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Review Article

Liposomal Delivery of Plant Bioactives Enhances Potency in Food Systems: A Review

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The potency of plant bioactives may decline drastically upon exposure to harsh external environments including gastrointestinal conditions. The protective role played by liposomes contributes to desirable properties including increased stability, slow/controlled release, improved bioactivity, and enhanced bioavailability of the encapsulated bioactives. Also, the incorporation of plant bioactives encapsulated liposomes in food matrices has resulted in augmented sensory attributes and improved quality of the foods further exhibiting the aptness of liposomal applications in food. Excitingly, new opportunities that circumvent the major shortfalls of utilizing liposomal formulations in the food industry have arisen paving the way to yield food products with high quality.

1. Introduction

Amongst the numerous nano-/microparticles, liposomes hold a prominent place in many fields including pharmaceuticals, nutraceuticals, and cosmeceuticals due to their biodegradability, biocompatibility, and nontoxicity together with a number of ameliorated attributes of those vesicles. Despite the plenteous research on potential applications in food, liposomes are meagerly used in food formulations mainly due to the relatively high cost of lipids and lack of methods for mass production of liposomes [1]. However, the continuous quest for alternate lipids and methods of mass production of liposomes has shed light on the future utilization of these delivery vehicles in food.

Plant bioactive compounds and plant extracts with prospective applications in food formulations are many [2, 3]. Instead of confining to expressing potential applications, this review article discusses recent advances of real applications of liposomes in food, carried out on the laboratory scale. Limitations and potentials are, finally, briefed.

2. Overview of Liposomes

A liposome is a spherical entity with an aqueous compartment enclosed by one or more lipid bilayers made usually of phospholipids and cholesterol. The successful formulation of liposomes using edible lipids enables their utilization in food applications. Furthermore, both water- and lipid-soluble compounds can be successfully encapsulated in the aqueous core and the lipid bilayer, respectively, enhancing the utility of liposomes [4]. The diverse lipid molecules, methods of preparation, and conditions used in preparation have enabled the fabrication of different types of liposomes. Liposomes may be classified as small, large, or giant according to the size; unilamellar, multilamellar, or multivesicular according to the lamellarity; negatively charged or positively charged according to the surface charge; conventional or long-circulating according to the longevity in blood; and targeted liposomes, pH-sensitive, thermo-sensitive, and many other types according to their specialized functions [4]. The general structure of a unilamellar liposome is illustrated below (see Figure 1).

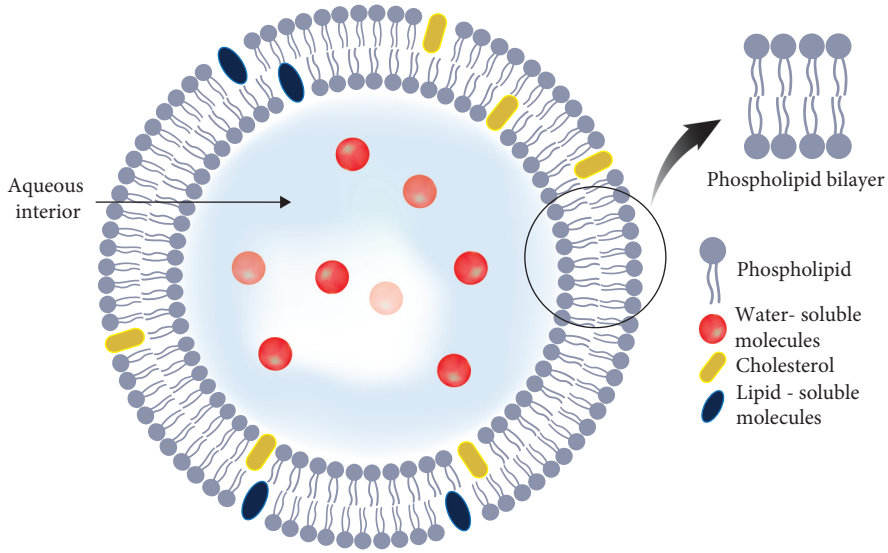

Figure 1: The cross-section of a unilamellar liposome.

2.1. Properties of Liposomes. The potential applications of liposomes in food are mainly due to their ability to increase stability providing protection against external conditions such as pH and temperature variations, to facilitate slow or controlled release, and to enhance bioactivity, bioaccessibility, and/or bioavailability of encapsulated material, thereby contributing to the quality of food. As expected, such properties depend on the size, charge, lamellarity, lipid composition, and modifications of liposomes, in addition to the encapsulated material [1, 2].

2.2. Lipid Component of Liposomes. The lipid bilayer of liposomes consists of numerous lipids making up the backbone and additives that modulate the properties of liposomes loaded with the cargo. The lipids used recently in the formulation of liposomal plant bioactive compounds and extracts are given in Tables 1 and 2, respectively. Lecithins are the most commonly used lipids forming the backbone of the lipid bilayers of liposomes. The main components of lecithins are phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylserine, and phosphatidic acid [1]. Although egg yolk lecithin and soy lecithin were used traditionally in the formulation of liposomes, the use of other types of lecithins or phospholipids that may reduce the cost of the main lipids used in the preparation of liposomes is now common [15, 17, 24, 28]. Edible lipids such as cholesterol and/or β-sitosterol are frequently used in the preparation of liposomes as additives to maintain the fluidity of the membranes. As mentioned previously, the properties of liposomes such as solubility of the encapsulated material, stability, and all other properties relevant to quality improvement of the host food depend largely on the lipid composition of liposomes [1, 49].

2.3. Methods of Preparation of Liposomes. The conventional methods that facilitate the preparation of small quantities of liposomes include thin-film hydration method, reverse phase evaporation method, sonication method, ethanol injection method, and proliposome method [9, 10, 23, 26, 50]. More recent methods utilized in the preparation of liposomes include electrospraying, supercritical carbon dioxide method, nanofiber weaving followed by spray drying, and microfluidization [5, 15, 18, 51]. Recently, a few methods including the proliposome method and microfluidization have been utilized to allow mass production of liposomes at reasonable costs making applications of liposomes in food plausible [1].

3. Liposome Delivered Plant Bioactive Compounds and Extracts

The utilization of plant bioactive compounds and extracts in food formulations is frequently reported in the literature. Plant natural products, extracts and phytochemicals, show a vast array of bioactivities that may give functional properties to food [52]. Furthermore, they are used to improve the sensory properties of food [53]. Interestingly, the benefits of incorporating plant bioactive compounds and extracts in food can be much amplified via liposomal encapsulation [19, 48]. Those benefits include improved protection, modulated release, amplified bioactivity, and increased bioaccessibility and bioavailability that may contribute to enhancing the quality of food [1]. This review article emphasizes the recent advances in food applications of liposomal plant bioactive compounds and extracts.

The basic details of the liposomal formulations encapsulating plant bioactive compounds and plant extracts are given in Tables 1 and 2, respectively. The bioactive compounds and extracts are arranged in alphabetical order. The prominent bioactivities, but not all, of the encapsulated materials are also given.

Table 1: Recently reported plant bioactive compound encapsulated liposomal formulations with potential applications in food, methods of preparation, and lipids used.

Encapsulated bioactive compound (bioactivity)	Type of formulation (diameter)	Method of preparation	Main lipids	References
Anthocyanin (antioxidant)	Nanoliposomes (D: 152–243 nm)	Supercritical carbon dioxide method	Soy lecithin and cholesterol	[5]
Anthocyanin (antioxidant)	Nanoliposomes (D: 53–93 nm)	Ethanol injection followed by ultrasound-assisted dispersion	Lecithin and cholesterol	[6]
Betanin (antioxidant)	Nanoliposomes (D: 36 nm)	Thin-film hydration method followed by sonication	Lecithin	[7, 8]
Carotenoids (antioxidant)	Chitosan-coated liposomes (D: approx. 100 nm)	Thin-film hydration method	Egg yolk phospholipid	[9]
Catechin (antioxidant)	Liposomes	Reverse phase evaporation method	Phosphatidylcholine and cholesterol	[10]
Catechin and curcumin (antioxidant)	Nanoliposomes (D: 200 nm)	Multihydrodynamic focusing using a microfluidic device	Dipalmitoylphosphatidylcholine	[11]
Catechins (antioxidant)	Nanoliposomes (D: 221 nm)	Reverse phase evaporation method	Phosphatidylcholine and cholesterol	[12]
Cinnamaldehyde (antioxidant and antimicrobial)	Nanoliposomes (D: 75–92 nm)	Ethanol injection method	Egg yolk lecithin	[13]
Curcumin (antioxidant and antimicrobial)	Liposomes agglomerated with corn starch	Proliposome method	Phospholipon 90H	[14]
Curcumin (antioxidant and antimicrobial)	Nanoliposomes (D: 53–96 nm)	Microfluidization	Sunflower lecithin	[15]
Curcumin (antioxidant and antimicrobial)	Eudragit-S100-coated liposome clusters small unilamellar liposomes (D: 40 nm) and eudragit-coated liposome clusters (D: >1 μm)	Micelle to vesicle transition (MVT) method	Lipoid S100 and cholesterol	[16]
Curcumin (antioxidant and antimicrobial)	Liposomes (D: 163–212 nm)	Thin-film evaporation and ultrasonic dispersion	Bovine milk phospholipids and krill phospholipids	[17]
Curcumin (antioxidant and antimicrobial)	Protein-coated liposomes	Electrospraying	Pure phosphatidylcholine	[18]
Lupulon (antibacterial) and xanthohumol (antioxidant)	Nanoliposomes (D: 150–394 nm)	Sonication method	Egg yolk lecithin	[19]
Lutein (vitamin A and antioxidant)	Nanoliposomes (D: 162–195 nm)	Supercritical carbon dioxide method	Soy lecithin	[20]
Phytosterols (hypocholesterolemic) and tocopherols (antioxidant)	Nanoliposomes (D: 186–260 nm)	Thin-film hydration method and thin-film hydration-sonication method	Phosphatidylcholine	[21]
Piperin (antioxidant and antimicrobial)	Nanoliposomes (D: 100–120 nm)	Modified reverse phase evaporation method	Phosphatidylcholine	[22]
Procyanidin and cocoa extract (antioxidant activity)	Nanoliposomes (D: 60–87 nm)	Sonication method	Soybean L-α-phosphatidylcholine	[23]
Quercetin (antioxidant)	Nanoliposomes (D: 157 nm)	Film sonication method	Rice bran phospholipids	[24]
Quercetin (antioxidant)	Nanoliposomes (D: 200–250 nm)	Ethanol injection method	Soy lecithin 1,2-dioleoyl sn-glycero-3-phosphatidylethanolamine and cholesterol	[25]
Resveratrol (antioxidant)	Liposomes in alginate microbeads and liposomes in microbeads coated with chitosan (D: 471 nm)	Proliposome method	Phospholipids	[26]
Vitamin B5: Pantothenic acid	Liposomes in alginate/alginate-pectin microparticles (D: 240–300 μm)	Proliposome method	Pure phophatidylcholine	[27]
Vitamin C (antioxidant)	Nanoliposomes (D: 78 nm)	Thin-film hydration followed by freeze thawing	Phospholipid extract from jack bean and cholesterol	[28]

Abbreviations: Diameter – D and approximately – approx.

Table 2: Recently reported plant extract encapsulated liposomal formulations with potential applications in food, methods of preparation, and lipids used.

Encapsulated plant extract (bioactivity)	Type of formulation (diameter)	Method of preparation	Lipids used to make liposomes	References
Armoracia rusticana leaves extract (antioxidant)	Nanoliposomes (D: <150 nm)	Thin-film hydration method	Phosphatidylcholine and sodium cholate	[29]
Basella rubra L. fruit juice (antioxidant)	Nanoliposomes (D: 55–74 nm)	Thin-film hydration-sonication	Soybean lecithin	[30]
Bay leaf extract (antioxidant and antimicrobial)	Nanoliposomes (D: 99 nm)	Sonication method	Lecithin tween 80	[31]
Bitter orange peel extract (antioxidant activity)	Multilamellar lipid vesicles	Thin-film hydration followed by vortexing	Liposome mixture from Sigma-Aldrich Co., USA	[32]
Cocoa hull waste phenolics (antioxidant activity)	Chitosan-coated liposomes (D: 230–300 nm)	High shear dispersion followed by high-pressure homogenization	Soybean phospholipids Ultralec® P	[33]
Coconut husk extract – ethanolic (antioxidant and antimicrobial)	Nanoliposomes (D: 261–676 nm)	Ethanol injection method	Soy phosphatidylcholine alone or combined with cholesterol, tween 80 or glycerol	[34]
Coconut husk extract – ethanolic (antioxidant and antimicrobial)	Reference [35]	Ethanol injection method	Phosphatidylcholine and cholesterol	[36]
Doum extract (antioxidant activity)	Chitosan-coated liposomes: (D: 260–480 nm)	Sonication method	Soy lecithin	[37]
Garlic extract (antimicrobial activity)	Nanoliposomes (D: 113 nm)	Thin-film hydration method	Phosphatidylcholine and oleic acid	[38]
Garlic extract and nisin (antimicrobial activity)	Nanoliposomes (D: 179 nm)	Thin-film hydration-sonication	Phosphatidylcholine	[39]
Ginger ethanolic extract (antioxidant activity)	Nanoliposomes (D: 165 nm)	Homogenization of blended lipid and aqueous phases	Lecithin and sunflower oil	[40]
Grape pomace extract (phenolic antioxidants)	Polymer-associated liposomes (D: 300 nm)	Sonication method	Soy lecithin	[41]
Grape seed extract (polyphenols)	Nanoliposomes regular liposomes (D: 87 nm) and coated liposomes D: 160 nm)	High pressure homogenization	Soy lecithin (lipoid S75)	[42]
Green tea extract (antioxidant activity)	Nanoliposomes (D: <100 nm or approx. 400 nm)	Homogenization	Soy lecithin (lipoid S75)	[43]
Olive leaf phenolics (antioxidant activity)	Nanoliposomes (D: 25–158 nm)	Ethanol injection	Phosphatidylcholine and cholesterol	[44]
Piperine extract (antioxidant activity)	Nanoliposomes (D: approx. 30 nm)	Sonication method	Soy phosphatidylcholine	[45]
Pistachio green hull extract (polyphenols)	Nanoliposomes (D: 102 nm)	Sonication method	Soybean lecithin	[35]
Sea fennel extract (antioxidant activity)	Nanoliposomes fresh liposomes D: 87–150 nm and freeze-dried liposomes (D: 171–317 nm)	Sonication	Soy phosphatidylcholine	[46]
Sour cherry extract (antioxidant)	Nanoliposomes (D: 276–342 nm)	Homogenization	Lecithin	[47]
Turmeric extract (antioxidant and antimicrobial)	Nanoliposomes (D: 92 nm)	Thin-film hydration-homogenization-sonication	Phosphatidylcholine	[48]

Abbreviations: Diameter – D and approximately – approx.

3.1. Stability/Protection. Liposomal encapsulation affords stability or protection to the encapsulated bioactive compounds and extracts against numerous external conditions such as heat, oxidation, pH, gastrointestinal conditions, and storage conditions [6–8, 28]. Some examples of increased stability of bioactive plant materials due to encapsulation are concisely discussed in the following sections.

3.1.1. Stability against Heat. Improving the heat stability of incorporated bioactive compounds and extracts is paramount in formulating functional foods since temperatures of a wide range are used in food processing and preservation. Bioactive compounds such as piperine and plant extracts such as *Basella rubra* L. fruit juice have shown increased heat stability due to liposomal encapsulation [22, 30]. In fact, the

stability of piperine loaded in liposomes was significantly higher than that of free piperine upon raising the temperature up to 47°C. Also, liposomal piperine was more stable than free piperine upon incubation at 37°C [22]. Furthermore, *B. rubra* juice-loaded nanoliposomes exhibited stability, while *B. rubra* native juice exhibited degradation upon incubation at 100°C for 20 min [30]. It has also been revealed that the thermal stability of the encapsulated bioactive material can be increased by changing the lipid composition of the liposomes. For instance, Peng et al. incubated liposomal curcumin at 80°C for 1 h and showed that retention of curcumin could be increased from 6% to 32% by using lecithin with increased phosphatidylcholine contents [15]. Indeed, liposomal encapsulation is a promising method for enhancing the heat stability of plant bioactive compounds and extracts.

3.1.2. Stability against Oxidation. Interestingly, liposomes and encapsulated plant bioactive compounds may protect each other from oxidation. For example, betanin has shown higher oxidation stability upon liposomal encapsulation. Amaji et al. incorporated free betanin and nanoliposomal betanin in gummy candies and revealed that the retention of the antioxidant potential of gummy candies incorporated with liposomal betanin was greater than that incorporated with free betanin. The 2,2-diphenyl-1-picrylhydrazyl (DPPH) inhibition retention percentage of candies incorporated with 5% liposomal betanin was as high as 82%, while that of candies incorporated with 5% free betanin was only 56%, after 60 days of storage. These results suggest that liposomal encapsulation has provided oxidative stability to the loaded plant bioactive compound-betanin [7]. On the other hand, encapsulated procyanidins and plant extracts rich in antioxidants have provided oxidative stability to the liposomes. In fact, procyanidins and free cocoa extract encapsulated in liposomes reduced the formation of lipid hydroperoxide and hexanal, which are primary and secondary lipid oxidation products, respectively, in soybean liposomes [23]. Increased oxidation stability may contribute to enhanced bioaccessibility and bioavailability of plant bioactive compounds encapsulated in liposomes.

3.1.3. Stability against pH Variations. Liposomes can protect encapsulated bioactive materials from pH variations. For example, nanoliposomes stabilize anthocyanins against variations of pH. In fact, anthocyanins encapsulated in liposomes showed retention rates of 94%, 90%, and 61%, whereas unencapsulated anthocyanins showed much lower retention rates of 88%, 80%, and 41%, at pH values of 3, 5, and 7, respectively [6]. Stability of plant bioactive compounds and extracts against pH changes is imperative for their utility in food systems.

3.1.4. Gastrointestinal Stability. As the gastrointestinal tract offers drastic pH changes, maintaining stability along the gastrointestinal tract is challenging to any orally taken substance. Like many other encapsulation methods, liposomal encapsulation has shown promise in increasing the gastrointestinal stability of numerous plant bioactive materials. Enhancing the gastrointestinal stability of betanin, which is a natural pigment with numerous bioactivities, and grape pomace extract, which is a rich source of antioxidants via liposomal encapsulation, is briefly discussed in this section [8, 41].

Amjadi et al. demonstrated that liposomal betanin exhibits increased gastrointestinal stability showing enhanced retention in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). They incubated liposomal betanin in SGF (pH 1.2) for 120 min and in SIF (pH 7.4) for 240 min at 37°C and determined betanin release, betanin retention, and DPPH inhibition retention. Liposomal betanin (LB) showed marked slower release and higher retention of betanin than betanin solution (BS) in both SGF and SIF. These results indicate that liposomal encapsulation confers stability to the encapsulated bioactive compounds in gastrointestinal conditions. Notably, the degree of retention of liposomal betanin was higher in SGF ($87 \pm 2.64\%$) than in SIF ($53.66 \pm 4.93\%$). These results indicate the ability of liposomes to retain and protect the encapsulated bioactive agent in the presence of pepsin in acidic gastric media [8]. However, lipase and phospholipase A2 in SIF can destabilize the liposomes via catalyzing the hydrolysis of lipids, leading to faster release of betanin. Also, bile salts in SIF may destabilize the liposome structure affecting the release properties of the liposomes [54]. Nevertheless, the protection given by the liposomes to the encapsulated material is substantial as revealed by the significantly higher DPPH inhibition retention shown by LB than BS. The DPPH inhibition retention values of BS and LB were $5 \pm 1\%$ and $85 \pm 4.58\%$, respectively, in SGF, while those were $6.33 \pm 1.04\%$ and $53.33 \pm 6.65\%$, respectively, in SIF. These results confirm that liposomal encapsulation provides gastrointestinal stability to betanin and that the protective effect of liposomes is greater in gastric conditions than in intestinal conditions [8].

Grape pomace extract encapsulated in polysaccharide-associated liposomes has shown increased gastrointestinal stability compared to the same extract encapsulated in regular liposomes. Although the size and polydispersity index of regular liposomes and sodium alginate-associated liposomes loaded with grape pomace extract were severely affected, Arabic gum-associated liposomes were affected only to an acceptable level at pH 2 (gastric pH). At pH 7 (intestinal pH), polysaccharide-associated liposomes exhibited much smaller changes in size than regular liposomes. These results indicate the aptness of using polysaccharide-associated liposomes as delivery vehicles for plant extracts including grape pomace extract since greater stability of liposomes leads to greater stability of the encapsulated material. Liposomal encapsulation of plant extracts is, thus, suggested for enhanced gastrointestinal stability [41].

3.1.5. Storage Stability. Liposomal bioactive compounds and extracts with high usage potential in food formulations need to show significant storage stability. Following are some

plant bioactive agents that have shown significant storage stability due to liposomal encapsulation. The storage stability of cinnamaldehyde has improved due to liposomal encapsulation [13]. Nanoliposomal vitamin C has shown increased stability at temperatures of 5°C, 25°C, and 37°C [28]. Liposomal quercetin has shown constant stability for a period of six months and five months at 4°C and 27°C, respectively [24]. Also, liposomal piperine extract has exhibited improved stability upon storage at 4°C in dark conditions [45]. These results indicate the possibility of utilizing these highly stable liposomal bioactive compounds and extracts for food applications.

3.2. Release Properties. Slow or sustained release of liposomal bioactive agents is paramount in protecting the encapsulated material in liposomes from external conditions, thereby imparting the desired effect constantly with time. Also, controlled release, where the encapsulated bioactive material shows burst release at the site of absorption, has increased the bioavailability of loaded species [24, 55].

Liposomal plant bioactive compounds resveratrol, vitamin B5, and quercetin have shown favorable release properties. Regular or modified liposomal resveratrol has shown slower release than the free bioactive agent [26]. Liposomal vitamin B5 has shown slower release properties than the free vitamin [27]. Liposomal quercetin has shown slow release in simulated gastric fluid and burst release at the intestinal pH, indicating possible stability in gastric conditions and improved absorption in the intestine [24]. Also, many plant extracts including pepper extract, *Armoracia rusticana* leaf extract, and turmeric have shown slow or sustained release due to liposomal encapsulation [29, 45, 48]. Hence, liposomes may be used as a means of increasing the bioactivity and bioaccessibility of plant compounds and extracts via modulating their release properties.

3.3. Bioactivities. Plant bioactive compounds and plant extracts have shown enhanced bioactivities upon encapsulation in liposomes. Increased antioxidant activity of encapsulated plant natural products may contribute to the protection of food systems against oxidation and increase the functional properties of foods [48]. Enhanced antimicrobial potency of encapsulated plant materials may contribute to increased shelf life and safety of foods [13].

3.3.1. Antioxidant Activity. Many reports on the increased antioxidant activity of bioactive compounds attributable to liposomal encapsulation have been published recently. The liposomal bioactive agents briefly deliberated in this section are piperine and quercetin. Liposomal piperine exhibited increased antioxidant activity than the free compound according to the DPPH assay [22]. Also, the antioxidant activity of quercetin increased with liposomal encapsulation according to the oxygen radical absorbance capacity (ORAC) assay [25].

Numerous plant extracts, also, show improved antioxidant capacity on liposomal encapsulation. Liposomal ethanolic ginger extract has exhibited higher antioxidant potency than nonencapsulated extract according to DPPH, ferric reducing antioxidant power (FRAP), and total antioxidant capacity (TAC) assays [40]. In addition, turmeric extract exhibited enhanced antioxidant activity over 40 days of storage, according to the DPPH radical scavenging assay, owing to liposomal encapsulation [48]. Although numerous reports on the enhancement of the antioxidant activity due to liposomal encapsulation of plant extracts have been published, many contradictory reports can be found in the literature. For example, ethanolic coconut husk extract exhibited reduced antioxidant activity due to poor release of the extract to the medium from the liposomes [34].

3.3.2. Antimicrobial Activity. Significant improvement of antimicrobial properties of plant bioactive compounds and extracts due to liposomal encapsulation has been reported. This enhancement is particularly important as such liposomal formulations may show positive effects on both shelf life and safety of food and may function as natural antimicrobial agents for food applications.

Liposomal cinnamaldehyde has maintained higher antimicrobial activity than the free compound during storage according to the killing log values against *Staphylococcus aureus* that is a food-borne pathogen. Thus, liposomal cinnamaldehyde may be suggested for an improved antibacterial effect on food products [13].

Also, plant extracts have shown augmented antimicrobial activity owing to liposomal encapsulation. Coencapsulation of garlic extract with nisin has resulted in a synergistic antimicrobial effect against food-borne pathogens such as *Listeria monocytogenes*, *Salmonella enteritidis*, *Escherichia coli*, and *S. aureus*. The ability of garlic extract to increase the number or size of the pores formed by nisin may have resulted in reduced viability of the bacterial cells [39]. Besides, liposomal turmeric extract has shown increased antimicrobial activity according to the minimum inhibitory concentration and minimum bacterial concentration against food-borne pathogens such as *E. coli*, *S. aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Streptococcus* mutants [48].

3.4. Bioaccessibility and Bioavailability. Liposomal encapsulation of plant bioactive agents has exhibited augmented bioaccessibility and bioavailability in numerous instances. The examples given in this section include liposomal curcumin-catechin and liposomal procyanidins. Liposomes dual-loaded with curcumin and catechin have exhibited much higher colon tumor cell inhibition than curcumin, catechin, or plain liposomes alone, indicating higher bioavailability facilitated by dual-loaded liposomes [11]. Procyanidins have shown increased bioaccessibility due to liposomal encapsulation. In fact, dimer, trimer, and tetramer fractions of procyanidins from cocoa extract have shown 4.5-, 2.1-, and 9.3-fold increases in bioaccessibility compared to the free extract, respectively [23]. The possibility of modulating bioaccessibility by changing the lipid composition was demonstrated by Wu and coworkers. Curcumin

encapsulated liposomes made of bovine milk phospholipids has shown slightly higher bioaccessibility than those made of krill phospholipids. The authors of this report ascribe this variation to the higher stability of liposomes made of bovine milk phospholipids than those made of krill phospholipids [17]. These findings indicate that bioaccessibility and bioavailability of plant compounds frequently used in food can be improved via liposomal encapsulation.

3.5. Plant Bioactives Encapsulated in Modified Liposomal Formulations. Modifications to regular liposomes facilitate modulation of properties, thus enabling various applications. This section discusses the modifications of liposomes that have led to improved properties, showing promise for food applications.

The modified liposomes obtained by incorporating liposomal resveratrol in alginate-sucrose and alginate-chitosan microbeads have shown slower release of resveratrol than their liposomal counterpart and free bioactive agent [26]. Furthermore, carotenoids such as lycopene, β-carotene, lutein, and canthaxanthin encapsulated in liposomes coated with chitosan have shown enhanced properties such as improved thermal stability, increased gastrointestinal stability, and uniform dispersion that will be of much use in functional foods [9]. Furthermore, Eudragit-coated clusters of liposomal curcumin have shown improved cellular internalization. The fact that Eudragit coatings dissolve at pHs greater than 7 while they are stable at low pHs indicates the suitability of these modified liposomes for delivering bioactive compounds to the small intestine [16].

Also, plant extracts encapsulated in coated liposomes have shown improved properties. Grape seed extract encapsulated liposomes coated with chitosan have shown a much slower release of the cargo than regular liposomes. The authors of this report suggest that coated liposomes encapsulating grape seed extract be used in water-based food products [42]. Green-tea-extract-loaded liposomes have been modified by adsorbing lysozymes, gum Arabic, whey protein, and chitosan on the surface. The modified liposomes have shown much higher polyphenol contents according to the Folin–Ciocalteu assay and much higher antioxidant activities according to the DPPH assay during the 28 days of storage [43].

4. Incorporation of Liposomal Plant Bioactives in Food Systems

4.1. Liposomal Plant Bioactive Compounds. A few examples of applications of liposomal plant bioactive compounds in food systems are discussed below. The liposomal bioactive compounds discussed include curcumin, catechin, lupulon-xanthohumol, and phytosterol.

A study on the effects of incorporating lyophilized liposomal curcumin in the cake batter was carried out by Ferreira and coworkers [14]. In fact, an agglomeration of corn starch and maltodextrin with liposomal curcumin, showing improved flowability and noncohesiveness, was incorporated in cake batter. Cake with agglomerated material showed improved properties such as high softness, low chewiness, and homogenous distribution of yellow color. This study clearly shows the aptness of utilizing liposomal curcumin to improve the properties of foods [14].

Liposomal catechin has exhibited higher antioxidant activity according to thiobarbituric acid reactive substance (TBARS) value and peroxide value (PV). It has also shown higher antimicrobial activity than free catechins according to the total viable count. Thus, liposomal catechin has been used to improve the sensory attributes of Chinese fried pork as well as to enhance the redness while decreasing the hardness of bacon [10, 12]. Also, liposomal catechins have reduced the formation of nitrosamines in fried traditional Chinese bacon than unencapsulated catechins [12]. These results indicate the possible incorporation of liposomal catechin in Chinese dried pork, Chinese fried pork, and Chinese bacon to improve their qualities.

Possible utilization of liposomes dual-loaded with xanthohumol and lupulon in meat products has been indicated by Khatib and coauthors. The dual-loaded liposomes have shown reduced oxidation of sausages. Also, these liposomes have indicated the possibility of partial replacement of nitrates, according to antimicrobial tests carried out using *Clostridium perfringens*, *Coliform*, total count, and mold and yeast [19]. These results indicate the prospect of using liposomal lupulon-xanthohumol to maintain the quality of sausages and other meat products by retarding deterioration caused by oxidation and microbial activity.

A mixture of brassicasterol, campesterol, and β-sitosterol that are phytosterols, and alpha/gamma/delta-tocopherols have been incorporated in liposomes that have then been used to fortify a model beverage of orange juice. The liposomes have shown stability for one month after pasteurization according to particle size analysis. This work indicates the possibility of using liposomal bioactive compounds in the formulation of functional beverages [21].

4.2. Liposomal Plant Extracts. The incorporation of numerous liposomal plant extracts in foods, such as dairy products, wheat bread, edible oils, fish products, and meat products, has shown ameliorated effects on the food systems. Such instances are concisely described in this section.

Liposomal plant extracts such as doum extract and olive leaf extract have been incorporated in set yogurt resulting in favorable properties [37, 44]. The liposomal extracts, as expected, have enhanced antioxidant properties of yogurt. Also, liposomal olive leaf extract incorporated in yogurt has shown a reduced rate of syneresis and higher scores for sensory attributes such as color, taste, texture, and overall acceptability [44]. In addition to set yogurt, stirred yogurt, and drinking yogurt have been incorporated with liposomal plant extracts. Although stirred yogurt incorporated with sour cherry extract encapsulated modified liposomes has shown similar pH and lower syneresis to regular yogurt, it has shown lower sensory properties than regular stirred yogurt [47]. Also, drinking yogurt has been incorporated with cocoa hull waste phenolics encapsulated in modified

spray-dried liposomes. The liposomal extract in drinking yogurt has exhibited higher oxidative stability and higher bioaccessibility according to antioxidant assays and in vitro digestion studies, respectively [33].

Another study demonstrated the inhibitory action of garlic extract and liposomal garlic extract against many fungal species, namely *Penicillium expansum*, *Aspergillus niger*, *Penicillium herquei*, *Fusarium graminearum*, and *Aspergillus flavus*, through an in vitro assay. The antimicrobial activity of garlic extract was unaltered upon liposomal encapsulation. Also, garlic extract and liposomal extract showed comparable antimicrobial activity in wheat bread. The thermal stability of liposomal extract was superior to the free liposomes indicating the possibility of liposomal extract to function as a natural food antimicrobial agent [38].

Also, liposomal plant extracts may be used as substitutes for antioxidants used in edible oils such as sunflower oil and soybean oil [35, 40]. The liposomal ginger ethanolic extract has decreased oxidation of sunflower oil according to peroxide and thiobarbituric acid values while liposomal pistachio green hull extract that exhibits antioxidant activity has prevented the color change caused by the incorporation of free pistachio extract in soybean oil [35, 40].

The shelf life of many fish products has been increased using liposomal plant bioactive extracts. Liposomes encapsulating bitter orange extract have increased the shelf-life of common carp fillets. Liposomal encapsulation has been particularly beneficial as fish fillet treated with 1% liposomal extract has shown significantly reduced lipid oxidation without altering the sensory attributes of the food [32]. Liposomal ethanolic coconut husk extract has increased the shelf life of Asian sea bass slices packaged under modified atmospheric conditions. Both the free extract and liposomal extract, combined with cold plasma treatment, have shown comparable antimicrobial activity and comparable antioxidant activity according to protein and lipid oxidation analysis. However, the utilization of liposomal extract is recommended due to the shielding of the color of the extract by the liposomes [36].

The prospect of utilizing liposomal *Laurus nobilis* leaf extract (bay leaf extract) for shelf life extension of minced beef has been evaluated. Interestingly, liposomal extract (1,500 ppm) incorporated in minced beef has resulted in lower peroxide value, lower thiobarbituric acid value, lower free fatty acid content, and lower total volatile basic nitrogen throughout the storage period of 16 days, displaying the higher antioxidant potential of the liposomal extract than the free extract. Also, liposomal extract (1,500 ppm) has shown a lower total viable count and psychrotrophic bacterial count compared to the free extract portraying the superior antimicrobial effect of liposomal encapsulation of plant extracts. To add to that, liposomal extract (1,500 ppm) has exhibited total annihilation of both *S. aureus* and *E. coli* inoculated in minced beef during storage. As the liposomal extract incorporated in minced beef has shown acceptable sensory attributes, the use of this liposomal extract as a natural preservative for meat products is recommended [31].

5. Limitations and Opportunities

The previous sections elaborated on the traits of liposomal plant bioactive compounds and extracts with potential usage in foods. However, the limitations of utilizing liposomal formulations in food must be emphasized. Nevertheless, advances in liposome technology have enabled circumventing a number of such hurdles.

Although scaling up of the production of liposomes has been a limitation for a number of years curbing the usage of these vesicles in food and beverages, numerous novel methods enabling scaling up have been reported. For instance, liposomal anthocyanins and liposomal lutein have been prepared using a scalable improved method using carbon dioxide supercritical fluid [5, 20]. In this method, the lecithin/bioactive agent/cholesterol suspension is pressurized using carbon dioxide, and then it is depressurized at a constant rate to allow the formation of liposomes. This method allows modulating the properties such as encapsulation efficiency, size, and zeta-potential of liposomes by changing the concentration of encapsulated material and lipid composition [5]. Large-scale production of liposomes can also be carried out utilizing membrane contactors that use the principle of ethanol injection. The lipid phase in an organic solvent is introduced to the aqueous phase in a membrane contactor where the lipids are hydrated and liposomes are formed [56]. Eugenol and clove essential oil have been encapsulated in liposomes on a large scale using membrane contactors [57]. Furthermore, a microfluidic assemblage of liposomes shows the potential of mass-scale production of these vesicles. For instance, high-throughput continuous assembly of β-carotene-loaded liposomes has been carried out using microfluidic devices [58]. Examples of plant bioactives dual-encapsulated in liposomes via microfluidic assemblage include curcumin and catechin [22]. Homogenization is another method that may be used for large-scale liposome production. Some examples of liposomes that have been prepared using homogenization include ethanolic ginger extract encapsulated liposomes, green tea extract encapsulated liposomes, and sour cherry extract encapsulated liposomes [40, 43, 47]. Large-scale production of liposomes is possible with homogenization often since the small-scale homogenizers have their corresponding large-scale equipment that can be used in liposome preparation [59]. In particular, methods involving nanoprecipitation and ionic interaction, solvent exchange, high shear, emulsification and solvent evaporation, packed bed reactors using high gravity technology, spray drying, freeze-drying, heating methods, and modified solvent-based methods score high as scalable methods of liposome preparation, and those methods were recently reviewed by Shah et al. [60]. Despite the introduction of these methods, large-scale utilization of liposomes in food has been rare.

A significant number of methods of liposome preparation involve organic solvents that may be unsuitable for food applications. However, a few green methods have been reported, thus paving the way to utilizing liposomal technology in food formulations. For instance, a high pressure-

high-temperature plant polyphenol extraction method coupled with the supercritical fluid-assisted formation of liposomes has been described [61]. Also, hydrating the lipid phase directly with aqueous media followed by homogenization and sonication has been reported as an organic solvent-free method of liposome preparation [62].

Numerous modified liposomes, especially those coated with polymers, encapsulating plant bioactive compounds and plant extracts have shown upgraded characteristics than regular liposomal formulations. Also, such modified liposomes have shown compatibility with food matrices while delivering favorable qualities such as improved stability, slow-release, and enhanced bioactivity to a number of foods [9, 26, 43]. Undoubtedly, there exists excessive potential to modulate the properties of liposomal formulations through modifications, especially by coating. Also, augmenting the qualities of foods via incorporating such modified liposomal formulations in foods is possible given the availability of plenteous edible polymers useable for coatings [63].

In addition to the liposomal formulations discussed in this review article, many other liposomal plant bioactive compounds or plant extracts have shown potency in enhancing the properties of functional foods [64–66]. In addition to liposomal plant bioactive compounds and extracts, there exists a prospect of utilizing liposomal plant essential oils to enhance the qualities of food formulations [67, 68]. Thus, it is suggested that liposomal plant products be used to much greater degrees to augment the physicochemical, sensory, and functional qualities of food.

6. Conclusions

Liposomes enhance the properties, such as solubility, stability, slow, or controlled release, bioactivities including antioxidant and antimicrobial activities, bioaccessibility, and bioavailability, of encapsulated plant bioactive compounds and extracts, thereby displaying the aptness of utilizing those vesicles in food formulations. As expected, modifications to the liposomes have resulted in further augmentation of properties favorable for food applications. Importantly, real food formulations, including dairy products, bakery products, and flesh products, incorporated with liposomal plant bioactive compounds and extracts have exhibited much-desired attributes including reduced oxidation of food material, increased microbial food quality, and even distribution of color. Although limitations in large-scale preparation of liposomes and essential utilization of organic solvents are characteristic of traditional methods of liposome preparation, novel methods including supercritical fluid assisted methods have alleviated those shortcomings. As numerous other edible plant-derived compounds and edible plant extracts with many bioactivities and properties valuable in the food formulations are reported, there is much prospect in using those plant products as liposomal encapsulates in food formulations. To conclude, liposomes may be exploited and hence may constitute an essential delivery vehicle in food and beverage sectors although these vesicles are still underutilized in those sectors.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Geethi K. Pamunuwa conceptualized, carried out literature collection, and wrote the original draft of the manuscript. D. Nedra Karunaratne critically reviewed the manuscript.

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