules to the desired target. The primary objective of nanoencapsulation is to protect bioactive substances from unfavorable environmental stress and deliver them in a controlled manner to the desired target organs. Nanoencapsulation, which produces particles of 100 nm, has additional advantages; it enhances bioavailability and protects the particles from enzymatic breakdown [60]. The nanoencapsulation structure consists of a core surrounded by a wall. Droplets can be structured as

1. Single-Core,
2. Multi-Core,
3. Single-Wall,
4. Multi-wall.

Core substances susceptible to nanoencapsulation include phenolic compounds, carotenoids, essential fatty acids, vitamins, peptides, and enzymes. As wall materials for encapsulating bioactive compounds, carbohydrates (e.g., chitosan, pectin, cellulose derivatives, modified starches), proteins (e.g., whey protein, soy proteins, gelatin, caseins), fat and waxes (e.g., hydrogenated vegetable oils, lecithin, bee wax), and polymers (e.g., polyethylene glycol, polyanhydrides, polyvinyl alcohol) are good candidates [61]. Numerous techniques for the nanoencapsulation of bioactive compounds have been developed.

1. Lipid-formulation-based techniques,
2. Natural nanocarrier-based techniques,
3. Specialized equipment-based techniques,
4. Biopolymer nanoparticle-based techniques, and
5. Other nanoencapsulation technologies [62].

Most bioactive components and nutraceuticals have a hydrophobic lipid structure, so the first category is widely used in the pharmaceutical and food industries. The subgroups of lipid-formulation-based techniques are as follows:

1. Nanoliposomes,
2. Solid lipid nanoparticles,
3. Nanostructured lipid carriers, and
4. Nano emulsions [62].

Liposomes composed of at least one lipid bilayer, particularly phospholipids, contain an aqueous core suitable for encapsulating hydrophilic substances. Liposomes composed of at least one lipid bilayer, particularly phospholipids, contain an aqueous core suitable for encapsulating hydrophilic substances [63]. Nanoliposomes have a size from 50 to 150 nm. They can be used as a spherical vesicle for delivering hydrophilic nutraceuticals and pharmaceuticals [64]. Solid lipid nanoparticles are lipid droplets that have been crystallized and loaded with lipophilic bioactive components in their lipid matrix. They are a novel delivery system predominantly employed in pharmaceutical applications [65]. Nanostructured lipid carriers are unstructured-matrix droplets composed of solid and liquid lipids. Since the inner phase of these nanocarriers is composed of liquid lipids, they have a higher encapsulation efficiency than solid lipid nanoparticles [66]. Nanoemulsions are one of the best vehicles for encapsulation, which will be discussed in greater depth in the following section.

Nanoemulsion as a Carrier for the Bioactive Compounds of Saffron

Low bioavailability and low chemical stability are the most significant obstacles to using saffron bioactive compounds [67]. Low water solubility, rapid degradation, and volatility are additional constraints on incorporating saffron bioactive compounds into food products [13]. Consequently, applying saffron bioactive compounds by nanoemulsion systems can circumvent these limitations and provide the necessary physicochemical conditions during processing and storage. Numerous studies have been conducted on the nanoemulsification of bioactive plant extracts. In a study, (Yang, et al. [68]) reported that citral, a significant component in lemongrass oil, became more stable using O/W nanoemulsions. The positive effect of ubiquinol-10 ($Q_{10}H_2$) addition to O/W nanoemulsion loaded with citral has also been reported [69]. Another study demonstrated that a beta-carotene nanoemulsion (a natural vitamin A precursor with antioxidant properties) in the aqueous inner phase increases beta-carotene stability. In this study, Tan, Nakajima [70] suggested that the nature of the emulsifier could improve the chemical stability of beta-carotene-loaded nanoemulsions. This study introduced polyglycerol esters of fatty acids (PGEs) as a nonionic emulsifier to improve beta-carotene's physicochemical properties and stability [71]. According to Wei, Gao [72], the best physicochemical properties for beta-carotene nanoemulsions were obtained when sodium caseinate-chitosan-epigallocatechin-3-gallate conjugates emulsifiers were applied. In a separate study, tea polyphenol nanoemulsion was utilized to enhance the bioavailability of beta-carotene [73].

In this study, the oily phase of the nanoemulsion contained beta-carotene, while the water phase contained tea polyphenols. This nanoemulsion's stability, retention rate, and adsorption were superior to beta-carotene nanoemulsion in both *in vitro* and *in vivo* studies [73]. The dairy industry has created nanoemulsions of vitamin D (cholecalciferol). (Golfomitsou et al. [74]) studied edible O/W emulsions as nanocarriers for vitamin D to fortify dairy emulsions. The emulsifiers and oil phase compositions consisted of polysorbate 20, soybean lecithin and their respective combinations, and soybean oil or mixtures of the oil with cocoa butter, respectively. Vitamin D (0.1-0.5g/mL) encapsulated in the oil core of nanocarriers (with mean diameters 1 nm) was added to whole-fat milk and was stable for at least ten days [74]. According to (Cheong, et al. [75]) kenaf seed O/W nanoemulsions containing sodium caseinate, beta-cyclodextrin, and Tween 20 encapsulating vitamin E and phytosterols can preserve the bioactive components' stability and antioxidant activity for up to 8 weeks at 4°C [75]. Many studies have examined nanoemulsification strategies to retain various bioactive functional chemicals and their bioavailability, a few of which have been cited (Table 1). Considering the benefits of saffron, there are few published research papers on the encapsulation of saffron. The research on this topic is examined and summarized in the next section.

Table 1: Summary of studies used nano emulsions for nanoencapsulation of plant bioactive compounds.

Bioactive compounds	Wall material	Oil phase	Processing Technique	Effect	Reference
Citral	Soy lecithin	Medium-chain triacylglycerol/undecane/$Q_{10}H_2$	High pressure homogenizer	With appropriate concentrations of $Q_{10}H_2$, major citral oxidation compounds can be inhibited to lower levels.	[69]
Citral	Gelatin/Tween 20	Medium chain triacylglycerl/ undecane	High pressure homogenizer	The mixture of gelatin and Tween 20 can enhance the citral nanoemulsions stability under acidic conditions.	[90]
β-Carotene	Starch	Medium chain triacylglycerl	High pressure homogenizer	Modified starches with lower film oxygen permeability have a higher retention of beta-carotene during storage.	[91]
β-Carotene	Starch caseinate/ chitosan-epigallocatechin-3-gallate	Sunflower oil	High pressure homogenizer	The produced bilayer nanoemulsions had better chemical stability, and dense and thick bilayer structure.	[92]
β-Carotene	Casein	Vegetable oil	Ultrasonication and Microfluidization	Sonication-assisted dissolving methods together with freeze drying are effective to prepare β-carotene-enriched functional foods and dietary supplements.	[93]
Carotenoids extracted	Gelatin/ whey protein isolate	Soybean oil	High pressure homogenizer	Gelatin can increase water solubility of nanoemulsions of melon carotenoids extract	[94]
Safranal	Tween 80	Glyceryl monostearate	Ultrasonication or high-pressure homogenization	Mean particle size for all formulas was approximately 106 nm by probe sonication and 233 nm using HPH method.	(Franklyn, et al. (2000))
Saffron extract	whey protein concentrat and polysaccharide (pectin) and maltodextrin	Sunflower oil	Homogenization and spray drying	Encapsulated double-layer W/O/W emulsions had the maximum encapsulation efficiency.	[77]
Saffron extract	Soy lecithin	sunflower oil	nano-liposomes using the heating method	Optimum nanoliposome formulated with 0.15% saffron, 35% oil and 1% lecithin	(Hadavi, et al. (2020))
Crocin, picrocrocin and saffranal	Polysaccharide (maltodextrin) Protein (whey protein concentrate) Polysaccharide (pectin)	Sunflower oil Span 80	Spray drying	Efficient encapsulation of crocin, picrocrocin and saffranal due to stable wall materials	[77]
Crocin, picrocrocin and saffranal	Polysaccharide (maltodextrin) Protein (whey protein concentrate) Polysaccharide (pectin)	Sunflower oil Span 80	Spray drying	A high stability and low release of encapsulated compounds up to 22 days	[78]
Crocin	Polyglycerol polyrecioleate	Virgin olive oil Span 80	Spontaneous method	Polyglycerol polyrecioleate is a suitable surfactant for the preparation of saffron nanoemulsions.	[80]
Saffron petal extract	Whey protein concentrate Basil seed gum Tween 80	Pure canola oil Vitamin D3	High pressure homogenizer Ultrasonic homogenizer	Basil seed gum is a good emulsifier for improving the bioavailability of vitamin D3 and saffron petal extracts.	[81]

Crocins and picrocrocin	Maltodextrin	---	Nano spray drying	Nanoencapsulation enhances the thermal stability and bioaccessibility of saffron bioactives.	[82]
Crocin	Polyglycerol polyrecioleae Whey protein concentrate Gum Arabic Angum gum	Virgin olive oil	Spontaneous method	The highest stability was seen when Angum gum was used in in outer aqueous phase of nanoemulsions.	[95]
Crocin, picrocrocin and saffranal	Tween 80 Span 80	---	Ultrasonic homogenizer	The properties of W1/O emulsion have a great impact on the stability of the W1/O/W2 emulsion system and the preservation of saffron biocompounds.	[96]
Curcumin	Sodium dodecyl sulphate	Medium chain triacylglycerl.	High pressure homogenizer	Multilayer nanoemulsions had a lower curcumin bioaccessibility than uncoated nanoemulsions	[97]
Curcumin	Tween 80 Lecithin Whey protein isolate Acacia	Canola oil Linseed oil Medium-chain triglyceride	High pressure homogenizer	Tween 80 with higher surfactant-to-oil ratio values produces more stable curcumin nanoemulsions	[98]
Curcumin	Tween 80 Glycerol	Cinnamon essential oil Garlic essential oil Sunflower oil	Spontaneous emulsification	Chilled chicken fillets coated with curcumin nanoemulsions make had higher sensory scores	[99]
Vitamin D	Polysorbate 20 Soybean lecithin	Soybean oil Cocoa butter	High pressure homogenizer	Since the concentration of vitamin D affects the size of the oil cores, the concentration should be such that the stability of the nanoemulsions is maintained.	[74]
Vitamin D	Pea protein	Canola oil	High pressure homogenizer	Pea protein is an effective emulsifier suitable for vitamin D nanoemulsions.	[100]
Vitamin D	Pea protein	Canola oil	Ultrasonic homogenizer	The pea protein nanoemulsions can be served as the potential carrier and stabilizer of vitamin D.	[101]
Vitamin D	Tween 80	Cinnamon oil	Ultrasonic homogenizer	Cinnamon oil is a good carrier of vitamin D.	[102]

Saffron Nanoemulsion

Saffron's active components contain aldehyde, ketone, and ester functional groups, making them susceptible to oxidation. Nanoencapsulation is a promising technique for encapsulating the bioactive ingredients of saffron behind several walls (Table 1). (Garavand, et al. [76]). categorized saffron nanoencapsulation technologies into five categories in their study:

1. Nanoparticles,
2. Nanostructured lipid dispersions,
3. Nano-hydrogels,
4. Electrospinning, and
5. Nanoemulsions and nanodroplets [76].

Each of these procedures possesses unique physicochemical features. This is a comprehensive review of the nanoemulsion process. The research on saffron nanoencapsulation conducted by Esfanjani and colleagues is one of the most informative studies. Components of saffron (crocin, picrocrocin, and safranal) were encapsulated in two model food systems with double or single-layer W/O/W multiple emulsions [77]. As wall materials, maltodextrin-whey protein concentrate or maltodextrin-whey protein concentrate-pectin was utilized. Furthermore, sunflower oil and Span 80 were employed for the oil phase. (Esfanjani, et al. [77]) demonstrated that double-layered W/O/W multiple emulsions stabilized by sequential adsorption of whey protein concentrate/pectin effectively preserved the active components of saffron and its surface with a mild yellow hue. In addition, the same authors demonstrated in their subsequent investigation that the W/O/W multiple emulsion system (maltodextrin-whey protein concentrate-pectin) could maintain the active components of saffron for up to 22 days. These technologies have a modest rate of encapsulated bioactive release and offer excellent protection against gastrointestinal disorders [78]. Pectin is a suitable wall material for the nanoemulsion of bioactive saffron due to its regulated release of bioactive components in the body. Using pectin with proteins, lipids, and other polysaccharides increases its positive benefits [79]. In separate work, (Mehrnia, et al. [80]) demonstrated that spontaneous emulsification as a low-energy technique and polyglycerol polyricioleate and Span 80 as nonionic surfactants can produce stable crocin nanoemulsions [80].

In work by (Gahruie, et al. [81]) saffron flower extract was co-encapsulated with vitamin D3 in nanoemulsions containing a variety of emulsifiers (whey protein concentrate, basil seed gum, and Tween 80). This work demonstrates that basil seed gum is an effective stabilizer for emulsifying vitamin D3 and saffron flower extracts in food nanoemulsions [81]. It has also been noted that the ratio of core to the wall is crucial in saffron extract encapsulation efficiency. By spray drying, (Kyriakoudi, et al. [82]) encapsulated saffron extract in maltodextrin. They utilized caffeic acid as a powerful antioxidant in the feed phase of nanoemulsions in order to test their thermal and gastrointestinal stability. The findings demonstrated that the ratio of core to wall significantly impacts the efficacy of nanocapsules and that caffeic acid boosts their stability under thermal and gastrointestinal conditions [82]. The United States Patent Application Publication recently revealed a unique nanoemulsion formulation of saffron extract and a preparation method (Pub. No.: US 2021/0046141 A1, Publication Date: February 18, 2021). In the formulation, liquid nitrogen was used for crushing saffron stigmas. The extract was then produced by ultrasonically dissolving the crushed saffron in a nonpolar solvent (n-decane). Polyoxyethylene (20) sorbitan monolaurate, glycerol, and maltodextrin were surfactants in the aqueous phase. To obtain an oil phase, sorbitan monooleate was combined with the extract. Using a high-speed homogenizer followed by an ultrasonic homogenizer, O/W nanoemulsions (particle size of 23 nm) were produced.

According to the inventors, this formulation gives saffron extract a more vibrant hue, a more robust and potent odor, a more pleasing aroma, and a superior flavor while extending its shelf life. In a different patent titled water-in-oil nanoemulsion of saffron and a method for its preparation (Pub. No.: US 2021/0161987 A1, Pub. Date: June 3, 2021), saffron stigmas were first crushed in liquid nitrogen, and then the extract was made in aqueous solvent using the ultrasonic process. A water-in-oil nanoemulsion was created using a high-speed homogenizer followed by an ultrasonic homogenizer. Surfactants employed in the oil phase (olive oil) included sorbitan monooleate (44.5%) and polyoxyethylene (20) sorbitan monolaurate (2.5%). According to the creators of this technique, it is a cost-effective procedure that uses minimal amounts of saffron and simultaneously improves the extract's physical qualities (color, odor, and flavor) and shelf life. The technology of saffron nanoencapsulation provides new prospects for the food and pharmaceutical industry to preserve the spice's color, flavor, aroma, and medicinal ingredients in both environmental and gastrointestinal conditions. Due to the low number of current studies, additional research and collaboration between research laboratories and the industry are required.

Nanoemulsions of Saffron as Natural Food Stabilizers

The presence of microorganisms is one of the most critical factors in food degradation. Microbiological activity in food is highly worrisome because it threatens consumer health and produces substantial economic losses. Using safe preservatives is one technique to prevent food degradation caused by microorganisms. Particular plant essential oils have significant antibacterial activity against food-borne pathogens. Unfortunately, they are hydrophobic, challenging their direct application in food packaging [83]. Nanoemulsions can assist in resolving this issue by retaining the antibacterial in the oil nanodroplets. Current research has been conducted on nanoemulsions made from plant oils to extend the shelf life of food goods. (Nasiri, et al.) for instance, described the effectiveness of nanoemulsions containing the essential oil of three distinct plants (Rosmarinus officinalis L., *Zataria multiflora Boiss*., and *Cuminum cyminum* L.). The author investigated the capacity of nanoemulsions to enlarge Acipenser stellatus filets. The results demonstrated that the nanoemulsion of Cuminum cyminum L. generated by ultrasonic homogenization had the most significant antibacterial impact on fish filets (Nasiri, et al.). Another study has validated the efficacy of *Polylophium involutum* nanoemulsions in reducing the number of microorganisms and extending the shelf life of green tiger prawns [84]. It has also been observed that curcumin essential oil nanoemulsions created via emulsion phase inversion can extend the shelf life of *Oncorhynchus mykiss* [85].

Like many other plants, such as orange, clove, and thyme, saffron contains antibacterial bioactive compounds [13]. Owing to its intrinsic antibacterial properties, saffron is regarded as a natural preservative that extends the shelf life of goods. Unlike other spices, saffron is resistant to diseases such as Salmonella and does not deteriorate. (Pintado, et al. [86]) studied saffron's antibacterial properties. They demonstrated that the bioactive components of saffron, particularly safranal (8-16 mg/mL) and crocin (64-128 mg/mL), significantly reduced the incidence of Salmonella contamination in saffron [86]. Other studies have shown the antimicrobial properties of saffron against bacteria, including *Microccucos luteus, Staphylococcus epidermitis, Staphylococcus aureus, Escherichia coli, Brucella*, and fungi, including *Candida albicans, Aspergillus niger*, and *Cladosporium sp*. [87,88]. Due to saffron's antibacterial qualities, saffron nanoemulsions can be a safe, natural preservative in food packaging. The current research examined the impact of saffron nanoemulsion on the shelf life of shrimp prepared by utilizing two distinct emulsification techniques (spontaneous emulsion and ultrasonic homogenization). This study showed that 5% saffron nanoemulsion produced by ultrasonication has significant antibacterial effects on shrimp deterioration [89-95]. Since saffron contains distinct nutritional and therapeutic characteristics and antibacterial action, additional research is required before this vibrant spice may be used as a food preservative.

Conclusions and Future Prospectives

Nanoemulsions are colloidal droplets created by the combination of two immiscible liquids. Due to their diverse physicochemical features, nanoemulsions are increasingly used in food. Saffron is the most expensive and essential ingredient due to its excellent nutritional, pharmacological, and antibacterial characteristics, color, and flavor. Many researchers have examined the use of nanoemulsions in saffron processing. These investigations can be categorized as extraction, encapsulation of bioactive substances, and application for extending food shelf life. We analyzed and summarized the literature on these three topics in the present study. Using nanoemulsions to extract the bioactive components from saffron permits the separation of hydrophilic and hydrophobic chemicals into distinct fractions. Due to the size of nanoparticles, saffron nanoencapsulation is a feasible method for improving the bioactivity and bioavailability of its bioactive components and their storage stability [96-102]. The use of infeed model food systems substantially impacts the preservation of encapsulated saffron extract and is extremely promising. Moreover, saffron nanoemulsions can potentially extend the shelf life of foods. Despite the various possibilities of saffron nanoemulsions, research has been restricted, and there is no unique approach for industrial and commercial usage in any of the three sectors. Many investigations are required to develop ways for extracting, encapsulating, and employing saffron as an antibacterial.

Conflict of Interest

Nothing to declare.

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