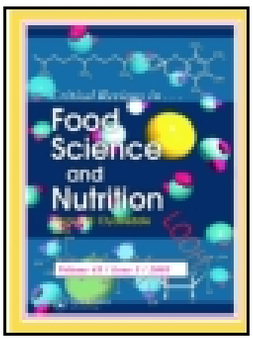

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REVIEW

Improving the cancer prevention/treatment role of carotenoids through various nano-delivery systems

Mahboobeh Zare[a], Zahra Norouzi Roshan[b], Elham Assadpour[c], and Seid Mahdi Jafari[c]

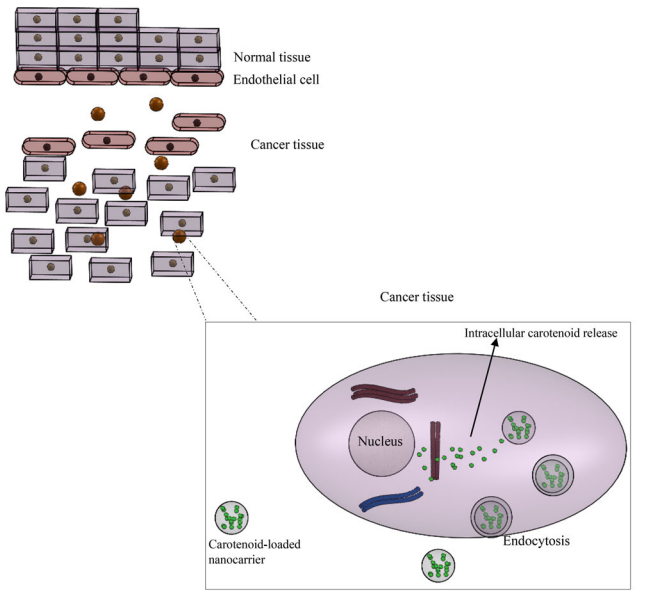
[a]Faculty of Medicinal Plants, Department of Basic and Science, Amol University of Special Modern Technologies, Amol, Iran; [b]Department of Biotechnology, Amol University of Special Modern Technologies, Amol, Iran; [c]Department of Food Materials and Process Design Engineering, Gorgan University of Agricultural Sciences and Natural Resources, Gorgan, Iran

ABSTRACT

One of the emerging and recent strategies to combat cancer is application of natural bioactive compounds and phytochemicals. Carotenoids including lycopene, β-carotene, astaxanthin, crocin, β-cryptoxanthin, and lutein, are the main group of plant pigments which play important roles in the prevention and healing process of different diseases including cancer. The pharmacological use of carotenoid compounds is frequently limited by their low bioavailability and solubility as they are mainly lipophilic compounds. The present study focuses on the current data on formulation of different carotenoid nanodelivery systems for cancer therapy and a brief overview of the obtained results. Encapsulation of carotenoids within different nanocarriers is a remarkable approach and innovative strategy for the improvement of health-promoting features and particularly, cancer prevention/treatment roles of these compounds through enhancing their solubility, cellular uptake, membrane permeation, bioaccessibility, and stability. There is various nanocarrier for loading carotenoids including polymeric/biopolymeric, lipid-based, inorganic, and hybrid nanocarriers. Almost in all relevant studies, these nano delivery systems have shown promising results in improving the efficiency of carotenoids in cancer therapy.

KEYWORDS

Cancer; carotenoids; encapsulation; nanocarriers; nano-delivery systems



Schematic illustration of carotenoid-loaded nanocarriers which can respond to tumor intracellular for controlled release of therapeutic agents.

CONTACT Seid Mahdi Jafari smjafari@gau.ac.ir Department of Food Materials and Process Design Engineering, Gorgan University of Agricultural Sciences and Natural Resources, Gorgan, Iran.

Introduction

Despite the remarkable technological progresses in diagnosis and treatment of neoplastic diseases in the past few decades, cancer happens to be one of the major causes of mortality around the world (Cassady, Baird, and Chang 1990; Miller et al. 2016). This disease harms different organs and occurs in various tissue levels. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018 (World Health Organization [WHO] 2020). Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women (WHO 2020; Miller et al. 2016). Also, blood cancer is the most common type of cancer in children (Lee and Ham 2010; Schottenfeld and Fraumeni 2006). So that is why cancer is considered a serious disease which affects the health of all human societies. Due to different types of cancer, its diagnosis and efficient treatment face lots of difficulties (Fisher, Pusztai, and Swanton 2013; Meacham and Morrison 2013). In general, this disease is the consequence of several changes in cell division, invasion and spread control processes. Although the exact biological fact of cancerous growth is not well-understood, current studies mention some cellular pathways which modify the multistage growth process of normal cells which convert them into malignant cells during the person's lifespan (White et al. 2013). Cancer is caused by both environmental factors (90–95%); e.g. lifestyle parameters like poor nutrition, food habits of having carbonated beverages, junk food, excess alcohol consumption and smoking, and genetic mechanisms (5–10%; Anand et al. 2008; Trichopoulos, Li, and Hunter 1996).

Lifestyle behaviors can prevent primary cancers; another means to prevent the growth of cancerous tumors is chemoprevention method. Cancer chemoprevention strategy is a fast-growing discipline concentrating on the discovery and implementation of natural, synthetic, or biologic chemical agents which can block, delay, or reverse the carcinogenesis before invasion (Benetou, Lagiou, and Lagiou 2015; Tanaka 1997a). On the other hand, there is no universal cancer treatment because of its heterogeneous nature; but four different general approaches including chemotherapy, radiotherapy, immunotherapy, and surgery have been applied either alone or in combination (Buyel 2018). Surgery and radiation are considered as local treatment procedures of cancer. According to the documents, surgery can leave scar marks, moreover, radiation is harmful to the living cells. Administration of intravenous cytotoxic drugs into the blood stream, is typically known as chemotherapy (Estanqueiro et al. 2015), which is coupled with surgery/radiotherapy. Although chemotherapy is a commonplace method of cancer treatment, adverse reactions, drug resistance and non-target activity of some drugs are some drawbacks for this method. Thus, the interest in developing novel drugs has increased to solve the mentioned problems.

Recently, the use of natural compounds has been the focus of many cancer researches due to their relatively non-toxic behavior and pleiotropic effects. Different biologically active phytochemicals such as dietary fibers, fatty acids, phenolics and carotenoids, can be applied to develop cutting-edge chemoprevention and/or chemotherapy methods. Also, these compounds can be used as complementary agents for conventional treatments like chemotherapy and radiotherapy (Arora and Jaglan 2016; Chang, Sheen, and Lei 2015; Fisher, Pusztai, and Swanton 2013; Meacham and Morrison 2013; Meybodi et al. 2017; Rao 2003; Tanaka 1997b; White et al. 2013). Carotenoids as bioactive phytochemicals are being studied regarding their anticancer properties (Jain et al. 2015), but their bioactivity is limited owing to the low solubility level, poor stability against oxidative degradation during storage and lower oral bioavailability (Faulks and Southon 2005). These problems can be solved by nanoencapsulation which guarantees the safe passage of carotenoids along the gastrointestinal tract (GIT) along with their sustained release and the intended delivery site (Assadpour and Jafari 2019; Rafiee et al. 2019a; Focsan, Polyakov, and Kispert 2019; Soukoulis and Bohn 2018; Polyakov and Kispert 2015). Further, encapsulation of carotenoids within nanocarriers enhances their solubility, shelf life, proper delivery at the intended site and physicochemical stability along with reduced toxicity (Koshani and Jafari 2019; Rezaei, Fathi, and Jafari 2019). Also, nanocarriers are capable of modulating the pharmacodynamic/pharmacokinetic profiles of carotenoids, as shown in Figure 1 (Rajendran et al. 2011; Rostamabadi, Falsafi, and Jafari 2019a).

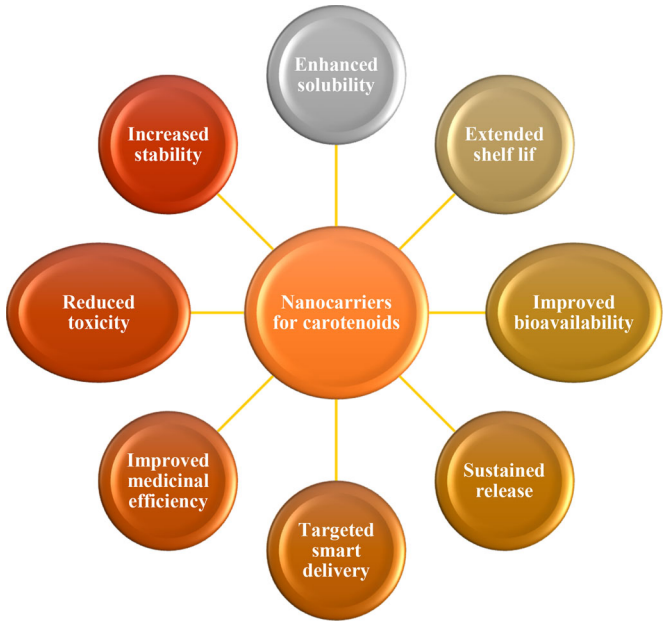


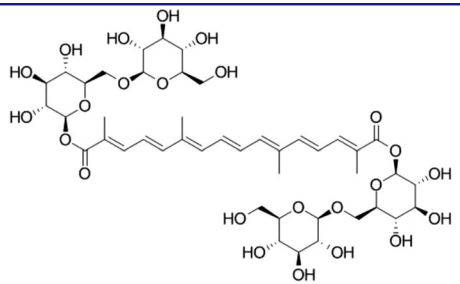
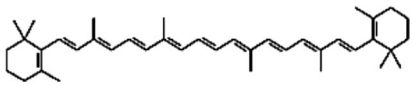
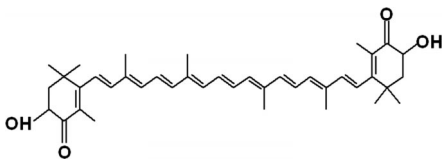
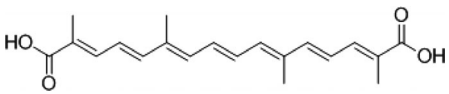
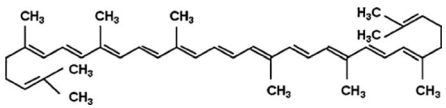
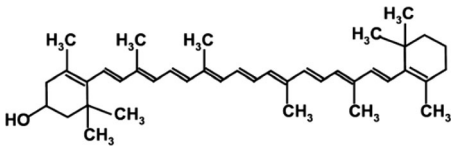
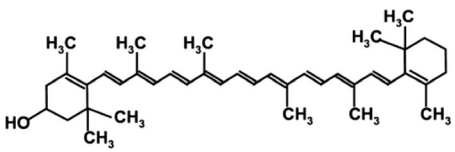
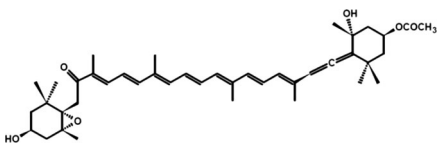
Figure 1. Various advantages of nanocarriers for carotenoid delivery.

In this revision, we present for the first time the usage of different nanovehicles for improving the performance of carotenoids in cancer chemotreatment and chemoprevention.

Carotenoids in cancer chemoprevention and treatment

Carotenoids are categorized in isoprenoid polyenes according to their chemical structure which are lipid-soluble,

Table 1. The structure and effects of some studied carotenoids against various cancers.

Carotenoid type	Chemical structure	Cancer target	Results	Reference
Crocin		Breast cancer	Inhibiting the proliferation and induction of apoptosis	(Hoshyar et al. 2016)
β-Carotene		Breast cancer	Decrease in breast cancer risk	(Aune et al. 2012)
Astaxanthin		Breast cancer	Reduced proliferation rates and inhibited breast cancer cell migration	(McCall et al. 2018)
Crocetin		Colorectal cancer	Reduced proliferation rates	(Gutheil et al. 2012)
Lycopene		Prostate cancer	Reduced risk of prostate cancer	(Chen et al. 2015)
β-Cryptoxanthin		Laryngeal cancer	Reduction in the risk of cancer	(Leoncini et al. 2015)
Lutein		Breast cancer	Inhibiting the growth of breast cancer cells through increased cell type-specific ROS generation	(Gong et al. 2018)
Fucoxanthin		Colon cancer	Inducing apoptosis and enhancing the antiproliferative effects and inhibiting the growth of human colon cancer cells	(Yonekura et al. 2010)

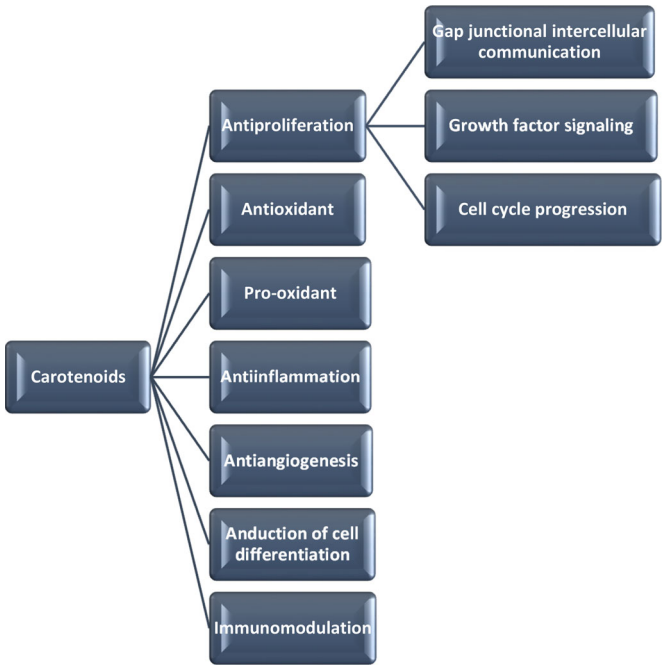


Figure 2. Proposed mechanisms of carotenoids to suppress carcinogenesis.

yellowish-orange pigments and biosynthesized by algae, bacteria, fungi, and plants (Armstrong and Hearst 1996; Tanaka, Shnimizu, and Moriwaki 2012). These compounds are classified in two major groups: (i) carotenes, such as β-carotene (BC) and lycopene (LYC) which contain hydrogen and carbon and could be cyclic or linear; (ii) oxycarotenoids (xanthophylls), for instance, xanthophylls and lutein (LUT) which contain hydrogen, carbon, and oxygen (Prakash and Gupta 2014). On the other hand, carotenoids may be categorized in provitamin A compounds, such as β-carotene and β-cryptoxanthin (BCR) and non-provitamin A compounds, e.g. lycopene and lutein (Milani et al. 2017; Toti et al. 2018). The beneficial features of fruits and vegetables can be referred to carotenoids which help our body in preventing various diseases like cardiovascular, cancer and other chronic diseases. The antioxidant properties of carotenoids is also another important feature (Paiva and Russell 1999). Carotenoids might be used for quenching process of free radicals in addition to reactive oxygen species (ROS) and for quenching singlet oxygen. The bioactive properties of these compounds are attributed to their structures (Prakash and Gupta 2014). The polyene chain in carotenoids possesses several conjugated double bonds, which makes them ideal candidates to scavenge free radicals (Bakan, Akbulut, and İnanç 2014).

Carotenoids have been found to be efficient compounds for the chemoprevention and treatment of different diseases due to their nontoxic nature. Table 1 highlights the anticancer attributes of carotenoids.

Carotenoids have a high efficiency in preventing and treating cancer, and their anticarcinogenic mechanisms are different (Lupulescu 1994). Several studies suggested that carotenoids may induce their anticancer features via various means like antioxidant and pro-oxidant effects, anti-inflammation, anti-angiogenesis, immunomodulation, triggering cell differentiation and anti-proliferation (growth factor signaling and cell cycle development), as displayed in Figure 2 (Johary, Jain, and Misra 2012; Milani et al. 2017; Olson and Krinsky 1995; Sharoni et al. 2004; Tanaka, Shnimizu, and Moriwaki 2012)

Carotenoids are considered as health-promoting compounds with respect to their antioxidant properties. Major carotenoids, such as β-carotene, β-cryptoxanthin, and lycopene have been extensively assessed for their chemopreventive ability to prevent cancer due to antioxidant properties via quenchers of ROS, peroxyl radicals and inducing the phase II enzymes such as heme oxygenase-1, NAD(P)H: quinone oxidoreductase, glutathione S-transferases, and glutamate-cysteine ligases (Bhuvaneswari et al. 2001; Burton and Ingold 1984; Devasagayam et al. 1992; Di Mascio, Kaiser, and Sies 1989; Tanaka, Shnimizu, and Moriwaki 2012). In addition, carotenoids may serve as pro-oxidants to propagate free radical-induced reactions (Polyakov et al. 2001). These molecules can induce oxidative stresses, depending on their structure, concentration, orientation in cell membranes, oxygen tension, cell redox state, and interactions with other redox agents. Some findings suggest that β-carotene and crocetin in high doses may effectively enhance intracellular oxidative stresses by enhancing ROS generation rate in tumor cells; therefore, these carotenoids can induce cell cycle arrest and apoptosis thus damaging the tumor cells (Kim et al. 2014; Palozza et al. 2002, 2003).

Angiogenesis defined as the formation of new vessels emanated from the proliferation of endothelial cells into a formerly avascular tissue plays a vital role in tumor advancement and metastasis processes. Therefore, preventing the development of feeding blood vessels in cancer diseases is an efficient approach to control and or eradicate them. It has been shown that β-carotene has anti-angiogenic effects on male C57BL/6 mice and B16F-10 cells, which is helpful in preventing cancer (Guruvayoorappan and Kuttan 2007; Sathasivam and Ki 2018). Also, cancer cells have a poor differentiation; therefore, induction of them to differentiate into mature cells with diverse functions like normal cells are effective for chemoprevention. The differentiation effect was tested for lycopene, β-carotene, lutein, and saffron carotenoids, mainly crocin. Studies have shown that these carotenoids induce differentiation of promyelocytic leukemia (HL-60) cells (Tanaka, Shnimizu, and Moriwaki 2012; Yan and Liu 2016). Inflammation is closely related to cancer, suggesting that chronic inflammation portrays a high risk of cancer cell formation. Thus, removing inflammation is a valid means for cancer prevention and therapy. In this manner, suppression of inflammatory cytokine expression results in halting of carcinogenesis process. Studies have demonstrated that astaxanthin, lycopene and lutein have significant inhibitory effects on various cancer cells, possibly due to their anti-inflammatory activities (Gong et al. 2018; Rayburn, Ezell, and Zhang 2009; Tanaka, Shnimizu, and Moriwaki 2012). The immune system has an active role in the inhibition of cancer cell formation. There is no doubt that carotenoids can influence immune cell function of our

body. β-carotene as an immunomodulatory agent decreases the risk of some cancers by enhancing immune cell functions (Hughes 1999).

Accordingly, other mechanisms are introduced to highlight the anticancer performance of carotenoids, including regulation of cell proliferation. This mechanism could be related to gap junctional intercellular communication (GJIC), cell cycle development, and growth factor signaling. Gap junctions are channels between cells in which low molecular weight materials (e.g. nutrients or signaling agents) flow. Lack of GJIC may be correlated with malignant transformation. Non-provitamin A carotenoid such as lycopene can increase GJIC and are definitely practical anticarcinogenic agents in oral carcinogenesis (Stahl et al. 1997). Growth factors can be implicated as major cancer risk factors which are necessary for tumor development. For example, elevated blood levels of insulin growth factor (IGF)−1, existing years before cancer diagnosis, can be related to increased risk of various cancers including lung, prostate, and breast cancers (Tanaka, Shnimizu, and Moriwaki 2012). Phytonutrients such as tomato extract and lycopene lower cancer risk related to IGF by reduction of IGF-1 blood levels and or interference with IGF-1 function in cancerous cells (Tanaka, Shnimizu, and Moriwaki 2012). On the other hand, growth factors promote cell cycle progression. Lycopene inhibits IGF-I-stimulated cell cycle shift from G1 to S stage (Nahum et al. 2006). Many studies have shown that carotenoids role in reduction of cancer cell proliferation can result from stopping the advancement of cell cycle, causing cell death or both. The cell growth inhibition and apoptotic activity of carotenoids like crocin and lycopene have been observed in cancer cells (Kelkel et al. 2011; Kim et al. 2014).

In brief, carotenoids modulate the processes of cycle progression, growth factor signaling, and gap-junction performance via manipulating the expression of different involved proteins, such as cyclins, cyclin-dependent kinases, connexins, as well as their inhibitors. These aforementioned activities suggest that the original effect of carotenoids involves transcription mainly by certain transcription agents, including ligand-activated nuclear receptors (Sharoni et al. 2004).

Carotenoid-loaded nanocarriers for cancer therapy

Approximately 40% of new anticancer drugs are hydrophobic, which is an important problem for drug discovery programs. Nanocarriers have attracted the attention of the pharmaceutical sector for the improvement of lipophilic drug delivery complexes because of their fantastic biological and physicochemical properties (Rezaei, Varshosaz et al. 2019). Bioavailability of nanocarrier-based delivery of lipophilic drugs often increases as the size of the developed loaded-nanovehicles decreases. Several mechanisms have been postulated for this bioavailability enhancement such as targeting lymphoid tissues of gut, absorption by Peyer's patches, and circumvention of P-glycoprotein flowing out from intestinal epithelial cells (which has an active role in drug absorption and disposition; this glycoprotein is also famous as the multidrug resistance protein since it imparts considerably in the development of drug resistance), and improvement in the GIT solubility (Arora and Jaglan 2016; Estanqueiro, Amaral, and Lobo 2017; Jafari and McClements 2017).

Recently, a wide range of nano delivery systems such as polymeric/biopolymeric nanocarriers, lipid-based nanocarriers, inorganic nanocarriers and hybrid nanocarriers have been expanded in order to improve the cancer treatment and prevention efficacy of bioactives including carotenoids (Johary, Jain, and Misra 2012; Livny et al. 2002; Weber, Zimmer, and Pardeike 2014; Jain et al. 2018; Rafiee et al. 2019b). A brief overview of these nanocarriers has been provided in the upcoming sections.

Polymeric nanocarriers

Polymeric/biopolymeric nanovehicles (nanoparticles, nano-hydrogels, nanotubes, and nanofibers) originated from biodegradable and biocompatible materials are perfect candidates for applying programable and targeted delivery of carotenoids (Katouzian and Jafari 2019; Ravi et al. 2018; Rostami et al. 2019). Various biodegradable synthetic polymers and natural biopolymers have been applied for the synthesis of these nanocarriers for carotenoids delivery like poly-D, L lactide-co glycolide (PLGA), polyaniline (PAni), poly-L-lysine (PLL), poly(ethylene glycol) (PEG), arabinogalactan, chitosan (Cs), gelatin, albumin, zein, whey proteins, casein, starch, and so forth. These delivery systems induce a controlled release trend by surface modification owing to the presence of functional groups, pH-dependent controlled liberation, and so on (Abaee, Mohammadian, and Jafari 2017; Faridi Esfanjani and Jafari 2016; Focsan, Polyakov, and Kispert 2019; Rostamabadi, Falsafi, and Jafari 2019a).

Lipid-based nanocarriers

Various lipid-based nanocarriers (Figure 3) such as vesicular carriers (nanoliposomes and niosomes) and particulate carriers (solid lipid nanoparticles [SLNs] and nanostructured lipid carriers [NLCs]) have been employed to enhance the anticancer efficiency of carotenoids (Rostamabadi, Falsafi, and Jafari 2019b; Rehman et al. 2020). Vesicular carriers as the spherical bilayer structures are formed when surfactant agents interact with an aqueous medium. Lipid nanoparticles do not share the same characteristics as vesicles since they remain solid at room and body. SLNs are formed by a combination of solid lipids dispersed in internal phase while NLCs are constituted by the mixture of solid and liquid lipids in the cores (Chuang et al. 2018; Estanqueiro, Amaral, and Lobo 2017; Katouzian et al. 2017).

Liposomes usually consist naturally occurring phospholipids and cholesterol as a stabilizing agent, which are flexible, nontoxic and biocompatible (Ghorbanzade et al. 2017; Sarabandi et al. 2019). The surface of these carriers is capable of being modified with intended ligands (e.g. folic acid, sialic acid and aptamers). An important modification of liposomes is incorporation of PEG on the surface and

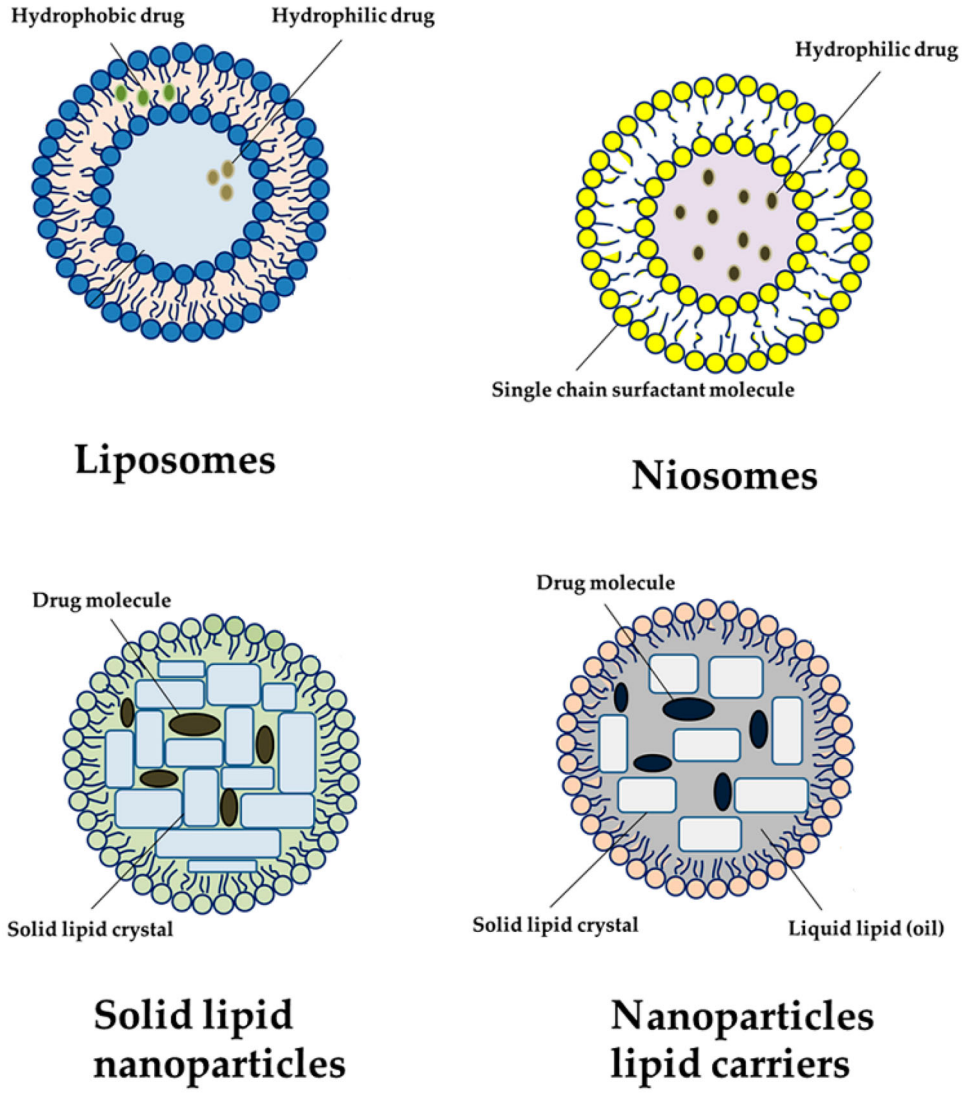


Figure 3. Simple scheme of different types of carotenoid-loaded lipid nanocarriers applied in cancer treatment. Reprinted with permission from Chuang, et al. (2018).

preparing long-circulatory nanostructures (Chuang et al. 2018; Sercombe et al. 2015; Zhao et al. 2015a, 2015b).

Niosomes are akin to liposomes in physical and structural terms, but instead of phospholipids they are composed of nonionic surfactants and cholesterol (Rafiee and Jafari 2018). These vesicles play a major role because of their nonionic properties and their advantages include immunological selectivity, nontoxic and high protection of carotenoids. Niosomes have the ability to inhibit P-glycoprotein by their nonionic properties (Chuang et al. 2018; Estanqueiro, Amaral, and Lobo 2017; Rajera et al. 2011).

Lipid nanoparticles are used for the sake of controlled release and targeted delivery; other advantages include low toxicity, no requirement for organic solvents, enhanced stability, high payload, improved bioavailability, and the possibility to scale-up (Estanqueiro, Amaral, and Lobo 2017). SLNs are commonly produced from lipids such as stearic acid, cholesterol, glyceryl monostearate and tristearin, dispersed in water or solutions composed of surfactants. SLNs can bypass P-glycoprotein via permeation through paracellular pathways (Saneja et al. 2014; Weber, Zimmer, and Pardeike 2014). NLCs are prepared from solid lipid matrix (esterified derivatives of glycerol and fatty acids such as beeswax, carnauba wax, Dynasan® 118, and stearic acid) mixed with liquid lipid or oil including fatty acid esters or alcohols such as 2-octyldodecanol (Iqbal et al. 2012; Li et al. 2017; Rizwanullah, Ahmad, and Amin 2016). The solid lipid network fixes the carotenoids and hinders the coalescence of particles, whereas liquid-oil droplets within the solid network can enhance the loading rate, allowing more carotenoids to be retained evenly and preventing surface diffusion of nanoparticles (Chuang et al. 2018). NLCs offer remarkable advantages such as the ability to bypass drug efflux as in multidrug resistance (MDR) tumor (because of the application of surfactants and emulsifiers), long circulation, and surface modification for targeting cancer chemotherapeutics (Rizwanullah, Ahmad, and Amin 2016).

Inorganic nanocarriers

Inorganic nanocarriers including gold nanoparticles (AuNPs), quantum dots, carbon nanotubes, and so forth

Table 2. Different carotenoid-loaded nanocarriers and their anticancer properties.

Carotenoid type	Nanocarrier	Clinical trials	Reference
Crocin	Gold nanoparticles (AuNPs)	Breast cancer	(Hoshyar et al. 2016)
	Polyethylene glycolated (PEG) nanoliposomes	Colon cancer	(Rastgoo et al. 2013)
	PEG functionalized selenium nanoparticles (PEG SeNPs)	Lung cancer	(Rastgoo et al. 2013)
β- Carotene	Zein nanoparticles	Breast cancer	(Bhuvaneswari et al. 2001)
	Lipid-polymeric hybrid nanoparticles	Breast cancer	(Kim et al. 2014)
	Colloidal carotene carbon nanoparticles	Melanoma and breast cancers	(Palozza et al. 2002)
Astaxanthin	AuNPs	Breast cancer	(Livny et al. 2002)
Crocetin	Poly-D,L lactide-co glycolide (PLGA) nanoparticles	Breast cancer	(Chuang et al. 2018)
Lycopene	Solid lipid nanoparticles (SLNs)	Breast cancer	(Rajera et al. 2011)
	Lipid carriers	Breast cancer	(Saneja et al. 2014)
	Nanogold nanoemulsions	Colon cancer	(Weber, Zimmer, and Pardeike 2014)
	Polyaniline nanofibers	Cervical cancer	(Li et al. 2017)
	Glass wool niosomes	Cervical and breast cancer	(Iqbal et al. 2012)
β-Cryptoxanthin	Nanoliposomes	Leukemia	(Alexis et al. 2010)
Lutein	Poly-L-lysine (PLL) decorated nanoliposomes	Colon carcinoma	(Jiao et al. 2018)
Fucoxanthin	Polymeric chitosan-glycolipid nanocarriers (polymeric hydrogels)	Colon cancer	(Ravi et al. 2018)

have been investigated for carotenoids delivery in cancer therapy (Johary, Jain, and Misra 2012; Livny et al. 2002; Weber, Zimmer, and Pardeike 2014). These nanoparticles are commonly employed in drug delivery considering their promising physiochemical attributes, such as shape, size, chemical structure, ability for surface functionalization, and higher surface to volume ratios (Ma et al. 2015). AuNPs are one of the most common nanocarriers extensively studied for bioactive delivery because of their low toxicity, simple development procedure and excellent biocompatibility; in particular, AuNPs have unique electric and optical properties which make them as promising nanocarriers of antitumor drugs in cancer therapy (Grigore 2017; Pugazhendhi et al. 2018; Zhao et al. 2015a, 2015b).

Hybrid nanocarriers

Lipid-polymer and organic-inorganic hybrid nanocarriers have been synthesized for cancer treatment (Burton and Ingold 1984; Kim et al. 2014; Palozza et al. 2002; Weber, Zimmer, and Pardeike 2014). They combine the advantages of existing systems with productive properties. These carriers are composed of minimum two different compounds to form the internal and external networks. In general, metallic materials and polymers construct the core phase which is then coated with single/multiple lipid layers that act as protection membranes (Alexis et al. 2010). The external layer in hybrid nanoparticles retards polymer degradation by restraining inward diffusion of water, thus facilitates slow and sustained release of loaded bioactives. Therefore, the outer lipid shield acts as a biocompatible coat and blockage restricting the prompt outflow of bioactive compounds. Lipid-polymer hybrid nanoparticles are safe, high-payload targeted, and effective delivery platforms for cancer therapy because of their programmed-release behavior, biodegradability, biocompatibility, and higher loading capability (Kim et al. 2014). On the other hand, the application of organic agents on the surface of inorganic nanocarriers are carried out to maximize the selectivity and efficiency of antitumor agents as well as lowering their toxicity (Burton and Ingold 1984; Ud Din et al. 2017).

In Table 2, the reported methods of preparing carotenoid-loaded nanocarriers and their anticancer applications have been presented.

Different nanoencapsulated carotenoids in cancer therapy

Crocin and crocetin

Crocin, one of the exceptional water-soluble carotenoids, is the main bioactive compound of saffron stigma (Rajabi et al. 2015; Sarfarazi et al. 2019). It suppresses oxidative stress in cells via its antioxidant activates (Pham et al. 2000). Hoshyar et al. (2016) applied crocin (as a reducing agent) for the green synthesis of AuNPs. In this experiment, the anticancer impact of crocin-AuNPs was assayed by MTT and LDL tests. Cellular data demonstrated that the proliferation of breast cancer cells was significantly reduced by crocin-AuNPs; so, these nanocarriers can improve the efficiency of crocin on cancer (Hoshyar et al. 2016). In another study, a solvent evaporation method plus extrusion was used to prepare PEG-coated nanoliposomes containing crocin and their in vitro cytotoxicity was studied against C26 colon carcinoma cells. Based on in vitro results, the best formulation of nanoliposomes was selected for an in vivo study and the antitumor activity of nanoliposomal crocin was evaluated in BALB/c mice bearing C26 colon carcinoma. The in vivo study indicated that nanoliposomal crocin (50 and 100 mg/kg) inhibited the tumor growth effectively; its effect being comparable to that of free doxorubicin and significantly prolonged survival time compared with crocin and free doxorubicin. It was revealed that retention of crocin in liposomes could improve its anti-tumorigenic activity (Rastgoo et al. 2013). Furthermore, Mary et al. (2016) prepared delivery systems using PEG SeNPs to wrap crocin and to achieve anticancer synergism. The in vitro test portrayed a rapid release behavior in acidic medium. Crocin thus could be liberated and induce its therapeutic effects under acidic environment around tumor tissues. As a result, PEG SeNPs could be a promising pH-mediated engineered delivery body for crocin cancer therapy. Also, crocin-loaded PEG SeNPs demonstrated an ideal

hemocompatibility and improved cytotoxicity to A549 cell-lines (human lung cancer cell lines) by apoptosis in mitochondria. In addition, crocin-PEG SeNPs remarkably inhibited the in vivo tumor development in the mice (nude model). Overall, the outcomes suggested that this mode could be a highly influential way of synergistic treatment of lung cancer by crocin-loaded nanocarriers (Mary et al. 2016).

Crocetin (Cro), a naturally-occurring carotenoid carboxylic acid, is the precursor of crocin within saffron (Zhang et al. 2009). Research indicates that oral crocetin intake in healthy people can reduce physical fatigue (Mizuma et al. 2009). In addition, it has suppressed the eye obstacle and improved sleep disorders (Kuratsune et al. 2010; Yamauchi et al. 2011). Langroodi et al. (2016) applied a double emulsion/solvent evaporation approach for synthesis of PLGA nanoparticles retaining doxorubicin (DOX) and crocetin (PLGA-DOX-Cro nanoparticles). In vitro cytotoxicity of DOX/Cro-loaded PLGA nanoparticles on MCF-7 cell lines was evaluated using MTT test. These loaded nanoparticles inhibited the growth of cancerous cells more efficiently compared to either naked form DOX or Cro at the same levels, measured via MTT test and flow cytometry. So, PLGA-DOX-Cro nanoparticles can have promising applications in breast cancer therapy (Langroodi et al. 2016).

β-Carotene

β-carotene is an orange-red pigment which is abundantly found in plenty of fruits and veggies, such as carrots, pink grapes, papaya, watermelon, and so forth (Lemmens et al. 2014; Thakur et al. 2017). It can strikingly limit the proliferation of many tumor cells, such as breast, colon, and prostate cancers (Jain et al. 2017a). Jain et al. (2018) evaluated the synthesis of BC nanoparticles by phase separation method using zein and the potential of prepared nanoparticles along with free BC was studied compared with antitumor activity of methotrexate (MTX) a well-known anticancer agent, in experimentally applied breast cancer rat model. In short, cellular uptake, cytotoxicity, and oral biopharmaceutical efficacy were ameliorated significantly by using zein nanoparticles. They concluded that these nanoparticles are suitable candidates for substituting the therapeutic benefits of anticancer chemicals (Jain et al. 2018). In another work, fructose-tethered lipid-nanohybrids co-loaded with BC and MTX were fabricated using self-assembled nano-precipitation technique. The in vitro cytotoxicity, subcellular localization, and apoptotic activity of prepared nanocarriers were evaluated against breast cancer cells (MCF-7) and an improved in vitro cell cytotoxicity was reported (Jain et al. 2017a).

Typically, the uptake, imaging and treatment by nanoparticles require the careful accretion of three different activities in a multiscale particle. Misra et al. (2016) presented a straightforward approach to multiplexing through the usage of one part of the system for multiple purposes. In their work, colloidal carbon nanoparticles (C3-NPs) with agave nectar and BC were synthesized. This single functional molecule was used to fulfill three purposes (uptake, imaging, and therapy). First, the passage of particles through cell membrane was enhanced due to the presence of carotene moieties. Second, the anti-tumor activity of the ligand is imposed on cancer cells (melanoma and breast cancers). Last, the ligands generated an optical contrast in complex cellular environments for robust microscopic detection. In comparative tests, C3-NPs were found to be impactful in intracellular delivery which provides both powerful detections at cellular and tissue scale, offering a remarkable therapeutic potential without changing the mode of intracellular activity of BC (Misra et al. 2016). The results of this investigation proved that the developed nanoparticles can provide multiple functions on the targeted cancerous cells.

Astaxanthin

Astaxanthin is a reddish-orange carotenoid which naturally exists in plants, crustaceans and microalgae such as algae, yeast, salmon, trout, crayfish, and shrimp (Ambati et al. 2014). The main function of this keto-carotenoid is sunray absorption during photosynthesis and it has a high capacity for anticancer and antioxidant activity (Jyonouchi et al. 2000); by stimulating immune cells, it can boost immune responses (Song et al. 2011). Since astaxanthin has beneficial effects on the biological system, FDA has approved the application of this pigment as a food coloring agent in animal and fish feed (Pashkow, Watumull, and Campbell 2008). Bharathiraja et al. (2016) produced AuNPs with astaxanthin as a natural reducer without implementation of any external chemical agents and the cytotoxic impact of prepared nanostructures was assessed by tetrazolium-based test against human breast cancer cells (MDA-MB-231). The astaxanthin-AuNPs represented a strong cytotoxic impact on breast cancer cells so that in treated cells, apoptotic morphology was detected. On the other side, the biogenic astaxanthin-AuNPs, take action as a practical contrast agent and provide an image of breast cancer cells in the near-infrared (NIR) wavelength range, which can be applied to therapeutic monitoring (Bharathiraja et al. 2016).

Lycopene

Lycopene is one of the natural carotenoids with strong antioxidant and anticancer properties, especially against prostate disorders. Lycopene intake was also related to a reduced risk of chronic diseases, such as malignancy and cardiovascular diseases (Dorgan et al. 1998). Several cell cultures and in vivo studies reported the anticarcinogenic and antiatherogenic abilities of lycopene, accredited chiefly to its antioxidant characteristics by quenching the singlet oxygen (Jain et al. 2017b; Wertz, Siler, and Goralczyk 2004; Islamian and Mehrali 2015).

Lycopene-loaded SLNs (LYC-SLNs) were fabricated via ingredients consisting Compritol 888 ATO and gelucire by homogenization-evaporation technique and the anticancer potential of LYC-SLNs compared with MTX, were subsequently investigated. A significantly improved cellular

uptake of LYC-SLNs in MCF-7 cells was seen in cell culture experiments in comparison to free LYC. Also, LYC–SLNs reduced the extent and time-dependent survival of MCF-7 cells strikingly compared to free LYC. In addition, the combined cytotoxicity effect of LYC and its encapsulated formulation was assessed with MTX. Cytotoxicity and apoptotic assays claimed a synergism at the entire studied times up to 48 h. This combination strategy endows a practical approach for improving the efficacy of anticancer molecules (Jain et al. 2017b). In another study, a nanoemulsion system incorporating both LYC and AuNPs together with Tween 80 (emulsifier) was prepared and the cytotoxic effect was evaluated against HT-29 colon cancer cell line. It was reported that this system was cytotoxic to carcinogenic cells (Huang et al. 2015). Singh et al. (2017) produced NLCs with Precirol ATO and LYC by ultrasonication method and it was assayed for the curing breast cancer by MTT test. The results showed that LYC-NLCs had a better permeation imposed higher cytotoxic activity than free LYC due to increased ex vivo gut permeation and penetration (Singh et al. 2017).

Konwarh et al. (2012) extracted LYC from tomato peel and conjugated it with polyaniline nanofiber using sonication. The impact of LYC-loaded nanofibers was assessed on the duplication of L929 as well as HeLa cell lines. The anticancer action of LYC-PAni nanofiber was proved by the nuclear fragmentation and membrane blabbing of apoptotic HeLa cells against the ordinary cell line. The biocompatibility potential with normal cell line coupled with anti-cancerous ability attested the suitability of this system in biomedical applications (Konwarh et al. 2012). Sharma et al. (2016) fabricated LYC-loaded niosome by adsorption-hydration method to maintain LYC activity and enhance its bioavailability. The anti-proliferative efficacy of developed niosomal composition was assessed against MCF-7 and HeLa cell lines which reflected an excellent response in the applied dose. The apoptosis test showed that anti-proliferative action was caused by an apoptotic route, which confirmed the potential of this carrier for the development of LYC formulation against cancer (Sharma et al. 2016).

β-Cryptoxanthin

β-cryptoxanthin is one of the main carotenoids present in some yellow or orange vegetables and fruits, such as pumpkin, orange, peas, and corn (Tanaka et al. 2011). Like other major carotenoids, BCR implicates a significant role in cancer therapy by quenching free radicals (Iskandar et al. 2013). Gharib, Faezizadeh, and Godarzee (2015) synthesized nanoliposomes loaded with BCR using soy lecithin and cholesterol downsized by extrusion technique and the anticancer effect of this system was investigated on human leukemia cell line (K562) employing 3-(4, 5-dimethylthiazol-2-yl)−2, 5-diphenyl tetrazolium bromide assay. Apoptotic performance was detected using flow cytometry following treatment with BCR in free and liposomal forms. Also, it was revealed that BCR-loaded nanoliposomes showed higher anticancer activity than free BCR; in the presence of nanoliposomal BCR, the number of apoptotic cells raised dramatically compared to free BCR. Therefore, this promising engineered nanostructure provides a basis for development of effective formulations in leukemia therapies (Gharib, Faezizadeh, and Godarzee 2015).

Lutein

Lutein is a hydroxyl-carotenoid present in seaweeds and dark green leafy vegetables; it is the main constituent of chloroplast, playing a role in capturing the energy of sunlight during photosynthesis process and protection during excess light. Lutein is a naturally-occurring pigment known for its numerous health-promoting properties via a set of putative bioactions comprising antioxidation, anti-inflammation, anticancer and filtration of blue light to protect eyes and skin from oxidative stresses (Boominathan and Mahesh 2015; Jiao et al. 2018). To raise the bioactivity, stability and liberation of lutein, Jiao et al. (2018) synthesized poly-L-lysine (PLL) decorated nanoliposomes loaded with lutein (PLL–LUT-NLP) as a state-of-the-art delivery system. The size of this nanocarrier was in the range of 264–367 nm, and the lutein entrapment efficiency was reported to be highest in nanoliposomes formulated with 0.06% (w/v) PLL. PLL could protect lutein within nanoliposomes from unwanted external conditions and promoted its release in simulated gastric and intestinal fluids. Furthermore, the PLL–LUT-NLP kept the antioxidant activity of lutein, in addition, the decorated-nanoliposomes induced higher antiproliferative activity on tumor cells. It was explained that PLL augmented the cellular uptake of lutein by manipulating the permeability of nanoliposomes and consequently inhibiting the development of human colon cells (Caco-2). These results suggest that PLL decorated nanoliposomes are efficient delivery systems for lutein and are ideal systems for application in food and pharmaceutical sectors (Jiao et al. 2018).

Fucoxanthin

Fucoxanthin (FUC), a marine carotenoid, is present in chloroplasts of brown algae, namely *Sargas sum fulvellum Undariapinnatifida* and *Saccharina japonica*. It shows antioxidant, anti-cancer, anti-angiogenic, anti-diabetic, antiobesity, anti-photoaging, and metastatic effects on a variety of biological models. Furthermore, FUC has attracted considerable attention from the food and nutrition scholars (Irvani, Hajiaghaee, and Zarekarizi 2018; Maeda 2015). Nanoencapsulated FUC with chitosan and glycolipid was produced by Ravi et al. (2018) to maximize its cellular uptake and anticancer action in human colon cells. Their results indicated that this delivery system improved cellular uptake and chemotherapeutic effects of FUC and it is an effective nanocarrier to damage cancer cells by ROS generation and by suppressing B-cell CLL/lymphoma-2 (Bcl-2) protein associated with an enhanced Bcl-2-associated X protein (Bax) concentration via a caspase-3 cascade route (Ravi et al. 2018)

Conclusion and perspectives

Recently, several nano-scale bodies are formulated for phytochemicals to improve their solubility, bioavailability, stability, and permeability. For instance, nanoparticles may be used to deliver carotenoids in cancer therapy. Thereby, studies on carotenoid-loaded nanocarriers for treatment of cancer are reviewed in the present revision. Future works could be centered on application of natural carriers in formulation of nanovehicles, and application of carotenoid-loaded nanocarriers in the treatment of different cancers. Industrial production of nano drugs, however, is still in the early stages of progress. Also, safety and health issues are to be deeply explored prior to their widespread consumption. Thus, First, each process or material must be approved by the regulatory authorities formally. On the other hand, the regulatory framework for incorporation of nano compounds in medicinal products is yet in a state of flux, and national bodies are expected to increase initiatives and certain legislations to regulate and monitor the proper development and application of nanoparticles in foods and drug formulations.

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