Review

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Nano-Liposomes as Effective Vehicles of Antioxidant Compounds in Food and Health

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Review

Nano-Liposomes as Effective Vehicles of Antioxidant Compounds in Food and Health

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Abstract: The use of nano-liposomes has increased exponentially since their discovery in the 1960s, primarily for encapsulating medicines or compounds that can improve human health. However, recent studies propose nano-liposomes as vehicles to protect, transport, and subsequently release compounds of various kinds to fortify the properties of foods and cause a prolonged release of encapsulated substances in a specific part of the body. Among the compounds successfully encapsulated are β-carotene, α-carotene, vitamins A, C, and D, lycopene, among others. The encapsulation of extracts with high contents of antioxidant pigments is still to be explored. Therefore, this review aims to compile the compounds that have been successfully encapsulated and have met the specific prolonged release criteria, highlighting areas of research opportunity and application such as biomedical, pharmaceuticals and nutraceutical industries.

Keywords: Nano-liposomes; encapsulation; antioxidant compounds; affinity; human health

1. Introduction

Nano-liposomes or nano-liposomal vehicles are molecules composed of a double membrane of phospholipids organized in a lipid bilayer: the polar ends are in the center, trapping a small volume of the aqueous phase, while the apolar tails are arranged outward and interact with the lipophilic ends of the external phospholipids, which position their polar heads outward. This creates a molecule capable of storing both lipophilic and hydrophilic compounds [14,84].

The encapsulation efficiency (EE) of nano-liposomes is higher than those with exclusively hydrophilic properties because the encapsulated substances remain firmly bound to the lipophilic tails [37]. Among the bioactive materials successfully encapsulated are genetic material, proteins, DNA, peptides, vaccines, enzymes, as well as anticancer, antimicrobial, antioxidant, antihemolytic, and anti-inflammatory agents [17]

Recent nano-liposome research has focused on adding them to foods to enhance and fortify the products properties for consumption. Factors determining a successful encapsulation and specific

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prolonged release include encapsulation efficiency, process yield, prolonged release factor, particle size and Z potential [17].

On the other hand, consumption of antioxidants and natural products is one of the most addressed issues today, as the population is becoming more health conscious. However, it's not just about consumption but the absorption of molecules that provide antioxidants to their biological activity. Beyond protecting pigments from enzymatic and acidic degradation in the digestive system, nano-liposomes aim to ensure the arrival and subsequent release of pigments into the intestine, where the absorption process occurs [34].

One of the current problems in society is people's concern regarding the consumption of functional foods. Due to the current high rates of development of chronic-degenerative diseases such as leukemia, blindness, osteoarthritis, diabetes, cardio-cerebrovascular diseases, and various types of cancer [53], research in food has chosen to explore the encapsulation of biocompounds with antioxidant, anti-inflammatory, antimicrobial, antihemolytic, medicinal and analgesic properties in vesicles formed by phospholipids (nano-liposomes).

Therefore, the objective of this review is to compile compounds with antioxidant, anti-inflammatory, antihemolytic, or photoprotective properties suitable for nano-encapsulation in liposomes, its application in foods and impact on health, as well as to provide a perspective on unexplored areas and future prospects for extracts of different sources.

2. Nano-Liposomes

2.1. Structure and Properties of Nano-Liposomes

In the field of nanotechnology, studies of structures such as nanoemulsions, microemulsions, lipid nanoparticles, biopolymeric nanoparticles, and finally, liposomes, can be found. These studies have focused primarily on using them as encapsulation and prolonged release systems of bioactive compounds, usually used in functional foods [85].

Liposomes are nano or micrometer sized structures (20 nm – 100 μm) whose structural organization is based on the interaction between phospholipids arranged in bilayers or multilayers. Phospholipids, composed of a polar head and a nonpolar tail, are arranged in such a way in an aqueous medium that they form a core where hydrophilic compounds can be encapsulated (aqueous center). Additionally, the nonpolar tails interact with the nonpolar tails of other phospholipids, forming an intermediate layer in which lipophilic compounds can be encapsulated (lipophilic interspace). Finally, the polar heads of the outer phospholipids complete the spherical structure [14,84] (Figure 1).

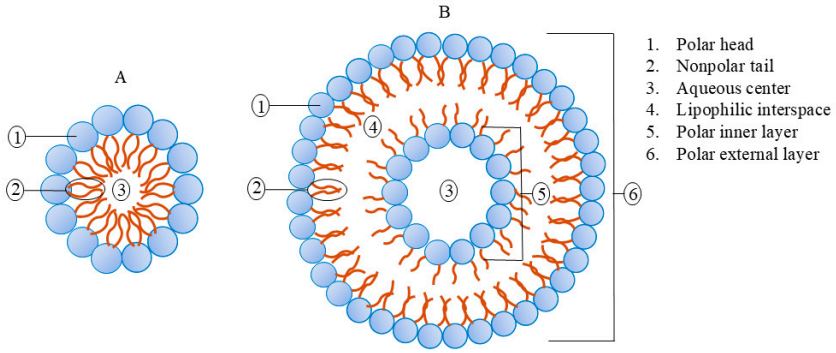

Figure 1. Comparative scheme between a micelle (A) and a nano-liposome (B).

The head determines the surface charge of the liposome (neutral, cationic or anionic) and is generally composed of choline, phosphate and glycerol. On the other hand, the hydrophobic tail is made up of one or two fatty acid chains of 14 - 18 carbons [59]. Phospholipids can be of natural origin

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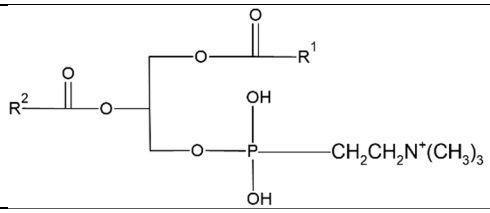
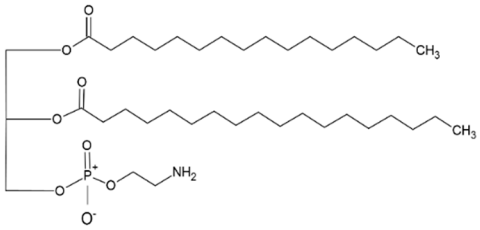
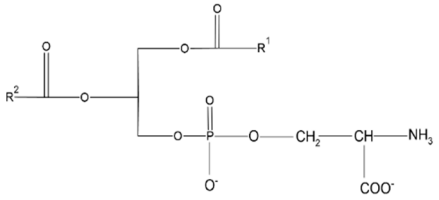
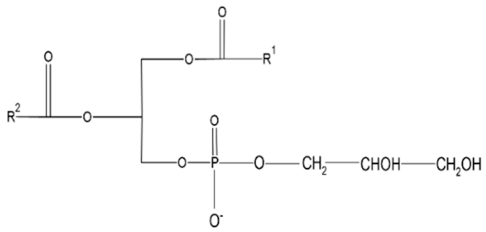
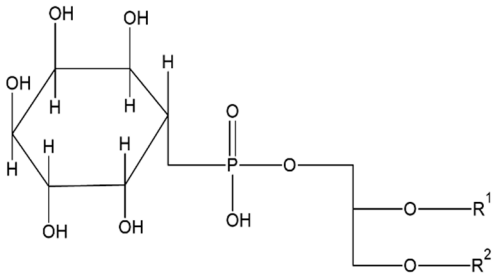
(commonly obtained from soy or egg yolk) or synthetic. The most used phospholipids in liposome preparation are shown in Table 1. In addition to phospholipids, liposomes may also contain sterols, with cholesterol being the most common. Cholesterol provides physical and biological stability as it can modify the viscosity or rigidity of the bilayer while reducing its permeability in the presence of biological fluids such as blood. In the absence of cholesterol, the bilayer could experience rupture [45,61].

Table 1. Most used phospholipids in liposome formation.

Natural	Synthetic	Chemical Structure	Function	Reference
Phosphatidylcholine (PC)	Dimyristoylphosphatidylcholine (DMPC)		Increase membranes fluidity and eicosanoid production	[44]
Phosphatidylethanolamine (PE)	Dioleoylphosphatidylcholine (DOPC)		PC precursor, promotes membrane fusion, oxidative phosphorylation and mitochondrial biogenesis	[16]
Phosphatidylserine (PS)	Distearoylphosphatidylcholine (DSPC)		PE decarboxylation, autophagosomes formation, morphology regulation and dynamics and functions of mitochondria	[94]
Phosphatidyl-glycerol (PG)	Dipalmitolphosphatidylglycerol (DPPG)		Important role in apoptosis and blood clotting, besides serving as a conduit for the transfer of lipids between organelles	[46]
Phosphatidylinositol (PI)	Distearoylphosphatidylglycerol (DSPG)		Regulates traffic to and from Golgi apparatus and helps protect against hepatic viruses	[13]

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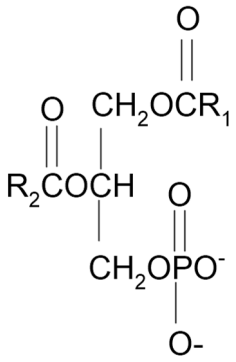
Phosphatidic acid (PA)		Serve as a fusogenic lipid, altering membrane structure and promoting membrane fusion, especially in neurons	[69]

2.2. Biological Activity of the Encapsulated Compounds

Encapsulated biocompounds can preserve their structure and properties due to the protection of the liposome. This is why this encapsulation process and subsequent addition to foods is considered very effective, both for treating chronic-degenerative diseases and for clinical cases.

Carotenoids are colored natural pigments belonging to a large family of C_{40} skeleton with eight isoprene molecules. They are classified into xanthophylls and carotenes with the former such as lutein, β-cryptoxanthin and astaxanthin containing one or more oxygen atoms, while the latter such as α- carotene and β-carotene, lycopene and phytoene consisting of hydrogen and carbon atoms [88]. Carotenoid-rich foods have received great attention in human health due to their physiological functions such as antioxidant and anti-cancer as well as the ability to prevent chronic diseases such as age-associated macular degeneration and cardiovascular disease [28,77]. It has been well demonstrated that the functional properties of carotenoids were associated with their chemical structure i.e., the number of conjugated double bonds and the presence of different kinds of end-groups. However, these structural properties are also responsible for the carotenoid's instability to light, high temperature, oxygen and metal ions, resulting in high susceptibility to oxidation and low bioavailability [28]. Given the multiple health benefits of carotenoids, they are widely used as a natural colorant and antioxidant in both pharmaceutical and food industries to prolong shelf-life in dairy, meat, confectionary, and beverage products. However, carotenoids may undergo loss in functional properties during food processing owing to their instability and interaction with other food ingredients. Also, the presence of digestive enzymes and some other nutrients *in vivo* as well as pH can alter carotenoid stability [77].

Astaxanthin (AST) is a kind of carotenoid natural pigment that has been widely found in plants, crustaceans shells, flamingos feathers, and microorganisms. Due to its various biological activities, AST has been suggested as an important compound in biochemical research and has great application potential in cosmetics, human nutritional health products, as well as medicines. Unfortunately, the poor water solubility, chemical instability, and low oral bioavailability make challenging to apply AST in food systems. Besides, the amount of natural AST is limited, and how to extract and utilize AST efficiently is in great demand [2]. AST is a non-vitamin A derived ketone lipid soluble carotene [104], which presents a red-orange color and widely exists in many crustacean animals such as shrimp and crab. It is also the highest level product of carotenoid oxygen-containing derivatives [52]. The molecular structure of natural AST contains C=C double chain conjugated olefin structure. The specificity of this structure supplies it an ability to extinguish reactive oxygen species and scavenge free radicals effectively.

As a member of the liposoluble carotenoid family, the special structure of AST may cause the following disadvantages regarding application properties. (1) Hydrophobicity: as a lipophilic substance, AST has a very poor solubility in non-polar solvents. Since there are two hydroxyl groups at each end of AST, and each of them links one hydroxyl group that may interact with fatty acids to form esters. Esterified AST has a stronger hydrophobicity than free AST [28]. (2) Instability: The AST monomers are extremely unstable because of the structures of unsaturated conjugated double bonds. During processing and storage, they are easily degraded and fade under changes in light,

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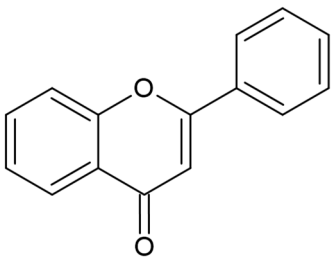
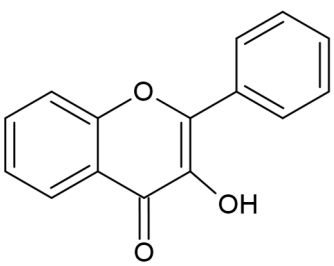
temperature, and oxygen content, resulting in further loss of their original biological activity and leading to poor quality and color of final products [104]. The above properties of AST may restrict AST application. To avoid shortcomings and increase the processing adaptability of AST in the food industry, delivery system designing is an effective way in terms of increasing its dispersibility and stability.

Besides, not only do carotenoids have the capacity to improve human health, other biocompounds gives great benefits to human health, such as phenols, alkaloids, and nitrogen and organosulfur compounds. Phenolic compounds are considered secondary metabolites with a wide variety of structures produced by plants. Structurally, phenolic compounds present a benzene ring (C6) with one or more hydroxyl (-OH) group(s), including other functional substituents (glycosides, methyl ethers or esters, etc.) [92].

There are two metabolic pathways through which phenols can be produced in plants: the shikimic acid and the acetic acid pathways. The first produces polyphenols, and the second produces simple phenols. Combining these two pathways produce flavonoids, the most plentiful group of phenolic compounds in plants [74]. Phenolic compounds can be classified in various ways because they consist of various heterogeneous structures, ranging from simple structures to highly polymerized compounds. Based on this, they have been classified into three categories: shortly distributed (e.g., phenols, pyrocatechol, and hydroquinone), widely distributed (e.g., flavonoids and their derivatives, coumarins and phenolic acids), and polymers (e.g., tannin and lignin) [15].

According to their chemical structure, they can also be classified as: soluble (e.g., phenol, flavonoids, and low or medium molecular weight tannins) and insoluble (e.g., condensed tannins and phenolic acids). The first group is not bound to cell membrane compounds, while the second group is bound to cell wall polysaccharides or proteins. This classification is of great importance from a nutritional perspective because the digestion, absorption, and utilization of these compounds largely depend on their solubility. The main interest in phenolic compounds lies in their antioxidant activity, which is associated with beneficial health effects and the prevention of certain diseases. Additionally, they are also used therapeutically for their pharmacological properties. This property entirely depends on the chemical structure, as it may or may not have double bonds or molecules with resonance capacity. Among the phenolic compounds with known high antioxidant activity are flavonoids and tannins [15]. Table 2 presents the structures of the main flavonoids with antioxidant activity.

Table 2. Chemical structures of the principal classes of flavonoids.

Flavonoid	Structure
Flavones	
Flavonols	

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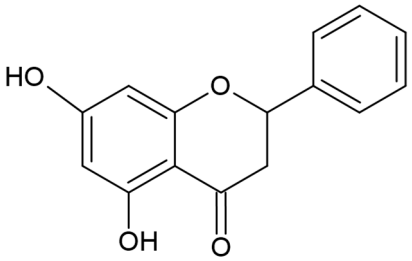
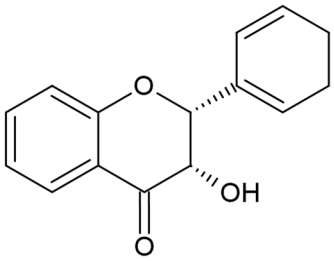
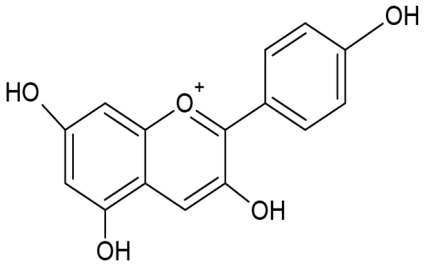
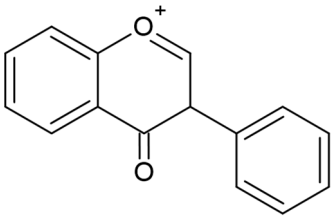
Flavanones	
Flavanols	
Anthocyanidins	
Isoflavones	

It has been determined that the high antioxidant capacity of flavonoids is due to their structural configuration, mainly the presence of the hydroxyl group (-OH) in the 3' and 4' positions of the B ring (intermediate), which also confers stability to the compound when it is transformed into a radical by electron donation. This activity is enhanced by the position of the double bonds present in the 2 and 3 carbons of the C ring, together with the carbonyl group in the 4th position, which allows for the movement of the electron between the benzene rings [47].

On the other hand, tannins can be classified into two major groups: hydrolysable tannins and non-hydrolysable tannins, or proanthocyanidins. Hydrolysable tannins have a glucose center or a polyhydric alcohol partially or completely esterified with gallic acid or hexahydroxydiphenic acid, forming gallotannins and ellagitannins, respectively [47].

Proanthocyanidins are polymers of catechins and/or leucoanthocyanidins that are not hydrolysable by acid treatment and are responsible for the astringent properties of plants. They are called proanthocyanidins because of their ability to transform into anthocyanidins. Although the antioxidant capacity of tannins has not been extensively exploited in the food industry, it is known that their activity depends on the degree of polymerization of their chemical structures [71]. Figure 2 shows the structure of a hydrolysable tannin and a non-hydrolysable tannin.

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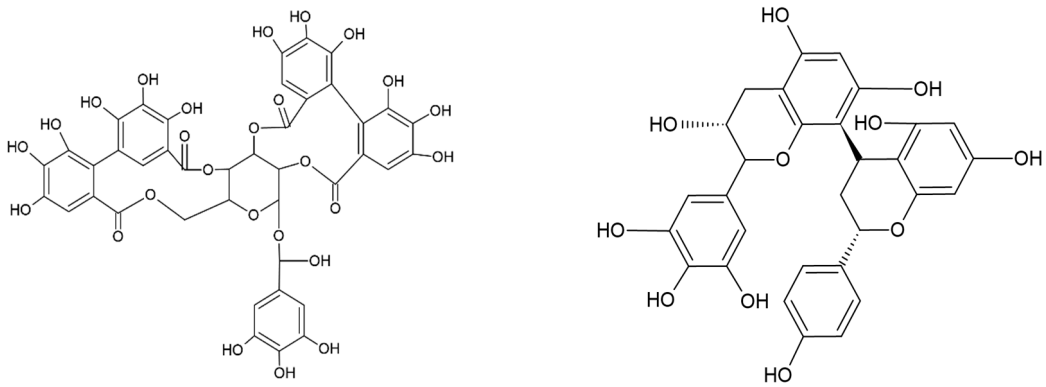


Figure 2. Chemical structures of a hydrolysable tannin (**A**) and a non-hydrolysable or proanthocyanidin tannin (**B**).

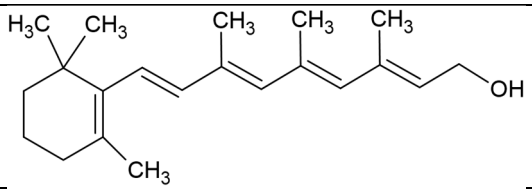
2.3. Bioactive Compounds Encapsulated in Nano-Liposomes

The food industry focuses on the use of liposomes for the encapsulation of bioactive compounds, primarily individual molecules such as retinol, retinoic acid, and retinol ester by retinoids [21,23], as well as carotenoids such as α-carotene, β-carotene, γ-carotene, astaxanthin, violaxanthin, zeaxanthin, and β-cryptoxanthin [24,26,66,76,91]. Phenols have been successfully encapsulated, including gallic acid, protocatechuic acid, caffeic acid, p-coumaric acid and salicylic acid [54,92]. Finally, among the most studied vitamins for encapsulation are A, B, C, D, E and K [27,42,89]. Generally, the compounds mentioned above have biological activity of the antioxidant type. The chemical structures and the type of nanoliposomes in which they were encapsulated are provided in Table 3.

The biological activity of compounds encapsulated in liposomes may not be altered. For example, the astaxanthin's antioxidant capacity with alpha-tocopherol does not change after they are encapsulated in liposomes. However, it should be noted that nano-liposomes can produce a controlled release of their contents. This leads to different kinetics of the original compound in transport throughout the body. Compounds encapsulated in liposomes must be endocytosed to be transferred inside the cell [43], implying that transport across biological membranes will be subject to this process. This could contrast with the transport of the unencapsulated compound, which may be different (simple diffusion, facilitated diffusion, active transport) and will depend on its physicochemical properties and the biological mechanisms available for that compound.

Almost all the techniques involve the dissolution of phospholipids in an organic solvent followed by the removal of the organic solvent, later in the process. This prior dissolution followed by removal of organic solvent is important for forming of liposomes. The building blocks of liposomes are phospholipids and/or cholesterol. The critical micelle concentration of most used phospholipids is in the nano molar range and the concentration of phospholipids used for liposomes manufacturing is much above the critical micelle concentration. This along with the three-dimensional cylinder like shape of each phospholipid leads to formation of liposomes along with lipid aggregates when phospholipids, as such, are exposed to an aqueous environment.

Table 3. Main antioxidant biocompounds encapsulated in nano-liposomes and their chemical structure.

Retinoids			
Name	**Chemical structure**	**Type of nano-liposome**	**Reference**
Retinol		Lecithin-cholesterol structure, small unilamellar (20-200 nm), retinol contained	[1,68]

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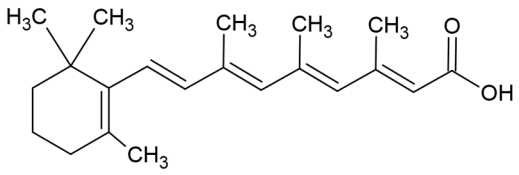
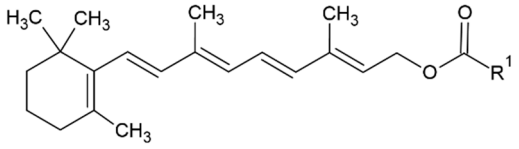
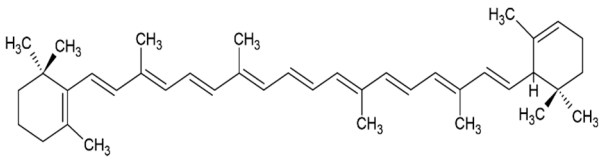
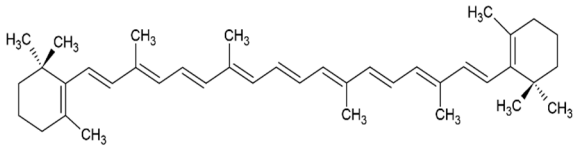
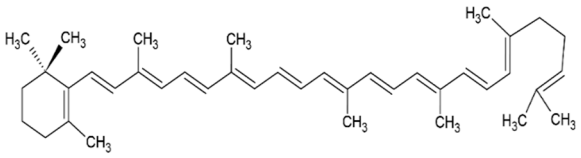
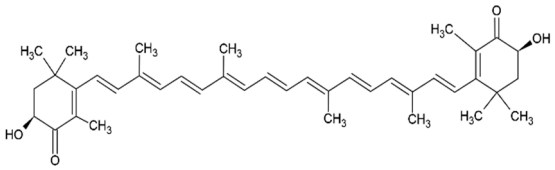
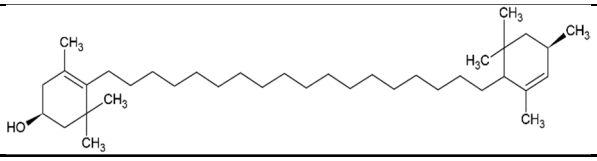
		in the lipid intermembrane section	
Retinoic acid		Lecithin-cholesterol structure, small unilamellar (20-200 nm), retinoic acid contained in the lipid intermembrane section	[1,68]
Retinyl ester		Lecithin-cholesterol structure, small unilamellar (20-200 nm), retinyl ester contained in the lipid intermembrane section	[1,68]
Carotenoids			
Name	**Chemical structure**	**Type of nano-liposome**	**Reference**
α-carotene		Lecithin, cholesterol and polysorbate 80 structure, giant unilamellar size (> 1 μm), α -carotene contained in the lipid intermembrane section	[1,51]
β-carotene		Lecithin, cholesterol and polysorbate 80 structure, giant unilamellar size (> 1 μm), β-carotene contained in the lipid intermembrane section	[1,51]
γ-carotene		Soy, egg or marine lecithin and cholesterol structure, giant unilamellar size (> 1 μm), γ -carotene contained in the lipid intermembrane section	[1,75]
Astaxanthin		Agarose oligosaccharides, phosphatidylcholine, phosphatidyl galactose and/or phosphatidyl neoagarobiose structure, small unilamellar (20-200 nm), astaxanthin contained in the lipid intermembrane section	[28,96]
Lutein		Supercritical carbon-dioxide method, small unilamellar size (20-200	[103]

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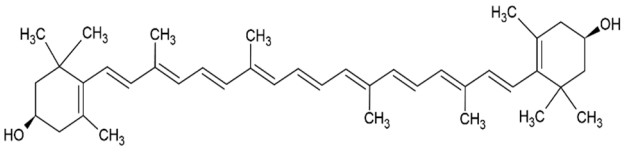
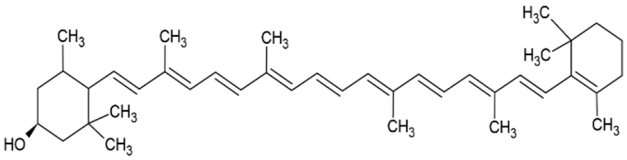
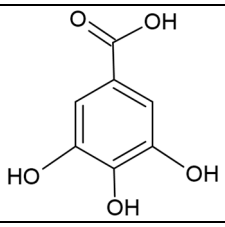
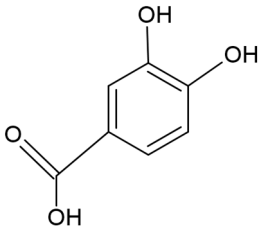
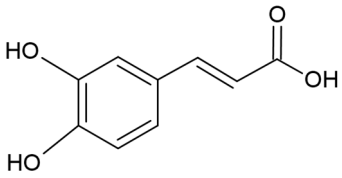
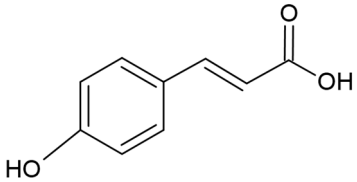
		nm), lutein contained in the aqueous center	
Zeaxanthin		Lecithin, cholesterol and polysorbate 80 structure, giant unilamellar size (> 1 μm), zeaxanthin contained in the lipid intermembrane section	[28,50]
β-criptoxanthin		Cholesterol and phosphatidylcholine structure, small unilamellar (20-200 nm), β-cryptoxanthin contained in the aqueous center	[26]
Phenols			
Name	**Chemical structure**	**Type of nano-liposome**	**Reference**
Gallic acid		Soy lecithin and cholesterol structure, small unilamellar size (20-200 nm), gallic acid contained in the aqueous center	[101]
Protocatechuic acid		Egg yolk phosphatidylcholine and cholesterol structure, small unilamellar size (20-200 nm), protocatechuic acid contained in the aqueous center	[58,65]
Caffeic acid		Egg yolk phosphatidylcholine and cholesterol structure, small unilamellar size (20-200 nm), protocatechuic acid contained in the aqueous center	[58,65]
p-cumaric acid		Soy lecithin and cholesterol structure, small unilamellar size (20-200 nm), *p*-coumaric acid contained in the aqueous center	[50]

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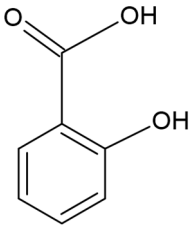
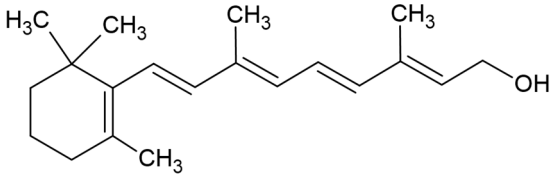
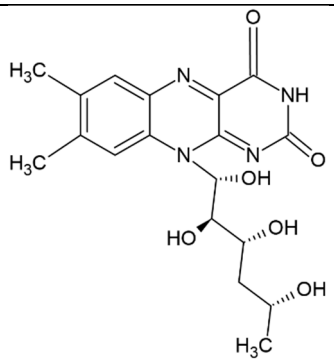
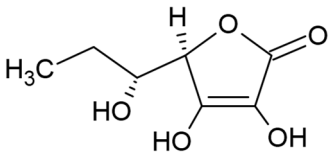
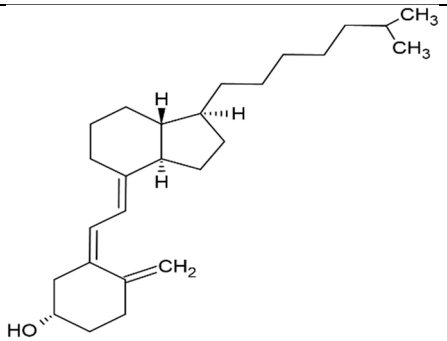
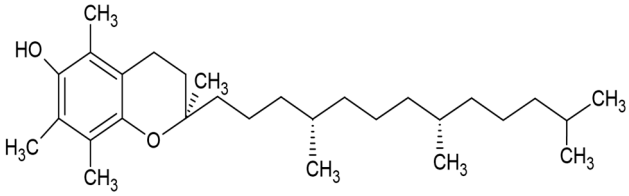
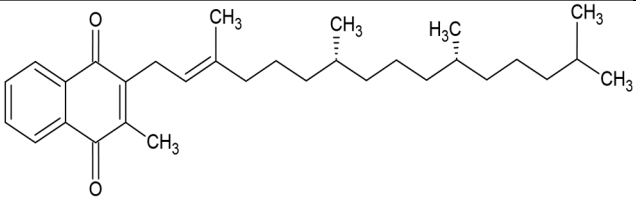
Salicylic acid		Soy lecithin and cholesterol structure, small unilamellar size (20-200 nm), *p*-coumaric acid contained in the lipid intermembrane section	[8]
Vitamins			
Name	**Chemical structure**	**Type of nano-liposome**	**Reference**
Vitamin A		Lecithin and cholesterol structure, small unilamellar size (20-200 nm), vitamin A contained in the lipid intermembrane section	[1,68]
Vitamin B2		Vegetable oil (chia, sunflower and virgin olive) structure, giant unilamellar size (> 1μm), vitamin B2 contained in the lipid intermembrane section	[1,22]
Vitamin C		Phosphatidylcholine, stearic acid and stearic calcium structure, giant unilamellar (> 1μm), vitamin C contained in the aqueous center	[1,37]
Vitamin D3		Soy phosphatidylcholine and cholesterol structure, giant unilamellar size (> 1μm), vitamin D3 contained in the lipid intermembrane section	[1,19]
Vitamin E		Phosphatidylcholine, stearic acid and stearic calcium structure, giant unilamellar (> 1μm), vitamin E contained in the aqueous center	[1,37]
Vitamin K		Phosphatidylcholine and cholesterol structure, giant unilamellar size (> 1μm), vitamin K	[1,40]

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				contained in the lipid intermembrane section		

To make uniform liposomal dispersions, it is important to make thin lipid sheets before exposing them to an aqueous phase or introducing the organic phospholipid solution in a controlled manner in an aqueous environment for the formation of liposomes. This is why all the reported techniques of liposome manufacturing, i.e. solvent evaporation, solvent dispersion/antisolvent addition, or detergent removal, focus on first disaggregating the phospholipids into individual phospholipid molecules followed by exposure to aqueous environment to enable formation of different types of liposomes [3,83].

Thus, transforming from microencapsulation to nanoencapsulation plays a pivotal role in reducing particles to nanosize by employing either top-down or bottom-up methods [60]. Recent advancements in the field of nanoscience and nanotechnology have enabled the preparation of nanoscale functional compounds by encapsulating into a wide variety of nanostructures, including nanoemulsions (NEs), nanoliposomes (NLs), nanocapsules (NCs), nanofibers (NFs), nanoparticles (NPs), solid lipid nanoparticles (SLNPs), nanostructured lipid carriers (NLCs) and supercritical fluid-based nanoparticles [73].

Due to the increasing prevalence rate of chronic diseases, the emerging challenges in delivering functional compounds to target tissues, organs and cells, as well as instability, poor aqueous solubility and bioavailability, and low release and absorption in vivo could not be overcome by microencapsulation techniques. Recent developments in the field of nanotechnology have provided some excellent means to reduce particle size through top-down (high energy method) or bottom-up (self-assembly) processes [70]. Such reduction in particle size has been shown to enhance the stability, targeting ability, bioavailability, and release properties [99]. Most importantly, the reduction in particle size enables penetration into deeper portions of cells or tissues, resulting in high bioavailability [86].

Research studies published within the last five years on nanoencapsulation of various carotenoid compounds mention that it can be done by using different preparation techniques. These studies demonstrated the impact of nanoencapsulation to improve physicochemical property, bioavailability, controlled release and bioactivity. Table 4 and Table 5 summarize various nanosystems used for encapsulation of carotenoids and highlight their advantages as well as disadvantages, respectively.

Table 4. Nanosystems for encapsulation of carotenoids. Obtained and edited from [73].

Nanosystem	Carotenoids	Particle Size (nm)	EE (%)	Zeta Potential (mV)	Storage Stability (Days)	References
Nanoemulsions	β-carotene	218	NA	40	21 at 37 °C	[6]
		143.7		−38.2	30 at 25 °C	
	Microbial carotenoids	142.1		NA	30 at 25 °C	[55]
	Carotenoids	290 to 350		−53.4 to −58.8	21 at 25 °C	[31]
	β-carotene	198.4 to 315.6		−29.9 to −38.5	90 at 4, 25, and 37 °C	[12]
	Carotenoids	<200		−30 to −45	35 at 25 °C	[87]
	Lycopene	145.1 to 161.9		−19.7 to −20.7	1 at 25 °C	[48]
		200.1 to 287.1	61 to 89.1	20 to 45	42 at 4, 25, and 37 °C	[102]
Polymeric/biopolymeric NPs	Carotenoids	153	83.7	NA	NA	[67]

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		84.4	>96	−41.3 to −43.6	60 at 41 °C	[9]
	β-carotene	77.8 to 371.8	98.7 to 99.1	−37.8 to −29.9	NA	[98]
	β-carotene	70.4	97.4	NA	NA	[76]
	Lycopene	152	89	58.3	NA	[49]
		~ 200	>95	−36	210 at 5 °C	[95]
		193	NA	−11.5	14 at 25 °C	[25]
	Lutein	<250	74.5	−27.2	NA	[11]
	Lutein	240 to 340	~91.9	NA	NA	[36]
	Crocetin	288 to 584	59.6 to 97.2	NA	NA	[35]
	Fucoxanthin	200 to 500	47 to 90	30 to 50	6 at 37 °C	[72]
Nanoliposomes/liposomes	Carotenoids	70 to100	75	−5.3	NA	[90]
	β-carotene	162.8 to 365.8	~98	64.5 to 42.6	70 at 4 °C	[38]
	Astaxanthin	80.6	97.6	31.8	15 at 4 and 25 °C	[63]
		60 to 80	97.4	NA	NA	[64]
	Lutein	264.8 to 367.1	91.8 to 92.9	−34.3 to −27.9	NA	[41]
SLNPs and NLCs	β-carotene SLNPs	200 to 400	53.4 to 68.3	−6.1 to −9.3	90 at 5, 25, and 40 °C	[39]
		<220	NA	20 to 30	10 at 25 °C	[56]
		120	NA	−30	56 at 25 °C	
	Lycopene SLNPs	125 to 166	86.6 to 98.4	NA	60 at 4 °C	[57]
	Lycopene NLCs	157 to 166	> 99	−74.2 to −74.6	120 at 4, 30, and 40 °C	[60]
		121.9	84.50	−29	90 at 25 °C	[85]
Supercritical fluid-based NPs	Astaxanthin	150 to 175	NA	NA	NA	[43]
		266	84	NA	NA	[93]
Metal/metal oxide-based NPs and hybrid nanocomposites	Carotenoids	20 to 140	NA	NA	NA	[7]
	Lycopene	3 to 5		−48.5	90 at 4 and 25 °C	[20]
		20.8		−25.3	NA	[82]

[1] EE = encapsulation efficiency, NPs = nanoparticles, SLNPs = solid lipid nanoparticles, NA = data not available and NLCs = nanostructured lipid carriers.

Table 5. The advantages and disadvantages of nanosystems for encapsulation of carotenoids. Obtained and edited from [73].

Nanosystem	Advantages	Disadvantages	References
Nanoemulsions	• High optical clarity and enhanced physical stability • Small-sized particles with improved bioavailability and absorption	• Use of large surfactant and co-surfactant • Low storage and chemical stability • Limited solubility for high melting substances	[24,88]

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	• Increased solubility of lipophilic compounds • Rapid and efficient penetration of the compound • Energy efficient method	• Bio-toxicity of the carrier	
Polymeric/biopolymeric NPs	• High stability and EE • Easy biodegradability and high bioavailability • Controlled release, drug targeting and the enhanced cellular uptake • Low cost	• Irritation after administration • Low storage stability	[24,28]
Nanoliposomes/liposomes	• Less toxicity Increased stability, efficiency and pharmacokinetic effects	• Low solubility, short half-life and low EE • Difficult to control size of liposomes • Less reproducibility • High cost ingredients • Poor resistance to gastrointestinal enzymes and at low pH	[24,73]
SLNPs	• High possibility to encapsulate lipophilic and hydrophilic compounds • No use of organic solvents • Easy scale-up process • High membrane permeability of liposomes and the ability of biopolymer NPs for controlled release • High bioactive absorption and easy biodegradability • Lack of biotoxicity	• Low EE and stability • Presence of others colloidal structures • Polymorphic transitions may result in expulsion of bioactive compounds • Conformational modification of the lipid NPs	[24,73,88]
NLCs	• High EE and stability • Controlled release • Simple preparation methods with controlled particle size	• Cytotoxic effect • Irritation and sensitizing action of surfactants	[24,88]

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	• High possibility for scale-up		
Supercritical fluid-based NPs	• Scalable, green, nontoxic and economical • Good particle size with controlled particle morphology • High production yield and EE • Homogeneous drug distribution • Reduced isomerization and thermal degradation of heat labile compounds • Solvent can be easily eliminated from food matrix • Minimizes harmful chemical residues • Low-temperature operation • Produces solvent-free and homogenous products • Single-step processing method	• Poor solubility of solutes in SCF CO_2 • Size of particles cannot be controlled	[18,73,88]
Metal/metal oxide-based NPs and hybrid nanocomposites	• No toxic solvent required • Great plasma absorption • Target site delivery • High surface area • Cost-effective • High uniformity in shape, size and branch length	• Particles instability • Toxic, carcinogenic and cause irritation • Less reproducibility of the processes • Low possibility for scale-up	[80,81]

[1] EE = encapsulation efficiency, NPs = nanoparticles, SLNPs = solid lipid nanoparticles and NLCs = nanostructured lipid carriers.

2.4. Nano-Liposomes Enhanced Foods and Human Health

In recent years, the food industry has played a prominent role in developing functional foods, which provide health benefits beyond the essential nutritional value inherent in the food. These foods contain bioactive components, either chemical compounds naturally present in the food or formed and added during processing, which can exert specific biochemical and physiological functions when consumed by humans [10]. For example, certain lipids in milk have recognized biological properties; among them, conjugated linoleic acid (CLA) can be mentioned. It is a generic term used to describe the mixture of positional and geometric isomers of linoleic acid (C18:2 9c12c) with conjugated double bonds. In recent years, they have gained considerable attention as it is believed that some of these isomers (C18:2 9c, 11t and C18:2 10t, 12c) have beneficial biological effects (reduction of body fat content and increase in muscle mass, stimulation of the immune system, among others) [5].

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The deterioration of CLA, especially through oxidation, leads to a decrease in its concentration, loss of bioactivity, and the appearance of unwanted molecules that negatively impact the nutritional and sensory quality of the food. An approach to achieve dairy products enriched in this bioactive compound with good characteristics, without the indicated adverse effects, is the addition of CLA protected by encapsulation, which constitutes a promising alternative. Among encapsulation methods, a very innovative strategy to protect pharmaceutical or food compounds is that of liposomes [5].

In previous study, [100] evaluated the impact of adding a lyophilized powder of liposomes with conjugated linoleic acid (NL-CLA) during yogurt production. They prepared yogurts with CLA in liposomes and control yogurts without CLA. They determined the stability of the fatty acid during storage (21 days at 4°C) and the parameters: pH, acidity, syneresis, microbiological counts (total lactic acid bacteria, molds, and yeasts, total aerobic mesophilic germs), dry residue, fat, and protein content using standardized techniques. Additionally, they observed the microstructure of the yogurts. Adding nano-liposomal vehicles loaded with CLA did not modify the fermentation time; at the end of maturation, the pH and acidity (°D) values remained within appropriate ranges for all yogurts: 4.3-4.4 and 96-99, respectively. The lactic acid bacteria count of the starter reached 10^9 CFU/g, and no contaminating microorganisms were detected. The total solids, protein, and fat contents showed typical values. At the end of storage, yogurts with liposomes exhibited lower syneresis than the controls.

These results correlated with microstructure observations, showing a modification in the protein matrix. The CLA content increased successfully in yogurts with the addition of the liposomal ingredient, as the basal amount of CLA tripled. Thus, the feasibility of applying an ingredient rich in bioactive lipids in the yogurt food matrix was verified.

With the aforementioned information and based on various studies, it can be confirmed that the addition of liposomes to food improves its characteristics and antioxidant properties. All of this is due to the minimal or no modification of the basic structures and the prolonged release of the compounds encapsulated in the liposomes.

The introduction of nano-liposomes enhanced food has sparked great intrigue in society, as they are believed to improve human health, whether through antioxidant, antihemolytic, antimicrobial, anti-inflammatory, photoprotective, and/or anticancer activity and their prolonged liberation property. Innovative encapsulation techniques are currently applied to protect the structure and function of food compounds as well as nutraceutical properties, and to improve their bioavailability. Nano-vehicles or nano-carriers offer the food processor several advantages by ensuring against nutritional loss, incorporating time-release mechanisms into the formulation [100].

[95] in their study, implies that regarding the development and application of nano-liposomes in food technology and food industries, it is considerably less compared to the pharmaceutical and cosmetic industries. However, it is speculated that the greatest advantages will be seen in the agriculture and dairy industries. The limited development is due to the challenges involved in finding safe, low-cost methods for production in the shortest possible time to produce liposomes on a large scale.

Studies to date indicate that the potential of nano-liposomes in food lies in their ability to enhance flavor or in accelerated maturation techniques (e.g., cheese maturation), prolonged and targeted release, the synergistic activity of different encapsulated antioxidant biocompounds and the stabilization of minerals, such as calcium and iron in dairy products [100]. The ability of nanoliposomes to provide targeted delivery of the encapsulated material in specific areas of the food system is highly beneficial for the dairy industry. For example, the employment of proteinase enzymes encapsulated in the lipid vesicles can significantly reduce the time and cost of cheese ripening.

Besides the previous statement, cheese can be improved in their nutritional properties by the addition of vitamin C, D and E, not necessarily in coencapsulation, although it can interact with each other once released. These vitamins has many properties, including: helping protect cells from

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damage caused by free radicals, collagen formation (necessary for the formation of this protein used to produce skin, tendons, ligaments and blood vessels), strengthening the immune system by helping to keep the immune system strong and reduce the chances of getting sick, regeneration of vitamin E, body calcium absorption (a mineral essential for the formation of strong bones), reduces the risk of cancer, cardiovascular disease, depression and autoimmune diseases [4,97].

Otherwise, minerals can also be encapsulated in nanocarriers, with the aim of avoiding principally iron deficiency, that causes the risk of developing anemia. This condition is mainly due to insufficiency in dietary intake of iron, lack of its bioavailability or both. Iron shortage in blood should not be ignored as it may cause anemia, when the blood hemoglobin level falls below standard levels, a disease that, if not threatened, can evolve to leukemia [32].

Hence, it is necessary to enrich dairy products with iron evading fat oxidation and metallic off-flavor. To achieve this, supplementation of dairy products with iron encapsulated in safe and non-toxic carriers has been developed. Towards this end, highly soluble form of iron (i.e., ferrous sulfate) is preferred due to its cost effectiveness and high bioavailability [100]. Another example of a mineral is magnesium. It is an essential mineral compound, which is associated with lowering the risk of some clinical disorders including cardiovascular disease, hypertension, type 2 diabetes and muscular weakness [33].

3. Conclusions

Nano-liposomes offer significant advantages by protecting encapsulated compounds from degradation by environmental and enzymatic factors, enabling controlled and targeted release in the body. Furthermore, their structural versatility allows for the encapsulation of both hydrophilic and lipophilic compounds, broadening the range of applications in the food, nutraceutical, and pharmaceutical industries. However, challenges remain related to optimizing encapsulation efficiency, storage stability, and site-specific release, aspects that must be addressed for their large-scale implementation. The use of various types of phospholipids increases the range of compounds that can be encapsulated, making this not only an innovative application but also one with a trend of expansion into various scientific fields such as healthcare, food industries, cosmetics, and pharmaceuticals.

4. Prospects

Prospects for the development and application of nanoliposomes in the field of antioxidants are promising. Research on the encapsulation of complex extracts rich in pigments and polyphenols is anticipated, as is the integration of smart release technologies that respond to specific physiological stimuli. Furthermore, the trend toward functional and personalized foods will drive innovation in nanoencapsulation systems tailored to different health needs and population groups. Long-term clinical and safety studies will be essential, as will the development of clear regulations for their use in food and nutraceutical products. Finally, interdisciplinary collaboration between food scientists, chemists, biotechnologists, and healthcare professionals will be key to translating these technological advances into tangible benefits for public health.

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