Carotenoids

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nanoencapsulation carotenoid in vitro release antioxidant activity

1. Introduction

Carotenoids are colored natural pigments belonging to a large family of C_{40} skeleton with eight isoprene molecules [1]. 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 [2]. 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 [3][4]. 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 [3].

Given the multiple health benefits of carotenoids, they are widely used as a natural colorant and antioxidant in both pharmaceutical and food industries for prolonging shelf-life in dairy, meat, confectionary and beverage products [2]. 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 [4]. Consequently, it is vital to develop novel techniques to prevent carotenoid degradation for enhancement of bioavailability and bioactivity. Over the past decade, micro- and/or nano-encapsulation have emerged as imperative techniques for formulating food-based carotenoid carriers with improved physicochemical property and release behavior, as well as for prolonging blood circulation and efficient cellular uptake [2][5]. Comparatively, the microencapsulation technique fails to produce nanoparticles that are capable of penetrating into deeper portions of specific organs and tissues, resulting in poor bioavailability and bioactivity in vivo [6][7]. Thus, the transformation from microencapsulation to nanoencapsulation plays a pivotal role in reducing particles to nanosize by employing either top-down or bottom-up methods [8].

Recent advancements in the field of nanoscience and nanotechnology have enabled 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 [4][5][9]. Based on the bibliometric search conducted in the Web of Science database (version 5.34) using keywords such as carotenoid nanoemulsion, carotenoid nanoparticle, carotenoid nanoencapsulation, carotenoid nanoliposome, carotenoid liposome, carotenoid micelle and carotenoid dispersion, the number of articles published from 2015-2020 was 441, of which the publications from 2019–2020 was higher (229) in terms of publication rate compared to that published between 2015–2018 (212). This trend is in line with the previous bibliometric studies [10][11]. Moreover, of the top 10 countries listed on research publications in carotenoid nanoencapsulation (2015–2020), China showed the highest publication output (23.7%) followed by USA (16.3%), Brazil (14.5%), Iran (14.5%), India (13.6%), while the other five countries including Saudi Arabia, Romania, Turkey, Pakistan and Italy, accounting for 17.4%, with an overall contribution from Asia, Europe and Americas being 60, 20 and 20%, respectively (Figure 1). Further analysis on difference in research characteristics among the top five highly-contributed countries during 2015–2020 showed that China (30) dominated with studies related to preparation and stability evaluation of nanocarotenoids, followed by Iran (20), India (19), USA (17) and Brazil (13). Likewise, most nanocarotenoid studies dealing with in vitro gastrointestinal release and bioavailability were from China (20), followed by USA (19), Iran (18), India (12) and Brazil (10). Many studies have also focused on fortification of nanoencpasulated carotenoids in a wide range of functional foods in dairy, bakery, and confectionary industries over last five years, with the top five countries accounting for 2.8–9.3% of total nanocarotenoid publications. For in vivo studies, although there was less publications by top 5 countries (5–22), a significant research output is apparent. Notably, China remained on the top with 22 publications dealing with determination of bioavailability and bioaccessibility, followed by USA (14), Iran/India (10 each) and Brazil (5). This highlights the need for many in vivo studies for proof-of-concept, functional validation, utility and clinical relevance of nanocarotenoids, which can be attained through promoting collaborative researches among institutes and countries for translation of nanocarotenoids into a botanic drug.

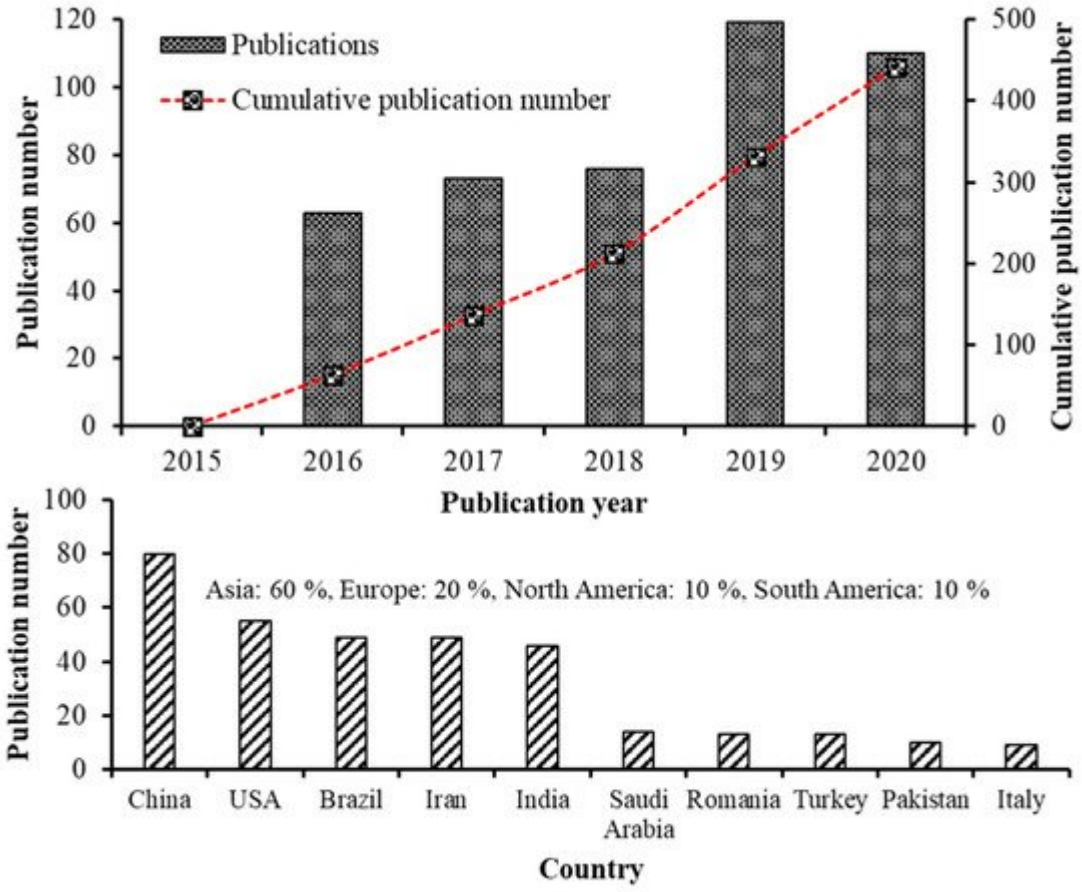

Figure 1. Research on carotenoid nanoemulsions over the last 5 years. The number of publications and global distribution. Source: Web of Science™.

Reported studies on nanocarotenoids were mainly dealing with formulation of nanosized carotenoid carriers by nanotechniques, characterization and stability evaluation as well as determination of in vitro release behavior, bioaccessibility, bioavailability and biological activity [5].

2. Carotenoid Biosynthesis and Stability-Overview

Carotenoids, a class of isoprenoids, are formed by the C_5 building units of isopentenyl diphosphate and dimethylallyl diphosphate, obtained separately by two different pathways including the mevalonate (MVA) and the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathways [12]. The isopentenyl diphosphate undergoes isomerization to yield dimethylallyl diphosphate, which further condenses with another molecule of isopentenyl diphosphate to yield C_{20} geranylgeranyl pyrophosphate. Then the two molecules of geranylgeranyl pyrophosphate combine with each other to yield the first carotenoid molecule phytoene (C_{40}) and sequential incorporation of double bonds at alternate positions of phytoene, resulting in formation of phytofluene, ζ-carotene, neurosporene and lycopene (Figure 2) [13]. Through branched cyclization of lycopene, carotenoids with one β-ring and one ε-ring (e.g., α-carotene and lutein) and two β-rings (β-carotene, zeaxanthin and antheraxanthin) are produced. Further advancement of carotenoid

synthesis occurred through attachment of oxygen moieties to hydrocarbon carotenoids such as α-carotene and β-carotene for formation of xanthophylls (Figure 2) [13].

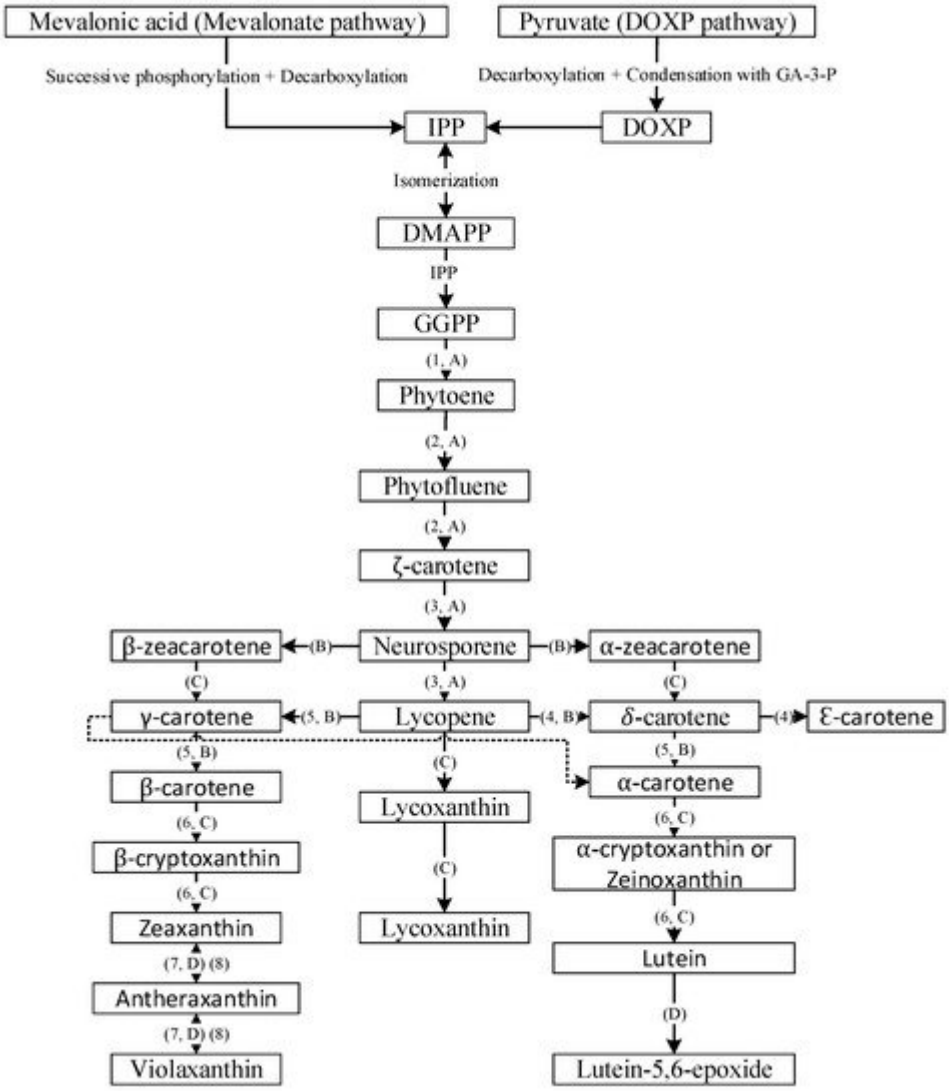

Figure 2. General overview of carotenoid biosynthesis pathway. DOXP = 1-deoxy-D-xylulose, GA-3-P = glyceraldehyde 3-phosphate, IPP = isopentyl diphosphate, DMAPP = dimethylallyl diphosphate and GGPP = geranylgeranyl pyrophosphate; 1 = phytoene synthase, 2 = phytoene desaturase, 3 = ζ-carotene desaturase, 4 = lycopene e-cyclase, 5 = lycopene β-cyclase; 6 = β-carotene hydroxylase, 7 = zeaxanthin epoxidase and 8 = violaxanthin de-epoxidase; A = desaturation, B = cyclization, C = hydroxylation and D = epoxidation.

The presence of long-chain conjugated double bonds in carotenoids makes them highly susceptible to degradation under acid, light and high temperature conditions [3]. For instance, carotenoids were shown to degrade at a faster rate in the presence of light through generation of singlet oxygen that eventually binds with the hydrocarbon chain in carotenoids leading to degradation [14]. More recently, two theories have been proposed for oxidative degradation of carotenoids, namely random and central cleavage theories, with oxidation occurring randomly at different sites or at the central bond of a carotenoid molecule, respectively [15]. In a study dealing with thermal degradation of lutein and β-carotene, Giménez, et al. [16] reported a progressive increase in degradation following a

rise in heating temperature from 30–90 °C. Also, β-carotene could undergo degradation to form epoxides and carbonyl compounds (apocarotenals) via a free radical reduction mechanism [13]. Thus, owing to the instability of carotenoids caused by multiple factors, it is important to develop appropriate strategies for preventing degradation, prolonging shelf-life and enhancing bioavailability of carotenoids.

3. Conventional Microencapsulation vs. Nanoencapsulation

Microencapsulation of unstable and water-insoluble bioactive compounds such as carotenoids involves trapping them within a special coating material for preparation of micron-sized particles with a mean size ranging from 1 to 500 μm. Micronized spherical particles are capable of controlling both loading and releasing of bioactive compounds [17]. The conventional microencapsulation process can be broadly classified into three categories depending on how microparticles are prepared including chemical, physicochemical and physicomechanical processes [18][19]. For example, Polyakov and Kispert [20] reviewed a carotenoid inclusion complex (e.g., β-carotene enriched inclusion complex) with polysaccharides including arabinogalactan, cyclodextrin and glycyrrhizin, and demonstrated increased stability and bioavailability compared to free carotenoids, while García, et al. [21] reported an enhanced thermal stability (up to 100 °C) of spherical microcapsules produced from carotenoid-rich mango, banana and tamarillo powders by spray-drying with maltodextrin. Likewise, several studies have demonstrated the ability of microencapsulated carotenoids to improve physicochemical characteristics, storage stability and bioavailability for further development into value-added functional foods [22][23][24][25][26]. Several microencapsulation techniques used for enhancement of carotenoid stability and bioavailability have been reviewed by Soukoulis and Bohn [2].

Although the microencapsulation techniques are efficient, the recent clean labelling trends have prevented the use of dairy, lactose, sugar, sodium, gluten, fats and carbohydrate as coating material, thus further limiting the choice of suitable encapsulation materials [27]. In addition, the most commonly used encapsulant maltodextrin possesses low emulsifying ability thereby reducing the encapsulation efficiency (EE) [28]. More recently, Sun, et al. [6] pointed out that the average size of microcapsules is a critical parameter which can significantly affect the physicochemical characteristics, stability, sensory property, bioavailability and release behavior. Also, micron-sized particles have many drawbacks such as nontargeting of specific organs, tissues and cells as well as instability, poor aqueous solubility and low bioavailability in human body [7]. Therefore, it is necessary to decrease the size of encapsulated material to sub-micron (0.10–10 μm) and nano size (<0.10 μm).

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 [7]. 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 [29]. Such reduction in particle size has been shown to enhance the stability, targeting ability, bioavailability and release properties [30]. Most importantly, the reduction in particle size enables penetration into deeper portions of cells or tissues resulting in high bioavailability [31]. In the following sections, we have reviewed the research articles published within the last five

years on nanoencapsulation of various carotenoid compounds by using different preparation techniques. These studies demonstrated the impact of nanoencapsulation to improve physicochemical property, bioavailability, controlled release and bioactivity. Table 1 and Table 2 summarize various nanosystems used for encapsulation of carotenoids and highlight their advantages as well as disadvantages, respectively.

Table 1. Nanosystems for encapsulation of carotenoids [1].

Nanosystem	Carotenoids	Particle Size (nm)	EE (%)	Zeta Potential (mV)	Storage Stability (Days)	References
Nanoemulsions	β-carotene	218	NA	40	21 at 37 °C	[32]
		143.7		−38.2	30 at 25 °C	[33]
	Microbial carotenoids	142.1		NA	30 at 25 °C	[34]
	Carotenoids	290 to 350		−53.4 to −58.8	21 at 25 °C	[35]
	β-carotene	198.4 to 315.6		−29.9 to −38.5	90 at 4, 25, and 37 °C	[36]
	Carotenoids	<200		−30 to −45	35 at 25 °C	[37]
	Lycopene	145.1 to 161.9		−19.7 to −20.7	1 at 25 °C	[38]
		200.1 to 287.1	61 to 89.1	20 to 45	42 at 4, 25, and 37 °C	[39]
Polymeric/biopolymeric NPs	Carotenoids	153	83.7	NA	NA	[40]
		84.4	>96	−41.3 to −43.6	60 at 41 °C	[41]
	β-carotene	77.8 to 371.8	98.7 to 99.1	−37.8 to −29.9	NA	[42]
	β-carotene	70.4	97.4	NA	NA	[43]
	Lycopene	152	89	58.3	NA	[44]

Nanosystem	Carotenoids	Particle Size (nm)	EE (%)	Zeta Potential (mV)	Storage Stability (Days)	References
		~ 200	>95	−36	210 at 5 °C	[45]
		193	NA	−11.5	14 at 25 °C	[46]
	Lutein	<250	74.5	−27.2	NA	[47]
	Lutein	240 to 340	~91.9	NA	NA	[48]
	Crocetin	288 to 584	59.6 to 97.2	NA	NA	[49]
	Fucoxanthin	200 to 500	47 to 90	30 to 50	6 at 37 °C	[50]
Nanoliposomes/liposomes	Carotenoids	70 to100	75	−5.3	NA	[51]
	β-carotene	162.8 to 365.8	~98	64.5 to 42.6	70 at 4 °C	[52]
	Astaxanthin	80.6	97.6	31.8	15 at 4 and 25 °C	[53]
		60 to 80	97.4	NA	NA	[54]
	Lutein	264.8 to 367.1	91.8 to 92.9	−34.3 to −27.9	NA	[55]
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	[56]
		<220	NA	20 to 30	10 at 25 °C	[57]
		120	NA	−30	56 at 25 °C	[58]
	Lycopene SLNPs	125 to 166	86.6 to 98.4	NA	60 at 4 °C	[59]
	Lycopene NLCs	157 to 166	> 99	−74.2 to −74.6	120 at 4, 30, and	[8]

Nanosystem	Carotenoids	Particle Size (nm)	EE (%)	Zeta Potential (mV)	Storage Stability (Days)	References
1					40 °C	available
		121.9	84.50	−29	90 at 25 °C	[60]
Supercritical fluid-based NPs	Astaxanthin	150 to	NA	NA	NA	[61]

Table 2. The advantages and disadvantages of different nanosystems for carotenoids.

Nanosystem	Advantages and Disadvantages	References
Nanoemulsions	**Advantages** • High optical clarity and enhanced physical stability • Small-sized particles with improved bioavailability and absorption • Increased solubility of lipophilic compounds • Rapid and efficient penetration of the compound • Energy efficient method **Disadvantages** • Use of large surfactant and co-surfactant • Low storage and chemical stability • Limited solubility for high melting substances • Bio-toxicity of the carrier	[2][5]
Polymeric/biopolymeric NPs	**Advantages** • High stability and EE • Easy biodegradability and high bioavailability • Controlled release, drug targeting and the enhanced cellular uptake	[3][5]

Nanosystem	Advantages and Disadvantages	References
	• Low cost **Disadvantages** • Irritation after administration • Low storage stability	
Nanoliposomes/liposomes	**Advantages** • Less toxicity Increased stability, efficiency and pharmacokinetic effects **Disadvantages** • 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	[5][9]
SLNPs	**Advantages** • 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	[2][5][9]

Nanosystem	Advantages and Disadvantages	References
	• High bioactive absorption and easy biodegradability • Lack of biotoxicity **Disadvantages** • Low EE and stability • Presence of others colloidal structures • Polymorphic transitions may result in expulsion of bioactive compounds • Conformational modification of the lipid NPs	
NLCs	**Advantages** • High EE and stability • Controlled release • Simple preparation methods with controlled particle size • High possibility for scale-up **Disadvantages** • Cytotoxic effect • Irritation and sensitizing action of surfactants	[2][5]
Supercritical fluid-based NPs	**Advantages** • Scalable, green, nontoxic and economical • Good particle size with controlled particle morphology	[2][9][66]

Nanosystem	Advantages and Disadvantages	References
	• 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 **Disadvantages** • Poor solubility of solutes in SCF CO_2 • Size of particles cannot be controlled	
Metal/metal oxide-based NPs and hybrid nanocomposites	**Advantages** • No toxic solvent required • Great plasma absorption • Target site delivery • High surface area • Cost-effective • High uniformity in shape, size and branch length **Disadvantages** • Particles instability	[67][68]

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Nanosystem	Advantages and Disadvantages	References
	• Toxic, carcinogenic and cause irritation • Less reproducibility of the processes • Low possibility for scale-up	

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

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