

Astaxanthin Nanoemulsion and Nanoparticle Formulations and Their Therapeutic Potential: A Review

Mazzura Wan Chik¹, Meor Mohd Redzuan Meor Mohd Affandi²,
Hanish Singh Jayasingh Chellammal³, Nurul Aqmar Mohd Nor Hazalin^{1,4},
Gurmeet Kaur Surindar Singh^{1,5,*}

¹Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Malaysia

²Department of Pharmaceutics, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Malaysia

³Department of Pharmacology and Pharmaceutical Chemistry, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Malaysia

⁴Integrative Pharmacogenomics Institute (iPROMiSE), Universiti Teknologi MARA, Malaysia

⁵Brain Degeneration and Therapeutics Group, Pharmaceutical and Life Sciences Community of Research, Universiti Teknologi MARA (UiTM), Malaysia

Received May 14, 2024; Revised October 29, 2024; Accepted April 14, 2025

Cite This Paper in the Following Citation Styles

(a): [1] Mazzura Wan Chik, Meor Mohd Redzuan Meor Mohd Affandi, Hanish Singh Jayasingh Chellammal, Nurul Aqmar Mohd Nor Hazalin, Gurmeet Kaur Surindar Singh, "Astaxanthin Nanoemulsion and Nanoparticle Formulations and Their Therapeutic Potential: A Review," *Advances in Pharmacology and Pharmacy*, Vol. 13, No. 3, pp. 342 - 354, 2025. DOI: 10.13189/app.2025.130306.

(b): Mazzura Wan Chik, Meor Mohd Redzuan Meor Mohd Affandi, Hanish Singh Jayasingh Chellammal, Nurul Aqmar Mohd Nor Hazalin, Gurmeet Kaur Surindar Singh (2025). *Astaxanthin Nanoemulsion and Nanoparticle Formulations and Their Therapeutic Potential: A Review*. *Advances in Pharmacology and Pharmacy*, 13(3), 342 - 354. DOI: 10.13189/app.2025.130306.

Copyright©2025 by authors, all rights reserved. Authors agree that this article remains permanently open access under the terms of the Creative Commons Attribution License 4.0 International License

Abstract Astaxanthin, a ketocarotenoid compound belonging to the xanthophyll class, has shown potent antioxidant characteristics when compared to other antioxidants. It has been widely studied and used in *in vivo* and *in vitro* models for its biological activity against diseases such as cancer, diabetes, Alzheimer's disease, and skin disease due to its antioxidant ability to combat the oxidative stress that causes inflammation. However, its lipid-soluble nature has limited its clinical applicability due to low oral bioavailability. Astaxanthin in the form of nanoemulsions and nanoparticles demonstrated better oral bioavailability, more stability, and higher cell penetration. Despite their superior properties, the use of astaxanthin nanoemulsions and nanoparticles in pre-clinical animal models for treating various chronic diseases remains limited. Four different databases, including PubMed, Web of Science, Scopus, and Science Direct, were searched using the keywords 'astaxanthin nanoemulsion' OR 'astaxanthin nanoparticles' AND 'disease' to find research journals for this review. The term 'disease' was replaced

with the names of specific diseases such as cancer, brain disorder, stress, diabetes, and liver disease. This review focuses on recent developments in the use of astaxanthin nanoemulsions and nanoparticles in chronic disease management, and it is expected to be useful for future research.

Keywords Astaxanthin Nanoemulsion, Astaxanthin Nanoparticle, Astaxanthin Therapeutic Potential

1. Introduction

Astaxanthin is a blood-red pigment found in reddish-orange marine life such as salmon, krill, algae, and red yeast. Astaxanthin was known for its intense red color when it first appeared in the food industry as a food coloring and dye. Because of its high concentration of antioxidants, astaxanthin has gained interest among

researchers. Astaxanthin contains 40 to 1,000 times more antioxidants than beta carotene and vitamin E [1]. Knowing the many benefits of astaxanthin to human health, researchers are currently exploring how this superfood could be used in treating diseases related to the skin, eye, heart, immune response, and neurological diseases [2].

Astaxanthin can be obtained either naturally or synthetically. Sources rich in astaxanthin include salmon, krill, shrimp, red yeast, and *Hematococcus pluvialis* (*H. pluvialis*) algae. The amount of antioxidants in astaxanthin derived from the *H. pluvialis* algae is known to be the highest of all natural astaxanthin sources [3]. Astaxanthin obtained synthetically has not been used as a human food supplement; rather, it has been predominantly used for animal feed. Synthetic astaxanthin is derived from petrochemicals, the safety of which is questionable, although the production cost is cheaper. Additionally, compared to naturally occurring astaxanthin, its synthetic form has 20 to 30 times fewer antioxidant properties, 50 times fewer singlet oxygen-quenching abilities, and 20 times fewer free radical scavenging abilities [4].

Nano-sized astaxanthin, in the form of either nanoparticles (NP) or nanoemulsions (NE), is widely accepted in the research community. Nanotechnology-based formulations open a new window in the system of delivering drugs containing bioactive substances. Reducing the size of bioactive substances to the nanoscale range can improve their activity due to the increased surface area. NP and NE allow for longer circulation times, easier cell penetration, and precise site targeting [5]. Traditionally, astaxanthin has been used in medical applications in its extract form. However, in recent years, there has been an increasing interest in formulating astaxanthin into nano-sized particles to increase its solubility, stability, and oral bioavailability. Recent developments have seen the isolation of exopolysaccharide from a novel marine bacteria as a replacement for synthetic emulsifiers for nanoemulsion. This emulsifier was able to produce astaxanthin nanoemulsion with exceptional encapsulation efficiency and controlled astaxanthin release. Furthermore, encapsulation of astaxanthin with fatty acids ligands improved the solubility, stability, and oral absorption of astaxanthin. The nano-sized fatty acids-astaxanthin complexes produced were also reported to accumulate in the serum, liver and eyes of mice treated with the nanoemulsion [6]. Due to these exceptional improvements, nano-sized astaxanthin has been widely studied in various medical fields. A study has found that astaxanthin nanoemulsion exerts protective effects on mammalian inner ear hair cells that are often destroyed when treated using commercialized antibiotics [7]. Additionally, another study revealed that astaxanthin nanoparticles successfully reduce reactive oxygen species (ROS) in tumor cells leading to the inhibition of their proliferation [8].

This review narrates the potential benefits of astaxanthin in the form of nanoparticles and nanoemulsions as intervention options in healthcare applications. Using a

search for the term "astaxanthin" in the PubMed database, 3698 articles were found for the period 1948 to 2024. We narrowed our search to the periods 2000 to 2010 (572 articles) and 2010 to 2024 (3011 articles) and discovered that research interest in astaxanthin has grown tremendously over the last 14 years. However, no review articles have investigated healthcare applications of astaxanthin nanoparticles or nanoemulsions. This review highlights scientific findings on the therapeutic potential of astaxanthin nanoemulsions and nanoparticles for a variety of diseases, as well as the most recent advancements in the use of astaxanthin nanoemulsions and nanoparticles in healthcare. The research articles used in the review were found by searching four different databases (PubMed, Web of Science, Scopus, and Science Direct) using the same keywords ((astaxanthin nanoemulsions) OR (astaxanthin nanoparticles) AND (disease)). We changed the term "disease" in the search string to the names of specific diseases such as cancer, brain disorder, stress, diabetes, and liver disease. We believe that exploring the use of astaxanthin nanoparticles or nanoemulsions in healthcare interventions has considerable potential.

2. The Structure of Astaxanthin

Astaxanthin ((3*S*,3'*S*)-3,3'-Dihydroxy- β,β -carotene-4,4'-dione) with a chemical formula of $C_{40}H_{52}O_4$ is a type of xanthophyll that belongs to the carotenoids class. Based on the presence of oxygen molecules, carotenoids can be divided into two sub-groups, carotenes (which consist of carbon and hydrogen molecules) and xanthophylls (which consist of carbon, hydrogen, and oxygen molecules). Astaxanthin, as indicated by its IUPAC nomenclature, has unique properties in that its molecule contains both the hydroxyl (OH) and carbonyl (C=O) functional groups, making it a keto-carotenoid [9]. The presence of hydroxyl and carbonyl groups on each ionone ring produces a polar-nonpolar-polar structure, allowing it to align in the cell membrane's phospholipid bilayer and exposing its polar hydrophilic ends to the internal cytoplasm and external cell membrane [10]. One benefit of having two polar ends is that it can serve as a bridge between the two different environments. This distinct characteristic of astaxanthin and its conjugated double bond have been linked to its powerful antioxidant activities [9].

3. Antioxidant Properties of Astaxanthin

Antioxidants prevent the damaging effects of free radicals. Astaxanthin, with its antioxidant properties, has an essential role to play in deactivating reactive oxidants to prevent the negative effects of free radicals that have been created [11]. Free radicals are produced in the body through normal metabolic processes, as well as external sources such as cigarette smoke, pollution, and industrial

contaminants. The overloading of free radicals in the body, particularly those from ROS, reactive nitrogen species (RNS), and reactive sulfur species (RSS), promotes a condition known as oxidative stress, which is the cause of many chronic diseases such as cancer, cardiovascular disease, cataracts, and neurodegenerative diseases [12]. Free radicals frequently have one or more unpaired electrons in their atomic orbital. Because of such exceptional characteristics, free radicals are highly reactive and unstable, and they may react with cellular components (such as proteins, lipids, and deoxyribonucleic acid) through a chain reaction of donating or receiving electrons, leading to cell damage, as well as protein and lipid oxidation [13].

Astaxanthin has the ability to quench singlet oxygen (O_2) and suppress lipid peroxidation by free radical scavenging. Singlet oxygen can degrade protein structures in the body, oxidizing protein residues (tryptophan, histidine, methionine, and cysteine) and oxidizing fatty acids in cell membranes to form lipid peroxides [9]. It can be formed through photosensitization (exposure to light) or chemical (not involving light) processes. The reaction between singlet oxygen and protein was believed to cause protein damage, which resulted in cataracts, sunburn, and skin cancers. When compared to other carotenoids such as canthaxanthin, zeaxanthin, β -carotene, fucoxanthin, and halo cynthiaxanthin, astaxanthin showed the highest singlet oxygen-quenching activity [9]. As for lipid peroxidation, astaxanthin exhibited inhibitory effects that were 100 times greater than those of α -tocopherol [14]. Lipid peroxidation induces diseases such as coronary stenosis, inflammation,

cardiovascular disease, and cancers. It has been proposed that free radical scavenging is mediated by a transfer of electrons, radical adduct synthesis, and hydrogen atom transfer. Meanwhile, the energy transfer between electrophilic singlet oxygen and the polyene backbone is mediated by singlet oxygen quenching.

A growing body of research has shown that the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) (Nrf2/ARE) signaling pathway protects cells against oxidative stress and inflammation by maintaining cellular redox homeostasis [15]. The Nrf2/ARE system can activate the transcription of cytoprotective genes, including glutathione defense system enzymes and proteasome (which promotes cell survival by degrading damaged proteins that have formed due to oxidative stress) components [16]. However, increasing antioxidant enzyme levels by activating the Nrf2 may be insufficient to combat oxidative stress. Hence, a simultaneous combination of Nrf2 activation, dietary supplementation, and endogenous antioxidant chemicals may reduce oxidative stress and inflammation [15]. Antioxidants promote the expression of the multitude of genes that encode phase II detoxification enzymes, antioxidant proteins (e.g., glutathione S-transferase and quinone reductase), and xenobiotic transporters, all of which provide protection against oxidative stress through the *cis*-acting element called the ARE [17]. Astaxanthin with potent antioxidant activity demonstrated cellular protection against oxidative stress in a HepG2-C8-ARE-luciferase cell line via regulation of the Nrf2–ARE pathway [18].

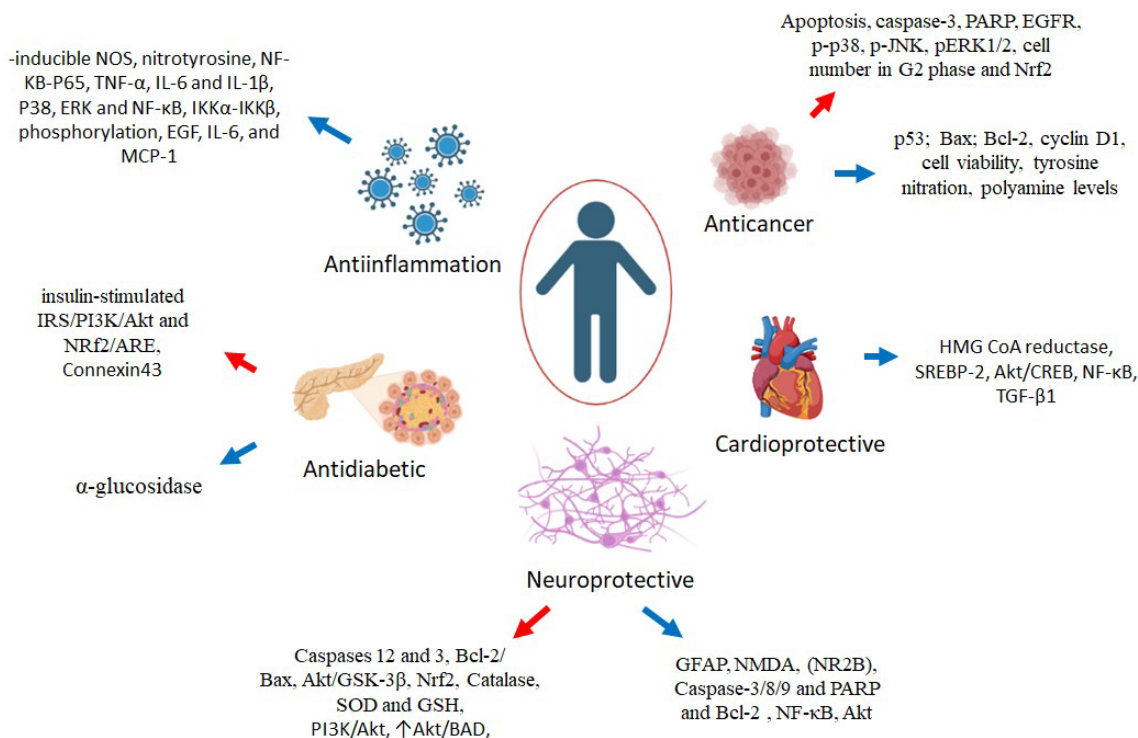


Figure 1. Pharmacological targets and various molecular streaming by astaxanthin indicated by the red arrow (increasing) and blue arrow (decreasing)

Astaxanthin exerts anti-inflammatory, anti-apoptosis, and anti-proliferation effects through the activation and suppression of various pathways in the body. As such, the activation of the Nrf2 signaling pathway using astaxanthin plays a neuroprotective role in the case of subarachnoid hemorrhage conditions [19]. Meanwhile, inhibiting the nuclear factor-kappa B (NF- κ B) and Wnt- β -catenin signaling pathways by activating the mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol-3-kinase (PI3K)/Akt (protein kinase B (PKB)/Akt) pathways induced intrinsic apoptosis in an oral cancer hamster model [20]. Besides that, astaxanthin led to the abrogation of cell proliferation, invasion, and angiogenesis in an oral cancer hamster model by inhibiting the JAK/ signal transducer and activator of the transcription 3 (STAT-3) signaling pathways [21]. All these reports indicated that astaxanthin is a promising candidate for the therapeutic targeting of various chronic diseases. Figure 1 illustrates the pharmacological targets and various molecular streaming by astaxanthin.

4. Astaxanthin Nanoemulsion and Nanoparticle Formulations

Although astaxanthin is widely used in the treatment of various diseases, it has several drawbacks, including low oral bioavailability in the body due to its slow dispersion rate in blood vessels and low cellular absorption. Astaxanthin becomes unstable in acidic conditions, and it is prone to oxidation due to its highly unsaturated structures. Heating astaxanthin, even for a short time, results in its degradation [22]. Hence, extensive efforts have been made to improve the bioavailability, stability, and solubility of astaxanthin to preserve its antioxidant properties.

Nanomedicine, which refers to the application of nanotechnology in medicine, has been adopted as an alternative drug-delivery strategy since it provides reliable diagnostic and therapeutic tools where fatal diseases such as cancer, infectious diseases, and neurodegenerative diseases are concerned [23]. In drug delivery applications, various uses of nanocarriers have been developed for efficient drug delivery. Nanocarriers can alter drug bioactivity, improve pharmacokinetics and biodistribution, reduce toxicity, and improve solubility and stability, while they are also controlled-released and site-specific for drug delivery [24].

4.1. Nanoemulsions

A nanoemulsion is a mixture of two immiscible liquids (oil in water (O/W), water in oil (W/O), or water-oil-water) stabilized by a surfactant, with a mean droplet size of less than 200 nm. In general, an emulsion consists of three

components: water, oil, and surfactant phases. The type of surfactant used determines whether the emulsion's continuous phase (external phase) is oil (oil-soluble surfactant - W/O emulsion) or water (water-soluble surfactant - O/W emulsion). A nanoemulsion is a lipid-based nanocarrier and can be prepared using either high-energy (high-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidization, and membrane emulsification) or low-energy (phase-inversion temperature, emulsion inversion point, and spontaneous emulsification) methods [25]. Although the high-energy method consumes more energy than the low-energy method, it has several advantages such as smaller droplet sizes, ease of preparation, and long-term stability [26]. The surfactant used in nanoemulsion production is critical because it determines not only the emulsion's continuous phase but also its stability and safety.

Emulsifiers reduce surface tension, prevent droplet aggregation, and produce strong repulsive interactions, all of which contribute to their stability. Although synthetic emulsifiers are known for producing highly stable emulsions, natural emulsifiers are becoming increasingly popular due to consumer health concerns. The consumption of synthetic emulsifiers in large amounts may cause gastrointestinal tract irritation. Hence, producing a nanoemulsion with just enough emulsifier to stabilize the nanoemulsion is important. Non-ionic emulsifiers are less harmful to use than ionic emulsifiers, so the former is becoming popular among researchers. To date, astaxanthin nanoemulsion formulation with natural emulsifiers (ginseng saponins) has been developed and characterized [27]. The ginseng saponins astaxanthin nanoemulsion produced was nano-sized (\approx 125 nm) and stable, with no droplet agglomerates at high temperatures (30 - 90 °C, 30 mins). It was, however, found to be unstable in acidic (pH 3 - 6) and salty environments ($>$ 25 mM NaCl). Nanoemulsion applications in the food industry [28], and drug delivery systems [29] were thoroughly reviewed. This review identified different formulations of astaxanthin nanoemulsion, as well as their characterization, stability assay, and biological application, as summarized in Table 1.

4.2. Nanoparticles

A nanoparticle is any particulate matter with a diameter in the nanometer range (1 - 100 nm). The term "nanoparticle" encompasses a variety of nanoparticle classes, based on their physical and chemical properties. Examples of well-known nanoparticles include carbon-based, metal-based, ceramic-based, semiconductor-based, polymeric-based, and lipid-based nanoparticles. Nanoparticles exhibit distinct structural, chemical, mechanical, magnetic, electrical, and biological characteristics, making them a unique type of candidate for

the drug delivery of bioactive compounds [30]. Nano-sized particles typically circulate in the bloodstream longer, release a specific amount of a bioactive compound, and cause fewer plasma changes that have negative effects [31].

Compared to large micrometer-sized particles, nano-sized particles have better tissue penetration, ensure action at the targeted location, and enable cells to have a higher drug uptake [5].

Table 1. Astaxanthin nanoemulsion formulation, characterization, stability, and biological assays

Types of nanoemulsion / emulsifier	Preparation methods	Characterization	Physicochemical study	Biological assay outcome	References
O/W / modified lecithin (ML) & sodium caseinate (SC)	High pressure homogenization	laser diffraction particle size analyser	One month storage stability and astaxanthin content assay, pH, temperature, and freeze-thawed assay.	In vitro small intestinal digestion assay of ML-astaxanthin nanoemulsions showed higher production of free fatty acids and bioaccessibility (> 32%) due to less oil aggregation after digestion.	[33]
O/W / tween 20	High pressure homogenization	DLS	35 days storage stability assay, temperature, pH and ionic strength assays.	In vitro mouth, gastric and small intestine digestion assays, bioaccessibility assay, antioxidants had effects on emulsion oxidative stability.	[34]
O/W / gypenosides & tween 20	High pressure homogenization	laser diffraction particle size analyser, zeta potential	30 days storage stability assay, pH, temperature and ionic strength assay.	Low free fatty acids were released in the intestinal digestion assay. Possessed high bioaccessibility.	[35]
O/W / Labrasol, Tween 20 and Cremophor EL	Low-energy emulsion phase inversion	DLS, TEM	90 days storage stability assay, temperature and astaxanthin content assay	Carboxymethyl chitosan astaxanthin nanoemulsion showed the highest permeability activity through the stratum corneum of the skin. Possessed low cytotoxicity.	[36]
O/W / polysorbate 20, 40, 60 & 80	Emulsification evaporation	DLS	None	Astaxanthin nanoemulsion alleviated the photoreceptor degeneration and visual function impairments in a retinal degeneration animal model with a rapid progress rate.	[37]
O/W / sodium caseinate	Low-energy spontaneous and ultrasonication emulsification	DLS, TEM	6 months stability assay at room temperature and 4 oC.	Reduced cancer cell viability (dose-dependent) and induced apoptosis. Enhanced wound repair and wound healing. Antimicrobial activity assay showed an inhibitory effect at a minimum concentration of 0.5 mg/mL.	[38]
O/W / sodium caseinate	Low-energy spontaneous and ultrasonication emulsification	DLS, TEM, FTIR, DSC, XRD, thermogravimetric.	Temperature and pH stability assay.	Reduced cancer cell line viability (dose-dependent). Induced apoptosis by necrosis. Induced mitochondrial membrane dysfunction and intracellular ROS generation.	[39]

Abbreviation: Oil in water (O/W), dynamic light scattering (DLS), transmission electron microscopy (TEM), field emission scanning electron microscope (FESEM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), reactive oxygen species (ROS).

Table 2. Astaxanthin nanoparticles formulation, characterization, stability, and biological assays

Types of nanoparticle	Preparation methods	Characterization	Physicochemical study	Biological assay	References
Astaxanthin-loaded core-shell in PLGA coated with chitosan oligosaccharides	Antisolvent precipitation and electrostatic deposition method	DLS, SEM, FTIR, DSC, XRD, UV/Vis spectroscopy	None	Astaxanthin nanoparticles exhibited low cytotoxicity to the Caco-2 cell line. Astaxanthin was constantly released from the coated nanoparticles under pH conditions simulating the stomach (pH 2.1) and small intestine (pH 7.4).	[49]
Astaxanthin-loaded polymer-lipid hybrid nanoparticles	Emulsion solvent evaporation method	DLS, TEM, LC-MS/MS	None	Astaxanthin nanoparticles penetrated through the ear round window membrane and maintained concentrations in the perilymph in the inner ear for 24 h after a single injection. Decreased expression of pro-apoptotic proteins (caspase 3/9 and cytochrome-c). Increased expression of the anti-apoptotic protein Bcl-2.	[50]
Astaxanthin-containing whey protein-based nanoparticles	Emulsification-solvent evaporation technique	DLS, encapsulation efficiency, ABTS radical scavenging assay	Temperature, pH, UV irradiation, Fe (III)-induced oxidation	<i>In vitro</i> simulated digestion assays showed 43% of astaxanthin released from nanoparticles (gastric phase) and 86% (bioaccessible of astaxanthin) after 3h of intestinal digestion.	[51]
Solid lipid-polymer hybrid astaxanthin nanoparticles	In situ conjugation	DLS, TEM	None	Exhibited significantly higher antioxidant activity at very low concentration (0.25 µg/mL). Astaxanthin was constantly released in simulated gastrointestinal fluid.	[52]
Astaxanthin-loaded chitosan-tripolyphosphate nanoparticles	Ionic gelation	DLS	None	An <i>in vitro</i> release study confirmed that the release of astaxanthin in simulated gastric (pH 1.2) and intestinal (pH 6.8) fluid was prolonged. The antioxidant activity of astaxanthin nanoparticles was significantly improved compared with free astaxanthin.	[53]
broccoli-derived extracellular vesicles-coated PLGA-encapsulated astaxanthin	Emulsion solvent evaporation and ultrasound method	DLS, TEM	None	Possessed better anticancer activity against HT-29 cell line.	[54]
Astaxanthin-loaded lecithin nano-liposol	Emulsion evaporation method	DLS, TEM	Four weeks of storage stability.	Exhibited no cytotoxicity (> 95% cell viability at a concentration of 1000 µg/mL). Exhibited significant antioxidant activity at low concentrations of 10 µg/mL against hydrogen peroxide (oxidative stress agent).	[55]

Abbreviation: Dynamic light scattering (DLS), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), ultraviolet (UV), poly(lactic-co-glycolic acid) (PLGA), 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), B-cell lymphoma 2 (Bcl-2), liquid chromatography - mass spectrometry and liquid chromatography - tandem mass spectrometry (LC-MS/MS).

Astaxanthin encapsulation with liposome (Ast-L) demonstrated improved stability and membrane transportability, with a total transport time of 6.00 h for the Ast-L to be delivered to the cell cytoplasm, instead of 7.55 h for free astaxanthin. Moreover, Ast-L activated significantly more antioxidant enzymes than free astaxanthin, including superoxide dismutase, catalase, and glutathione S-transferase [32]. Astaxanthin-loaded liposomes, which were developed and stabilized using novel sea cucumber-derived sulphated sterols rather than cholesterol, demonstrating a longer period of stability, improved antioxidant activity, and greater bioavailability [40]. Astaxanthin in the form of stealth solid lipid nanoparticles (AST-SSLNs) was produced to overcome the instability properties of astaxanthin. Compared to other colloidal carriers such as liposomes and polymeric nanoparticles, solid lipid nanoparticles (SLNs) offered higher drug stability and no toxicity, while they could contain both hydrophilic and lipophilic drugs, were easy to produce on a large scale, and could lyophilize [41]. However, the systemic administration of SLNs is limited due to the opsonization process, an immune system mechanism for fighting pathogens that causes a short half-life (3 – 5 mins) in the systemic environment [42]. The intervention of stealth carriers (SSLN) loaded with astaxanthin allowed the latter to bypass the immune system's defense line and improved the drug stability for optimal bioavailability in the brain through a systemic administration [43]. Different formulations of astaxanthin nanoparticles and their characterization and biological applications are summarized in Table 2.

5. Therapeutic Potential of Astaxanthin Nanoemulsion and Nanoparticle

Astaxanthin in free form (oil extract) has been studied to treat conditions such as cancer [44], cardiovascular disease, liver disease, diabetes, skin disease, muscle issues, and neurodegenerative disease [2]. Astaxanthin may have therapeutic potential to target disease-related oxidative stress, apoptosis, and inflammation. The use of astaxanthin nanoemulsions and nanoparticles in disease treatment has gained interest from researchers due to their superior behavior in terms of stability, bioavailability, and solubility in the body. Thus, this review aimed to highlight works in the literature that have investigated the therapeutic potential of astaxanthin prepared in nanoemulsions and nanoparticles to treat cancer, diabetes, lung disease, ocular-related diseases, nervous disorders, and hearing-related diseases.

5.1. Cancer

Cancer is a disease characterized by the uncontrolled proliferation and accumulation of cells in an organism. It is the outcome of insufficient apoptosis, resulting in

malignant cells that do not die. Many researchers are exploring therapies that target the apoptotic pathways in combination with traditional anticancer medications as a feasible way of finding new treatments for various types of cancer. Although existing cancer treatments such as chemotherapy can destroy cancer cells, they have adverse effects such as liver and heart toxicity, nausea, vomiting, discomfort, diarrhea, and inflammation of the mucous membranes. Antioxidants are frequently prescribed to counteract such negative effects without affecting the treatment's effectiveness.

In general, astaxanthin plays a significant role in cancer treatment by suppressing cell growth and metastasis, promoting cell apoptosis, and improving overall immunity [44]. Astaxanthin nanoemulsions containing cellulose nanocrystals or nanofibrils have been used to treat skin cancer cells. The efficacy of the nanoemulsion treatment was improved by using low-level laser therapy enhancing cell proliferation and differentiation, as well as inducing apoptosis in skin cancer cells [45]. An astaxanthin nanoemulsion also was found to cause apoptosis in lung metastatic melanoma, whereby the apoptosis pathways' components such as β -cell lymphoma 2 (Bcl-2), cyclins D1 and E, the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B), extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MEK), and matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-9 (MMP-9) were inhibited, while cleaved caspase-9 and caspase-3, ataxia-telangiectasia mutated kinase (ATM), and cyclin-dependent kinase inhibitor p21 were increased [46]. Figure 2 illustrates the mechanisms of cancer and possible protective effects of nano-sized astaxanthin.

5.2. Diabetes

Diabetes mellitus (DM) is one of the ten leading causes of death worldwide. It is caused by improper or dysfunctional insulin action, which leads to hyperglycemia (high blood glucose levels). If not controlled, this condition can result in serious illnesses such as retinal disease, neuropathy, nephropathy, and cardiovascular disease, as well as slow wound healing [47]. The wound healing process in diabetic patients is usually slower due to several factors, such as high blood sugar levels (which increases inflammation in the cells), nerve damage (which numbs the hands and feet; the patient may not know they are injured), and poor blood circulation (owing to narrow blood vessels and blood thickening due to high blood sugar levels). Astaxanthin/ α -tocopherol with κ -carrageenan nanoemulsion (astaxanthin-TP@KCNE) was synthesized to study the effect of astaxanthin in wound healing applications for diabetics. The nanoemulsion produced was able to restore body weight significantly, reduce fasting blood glucose levels, and improve glucose tolerance. It was able to aid wound healing in diabetic mice, and it showed accelerated wound closure and better control of hyperglycemia [48].

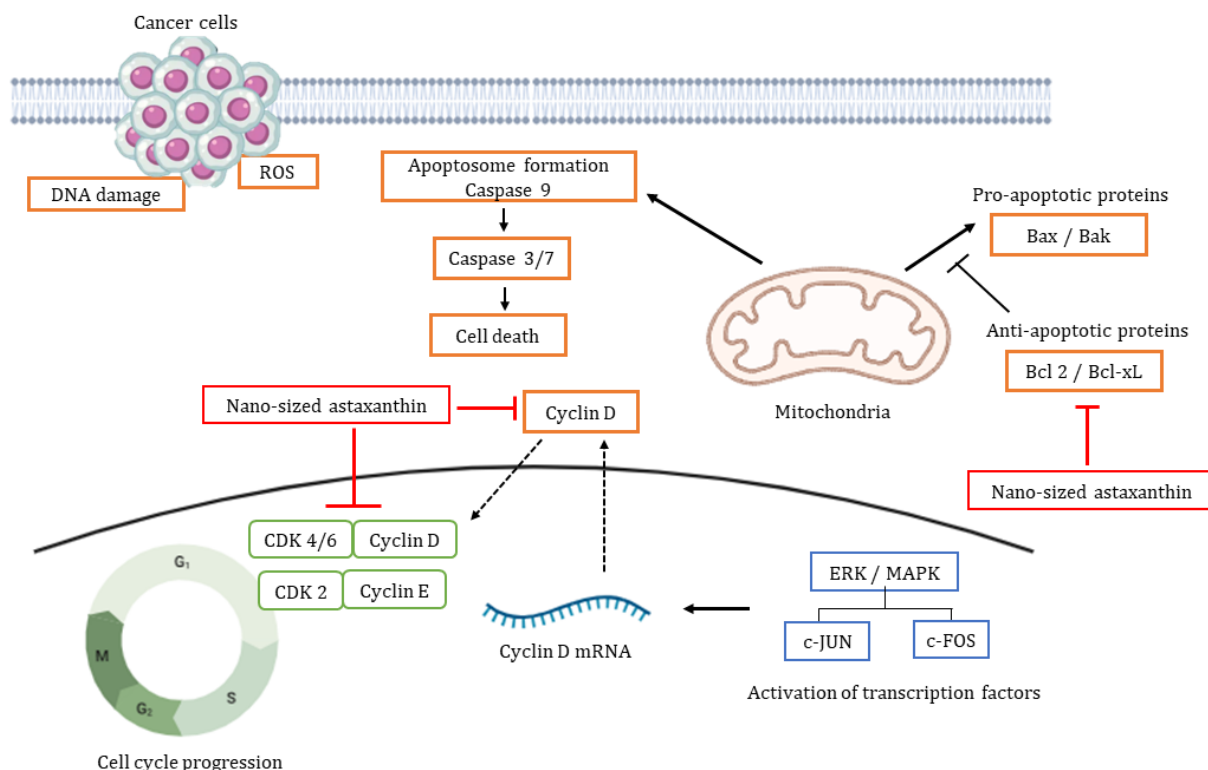


Figure 2. Illustration of possible protective mechanisms of nano-sized astaxanthin in cancer. Cancer cells induce the formation of reactive oxygen species (ROS) and DNA damage. This internal stress triggered mitochondria to become permeable toward balance-regulated pro-apoptotic and anti-apoptotic proteins. In cancer, these anti-apoptotic proteins are often overexpressed, helping the cells avoid apoptosis. Nano-sized astaxanthin could inhibit anti-apoptotic proteins, upregulate pro-apoptotic proteins, and activate caspase proteins to induce cancer cells' death. ERK/MAPK in the nucleus activates transcription factors, which increase the transcription of cyclin D mRNA and production of cyclin D and cyclin E complexes with cyclin-dependent kinase (CDKs) 4 and 6 to produce cyclin E complexes with CDK 2. Cyclin E allows the cell cycle to transition from the G_1/S phase towards G_2 and mitosis. As shown in red, nano-sized astaxanthin causes G_1 arrest in cancer cells due to inhibition of cyclin D or cyclin E

Uncontrolled diabetes damage the blood vessels in the kidney, leading to kidney damage (diabetic nephropathy) and high blood pressure. Recently, a nano-sized astaxanthin known as astaxanthin-GLU-LIP (glucose-PEG600-DSPE ligand-modified astaxanthin liposomes) was produced to study the effect of using natural astaxanthin in diabetic nephropathy (DN) therapy. As previously documented, astaxanthin-GLU-LIP could scavenge ROS and improve the pathological morphology of the kidney, indicating a potential therapeutic capability against DN. Moreover, the drug delivery of the liposomes produced was specifically transported and kidney-targeted [56]. The thin film containing an astaxanthin-loaded nanoemulsion (FDT-astaxanthin-NE) demonstrated good physical and mechanical properties, making it suitable for oral administration. FDT-astaxanthin-NE significantly reduced elevated blood glucose levels in diabetic rabbits, compared to treatment with pure astaxanthin. A histopathological examination of pancreatic tissue from the FDT-astaxanthin-NE group revealed normal pancreatic β -

cell conditions, indicating the absence of pathological lesions [57].

5.3. Pulmonary Fibrosis

Astaxanthin and trametinib loaded in surface-engineered nanoparticles (PER NPs) and adhered to monocyte-derived multipotent cells (MOMC) (named MOMC/PER) were synthesized to target idiopathic pulmonary fibrosis (IPF) [58]. IPF is a progressive interstitial pulmonary disease with a median survival rate of less than five years after diagnosis. The MOMC/PER was precisely designed to be lung-targeted to reverse IPF by improving the drug accumulation. The astaxanthin and trametinib had the dual effects of synergistically neutralizing superoxide to repair injured type-II alveolar epithelial cells and suppressing the activation of myofibroblast by inhibiting the connective tissue growth factor production, respectively, for IPF therapy.

5.4. Ocular-Related Disease

Age is a frequent factor in the development of eye conditions like macular degeneration, cataracts, diabetic retinopathy, and glaucoma. There are, however, hereditary ocular disorders caused by gene mutation. Inherited retinal degeneration (RD) is a genetic and phenotypical eye disorder that causes night blindness, a narrower visual field, and decreased visual acuity. With more than 160 types of gene mutations linked to RD, the mutation of rod-specific genes exclusively causes rod apoptosis followed by cone death, leading to the high visual acuity of RD patients [59]. Astaxanthin can be used in cases of RD to counteract the oxidative stress caused by ROS, which is typically produced in excess due to the enhanced activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This is caused by the rods' drastically reduced oxygen consumption, which results in significantly higher oxygen tension in the lateral retina layers. Astaxanthin nanodispersion using a non-ionic emulsifier was shown to alleviate photoreceptor loss and visual impairments in N-methyl-N-nitrosourea-treated mice by modulating apoptosis and alleviating oxidative stress [37].

The therapeutic effects of astaxanthin against ultraviolet (UV)-induced photokeratitis in mice were evaluated by comparing the results of astaxanthin nanopowder, astaxanthin oil, *Tagetes erecta* (lutein), and *Vaccinium myrtillus* (anthocyanidin) extract. Photokeratitis is a painful eye condition that occurs due to exposure to UV rays. Longer exposures cause excruciating pain because the corneal epithelial cells are damaged, exposing the underlying sub-epithelial nerve plexus [60]. In the study, various assays were conducted - such as immunohistochemistry, western blot, and quantitative polymerase chain reaction (qPCR) - on cornea samples collected 24 hours after UV irradiation. Treatments given through oral administration three hours before and shortly before UV irradiation showed significantly thicker corneal epithelium in the astaxanthin nanopowder group, compared to the others. Furthermore, the treatment significantly reduced the expression of cyclooxygenase-2 (COX-2), p-IB-, tumor necrosis factor (TNF), and CD45, indicating that astaxanthin nanopowder has anti-inflammatory and anti-apoptotic activity [61].

5.5. Nervous System Disorders

The nervous system is a complex and crucial component of the human body since it controls and coordinates body function. Its three main components are the brain, spinal cord, and nerves, and it receives and sends electrical signals to the cells, glands, and muscles throughout the body, controlling critical processes such as movement, thought, and memory. Subarachnoid hemorrhage (SAH) is a type of stroke caused by bleeding on the brain's surface, and it can be fatal. Mortality and disability in SAH patients are caused by the destruction of the blood-brain barrier, apoptosis, brain cell autophagy, and the oxidative stress that occurs

during early brain injury. The detection of astaxanthin in the nanoemulsion form in several brain regions associated with memory function (hippocampus, cortex, and cerebellum) provides a new insight into how to utilize astaxanthin's full therapeutic potential to treat neuro-related diseases [62]. Transferrin conjugated to poly (ethylene glycol) (PEG)-encapsulated astaxanthin nanoparticles (astaxanthin-NPs) were synthesized for SAH treatment in an *in vitro* study. The transferrin astaxanthin-NPs were water-dispersible and biocompatible, and they exhibited high cellular uptake in primary cortical neurons. The nanoparticles were stable and significantly improved neuronal survival while decreasing apoptotic markers [63]. In a recent *in vivo* study of SAH rats, astaxanthin-loaded polydopamine nanoparticles (AUT NPs) demonstrated no toxicity, inflammation, or hemolysis. The AUT NPs improved behavior, alleviated brain oedema, and significantly reduced neuronal apoptosis in the rat [64].

5.6. Hearing-Related Diseases

Hearing loss can occur due to the release of ototoxic drugs like aminoglycosides and anticancer agents, which cause oxidative stress and inflammation in the cochlear. Astaxanthin-loaded polymer-lipid hybrid nanoparticles (astaxanthin-LPN) were first developed to overcome the poor solubility characteristics of astaxanthin. Later, astaxanthin-LPN was tested for its otoprotective effects against cisplatin-induced ototoxicity. The nanoparticles were able to penetrate the round window membranes and maintain their concentration in the inner ear for one day. Astaxanthin-LPN increased the potential of the mitochondrial membrane, as well as reducing apoptosis and ROS [50]. In a recent study by the same author, astaxanthin and ROS-responsive/consuming nanoparticles (astaxanthin-PPS-NP) were synthesized to enhance the antioxidant properties of astaxanthin by encapsulating it in ROS-responsive nanoparticles. Astaxanthin-PPS-NP protected the spiral ganglion neurons by reducing ROS production and inflammatory chemokine release, increasing antioxidant glutathione, and inhibiting the mitochondrial apoptotic pathway [65].

6. Conclusions

Several *in vitro* and *in vivo* studies of the therapeutic effects of using astaxanthin nanoemulsions and nanoparticles in the treatment of various diseases were detailed in this review, which will furnish researchers' knowledge of the current therapeutic interventions involving nano-sized astaxanthin. The preparation of astaxanthin in nanoemulsion form has advantages in oral drug delivery systems, including protection from hydrolysis and oxidation, increased bioavailability, and even masking the unpleasant taste of oily liquids. Moreover, nanoparticles are versatile and efficient carriers in the drug delivery system, enabling the delivery of bioactive

compounds to target delivery sites. However, very few studies have examined the use of astaxanthin nanoemulsions and nanoparticles in the treatment of chronic diseases. Future research ought to investigate the protective effects of nano-sized astaxanthin in diseases driven by inflammation and oxidative stress. For example, it could play a therapeutic role in the treatment of hypertension, Parkinson's disease, metabolic disorders such as diabetes or obesity, and skin disorders including psoriasis or atopic dermatitis. In the last decade, the growth of research on the use of nano-sized astaxanthin in a variety of disease treatments has created new opportunities to find possible treatments.

Conflict of Interest

The authors declare that there are no competing interests.

Acknowledgements

We would like to express our deepest appreciation to the Faculty of Pharmacy, UiTM Puncak Alam, Selangor, Malaysia, for the facilities, support, and assistance.

REFERENCES

- [1] Naguib Y. M. A., "Antioxidant activities of astaxanthin and related carotenoids," *Journal of Agricultural and Food Chemistry*, vol. 48, no. 4, pp. 1150–1154, 2000, doi: 10.1021/jf991106k.
- [2] Donoso A., González-Durán J., Muñoz A. A., González P. A., Agurto-Muñoz C., "Therapeutic uses of natural astaxanthin: An evidence-based review focused on human clinical trials," *Pharmacological Research*, vol. 166, no. 2021, p. 105479, 2021, doi: 10.1016/j.phrs.2021.105479.
- [3] Boussiba S., "Carotenogenesis in the green alga *Haematococcus pluvialis*: Cellular physiology and stress response," *Physiologia Plantarum*, vol. 108, no. 2, pp. 111–117, 2000, doi: 10.1034/j.1399-3054.2000.108002111.x.
- [4] Niu T., Zhou J., Wang F., Xuan R., Chen J., Wu W., Chen H., "Safety assessment of astaxanthin from *Haematococcus pluvialis*: Acute toxicity, genotoxicity, distribution and repeat-dose toxicity studies in gestation mice," *Regulatory Toxicology and Pharmacology*, vol. 115, no. 2020, p. 104695, 2020, doi: 10.1016/j.yrtph.2020.104695.
- [5] Awasthi R., Roseblade A., Hansbro P. M., Rathbone M. J., Dua K., Bebawy M., "Nanoparticles in cancer treatment: Opportunities and obstacles," *Current Drug Targets*, vol. 19, no. 14, pp. 1696–1709, 2018, doi: 10.2174/1389450119666180326122831.
- [6] Huang L., Li D., Ma Y., Liu Y., Liu G., Wang Y., Tan B., "Dietary fatty acid-mediated protein encapsulation simultaneously improving the water-solubility, storage stability, and oral absorption of astaxanthin," *Food Hydrocolloids*, vol. 123, no. August 2021, 2022, doi: 10.1016/j.foodhyd.2021.107152.
- [7] Kobayashi Y., Sugahara K., Takemoto Y., Tsuda J., Hirose Y., Hashimoto M., Yamashita H., "Protective effect of astaxanthin nanoemulsion on mammalian inner ear hair cells," *PeerJ*, vol. 9, 2023, doi: 10.7717/peerj.15562.
- [8] Xie W., Tan S., Ren X., Yu J., Yang C., Xie H., Ma Z., Liu Y., Yang S., "Tumor-targeted astaxanthin nanoparticles for therapeutic application in vitro," *Colloids and Interface Science Communications*, vol. 55, no. May, p. 100721, 2023, doi: 10.1016/j.colcom.2023.100721.
- [9] Kraboun K., Phanumong P., Kongbangkerd T., Rojsuntornkitti K., Saimek M., Jommark N., "Antioxidant properties and encapsulation methods of astaxanthin: A review," *Food and Applied Bioscience Journal*, vol. 9, no. 2, pp. 1–50, 2021, doi: 10.1080/2325548x.2021.1889915.
- [10] Elbahaswy S., Elshopakey G. E., "Recent progress in practical applications of a potential carotenoid astaxanthin in aquaculture industry: a review," *Fish Physiology and Biochemistry*, vol. 50, no. 1, pp. 97–126, 2024, doi: 10.1007/s10695-022-01167-0.
- [11] Bjørklund G., Gasmí A., Lenchyk L., Shanaida M., Zafar S., Mujawdiya P. K., Lysiuk R., Antonyak H., Noor S., Akram M., Smetanina K., Piscopo S., Upyr T., Peana M., "The Role of Astaxanthin as a Nutraceutical in Health and Age-Related Conditions," *Molecules*, vol. 27, no. 21, pp. 1–17, 2022, doi: 10.3390/molecules27217167.
- [12] Chaudhary P., Janmeda P., Docea A. O., Yeskalyieva B., Abdull Razis A. F., Modu B., Calina D., Sharifi-Rad J., "Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases," *Frontiers in Chemistry*, vol. 11, no. May, pp. 1–24, 2023, doi: 10.3389/fchem.2023.1158198.
- [13] Lobo V., Patil A., Phatak A., Chandra N., "Free radicals, antioxidants and functional foods: Impact on human health," *Pharmacognosy Reviews*, vol. 4, no. 8, pp. 118–126, 2010, doi: 10.4103/0973-7847.70902.
- [14] Yamashita E., "Astaxanthin as a medical food," *Functional Foods in Health and Disease*, vol. 3, no. 7, pp. 254–258, 2013, doi: 10.31989/ffhd.v3i7.49.
- [15] Prasad K. N., "Simultaneous activation of Nrf2 and elevation of dietary and endogenous antioxidant chemicals for cancer prevention in humans," *Journal of the American College of Nutrition*, vol. 35, no. 2, pp. 175–184, 2016, doi: 10.1080/07315724.2014.1003419.
- [16] Kwak M.-K., Wakabayashi N., Greenlaw J. L., Yamamoto M., Kensler T. W., "Antioxidants enhance mammalian proteasome expression through the Keap1-Nrf2 signaling pathway," *Molecular and Cellular Biology*, vol. 23, no. 23, pp. 8786–8794, 2003, doi: 10.1128/mcb.23.23.8786-8794.2003.
- [17] Rushmore T. H., Morton M. R., Pickett C. B., "The antioxidant responsive element: Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity," *Journal of Biological Chemistry*, vol. 266, no. 18, pp. 11632–11639, 1991, doi: 10.1016/s0021-9258(18)99004-6.
- [18] Saw C. L. L., Yang A. Y., Guo Y., Kong A. N. T., "Astaxanthin and omega-3 fatty acids individually and in combination protect against oxidative stress via the Nrf2-

- ARE pathway,” *Food and Chemical Toxicology*, vol. 62, no. 2013, pp. 869–875, 2013, doi: 10.1016/j.fct.2013.1.0023.
- [19] Zolnourian A., Galea I., Bulters D., “Neuroprotective role of the Nrf2 pathway in subarachnoid haemorrhage and its therapeutic potential,” *Oxidative Medicine and Cellular Longevity*, vol. 2019, no. 6218239, pp. 1–21, 2019, doi: 10.1155/2019/6218239.
- [20] Kavitha K., Kowshik J., Kishore T. K. K., Baba A. B., Nagini S., “Astaxanthin inhibits NF- κ B and Wnt/ β -catenin signaling pathways via inactivation of Erk/MAPK and PI3K/Akt to induce intrinsic apoptosis in a hamster model of oral cancer,” *Biochimica et Biophysica Acta - General Subjects*, vol. 1830, no. 10, pp. 4433–4444, 2013, doi: 10.1016/j.bbagen.2013.05.032.
- [21] Kowshik J., Baba A. B., Giri H., Reddy G. D., Dixit M., Nagini S., “Astaxanthin inhibits JAK/STAT-3 signaling to abrogate cell proliferation, invasion and angiogenesis in a hamster model of oral cancer,” *PLoS ONE*, vol. 9, no. 10, 2014, doi: 10.1371/journal.pone.0109114.
- [22] Takeungwongtrakul S., Benjakul S., “Astaxanthin degradation and lipid oxidation of Pacific white shrimp oil: Kinetics study and stability as affected by storage conditions,” *International Aquatic Research*, vol. 8, no. 1, pp. 15–27, 2016, doi: 10.1007/s40071-015-0120-z.
- [23] Roberts T. C., Langer R., Wood M. J. A., “Advances in oligonucleotide drug delivery,” *Nature Reviews Drug Discovery*, vol. 19, no. 10, pp. 673–694, 2020, doi: 10.1038/s41573-020-0075-7.
- [24] Din F. U., Aman W., Ullah I., Qureshi O. S., Mustapha O., Shafique S., Zeb A., “Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors,” *International Journal of Nanomedicine*, vol. 12, no. 2017, pp. 7291–7309, 2017, doi: 10.2147/IJN.S146315.
- [25] Jaiswal M., Dudhe R., Sharma P. K., “Nanoemulsion: An advanced mode of drug delivery system,” *3 Biotech*, vol. 5, no. 2, pp. 123–127, 2015, doi: 10.1007/s13205-014-0214-0.
- [26] Kumar-Narendra, Mandal A., “Surfactant stabilized oil-in-water nanoemulsion: Stability, interfacial tension, and rheology study for enhanced oil recovery application,” *Energy and Fuels*, vol. 32, no. 6, pp. 6452–6466, 2018, doi: 10.1021/acs.energyfuels.8b00043.
- [27] Shu G., Khalid N., Chen Z., Neves M. A., Barrow C. J., Nakajima M., “Formulation and characterization of astaxanthin-enriched nanoemulsions stabilized using ginseng saponins as natural emulsifiers,” *Food Chemistry*, vol. 255, no. 2018, pp. 67–74, 2018, doi: 10.1016/j.foodchem.2018.02.062.
- [28] Aswathanarayan J. B., Vittal R. R., “Nanoemulsions and their potential applications in food industry,” *Frontiers in Sustainable Food Systems*, vol. 3, no. 2019, pp. 1–21, 2019, doi: 10.3389/fsufs.2019.00095.
- [29] Singh Y., Meher J. G., Raval K., Khan F. A., Chaurasia M., Jain N. K., Chourasia M. K., “Nanoemulsion: Concepts, development and applications in drug delivery,” *Journal of Controlled Release*, vol. 252, no. 2017, pp. 28–49, 2017, doi: 10.1016/j.jconrel.2017.03.008.
- [30] Patra J. K., Das G., Fraceto L. F., Campos E. V. R., Rodriguez-Torres M. D. P., Acosta-Torres L. S., Diaz-Torres L. A., Grillo R., Swamy M. K., Sharma S., Habtemariam S., Shin H. S., “Nano based drug delivery systems: Recent developments and future prospects,” *Journal of Nanobiotechnology*, vol. 16, no. 1, pp. 1–33, 2018, doi: 10.1186/s12951-018-0392-8.
- [31] Emeje M. O., Obidike I. C., Akpabio E. I., Ofoefule S. I., “Nanotechnology in drug delivery,” in *Recent Advances in Novel Drug Carrier Systems*, vol. 3, London: IntechOpen, 2012, pp. 69–106.
- [32] Peng C. H., Chang C. H., Peng R. Y., Chyau C. C., “Improved membrane transport of astaxanthine by liposomal encapsulation,” *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 75, no. 2, pp. 154–161, 2010, doi: 10.1016/j.ejpb.2010.03.004.
- [33] Khalid N., Shu G., Holland B. J., Kobayashi I., Nakajima M., Barrow C. J., “Formulation and characterization of O/W nanoemulsions encapsulating high concentration of astaxanthin,” *Food Research International*, vol. 102, no. 2017, pp. 364–371, 2017, doi: 10.1016/j.foodres.2017.06.019.
- [34] Sotomayor-Gerding D., Oomah B. D., Acevedo F., Morales E., Bustamante M., Shene C., Rubilar M., “High carotenoid bioaccessibility through linseed oil nanoemulsions with enhanced physical and oxidative stability,” *Food Chemistry*, vol. 199, pp. 463–470, 2016, doi: 10.1016/j.foodchem.2015.12.004.
- [35] Chen Z., Shu G., Taarji N., Barrow C. J., Nakajima M., Khalid N., Neves M. A., “Gypenosides as natural emulsifiers for oil-in-water nanoemulsions loaded with astaxanthin: Insights of formulation, stability and release properties,” *Food Chemistry*, vol. 261, no. 2018, pp. 322–328, 2018, doi: 10.1016/j.foodchem.2018.04.054.
- [36] Hong L., Zhou C. L., Chen F. P., Han D., Wang C. Y., Li J. X., Chi Z., Liu C. G., “Development of a carboxymethyl chitosan functionalized nanoemulsion formulation for increasing aqueous solubility, stability and skin permeability of astaxanthin using low-energy method,” *Journal of Microencapsulation*, vol. 34, no. 8, pp. 707–721, 2017, doi: 10.1080/02652048.2017.1373154.
- [37] Xu L., Yu H., Sun H., Yu X., Tao Y., “Optimized nonionic emulsifier for the efficient delivery of astaxanthin nanodispersions to retina: In vivo and ex vivo evaluations,” *Drug Delivery*, vol. 26, no. 1, pp. 1222–1234, 2019, doi: 10.1080/10717544.2019.1682718.
- [38] Shanmugapriya K., Kim H., Saravana P. S., Chun B. S., Kang H. W., “Astaxanthin-alpha tocopherol nanoemulsion formulation by emulsification methods: Investigation on anticancer, wound healing, and antibacterial effects,” *Colloids and Surfaces B: Biointerfaces*, vol. 172, no. 2018, pp. 170–179, 2018, doi: 10.1016/j.colsurfb.2018.08.042.
- [39] Shanmugapriya K., Kim H., Kang H. W., “In vitro antitumor potential of astaxanthin nanoemulsion against cancer cells via mitochondrial mediated apoptosis,” *International Journal of Pharmaceutics*, vol. 560, no. 2019, pp. 334–346, 2019, doi: 10.1016/j.ijpharm.2019.02.015.
- [40] Srihera N., Li Y., Zhang T. T., Wang Y. M., Yanagita T., Waiprib Y., Xue C. H., “Preparation and characterization of astaxanthin loaded liposomes stabilized by sea cucumber sulfated sterols instead of cholesterol,” *Journal of Oleo Science*, vol. 71, no. 3, pp. 401–410, 2022, doi: 10.5650/jos.ess21233.

- [41] Shidhaye S., Vaidya R., Sutar S., Patwardhan A., Kadam V., "Solid lipid nanoparticles and nanostructured lipid carriers – Innovative generations of solid lipid carriers," *Current Drug Delivery*, vol. 5, no. 4, pp. 324–331, 2008, doi: 10.2174/156720108785915087.
- [42] Panagi Z., Beletsi A., Evangelatos G., Livaniou E., Ithakissios D. S., Avgoustakis K., "Effect of dose on the biodistribution and pharmacokinetics of PLGA and PLGA-mPEG nanoparticles," *International Journal of Pharmaceutics*, vol. 221, no. 1–2, pp. 143–152, 2001, doi: 10.1016/S0378-5173(01)00676-7.
- [43] Santonocito D., Raciti G., Campisi A., Sposito G., Panico A., Siciliano E. A., Sarpietro M. G., Damiani E., Puglia C., "Astaxanthin-loaded stealth lipid nanoparticles (AST-SSLN) as potential carriers for the treatment of Alzheimer's Disease: Formulation development and optimization," *Nanomaterials*, vol. 11, no. 2, pp. 1–17, 2021, doi: 10.3390/nano11020391.
- [44] Zhang L., Wang H., "Multiple mechanisms of anti-cancer effects exerted by astaxanthin," *Marine Drugs*, vol. 13, no. 7, pp. 4310–4330, 2015, doi: 10.3390/md13074310.
- [45] Shanmugapriya K., Kim H., Lee Y. W., Kang H. W., "Cellulose nanocrystals/nanofibrils loaded astaxanthin nanoemulsion for the induction of apoptosis via ROS-dependent mitochondrial dysfunction in cancer cells under photobiomodulation," *International Journal of Biological Macromolecules*, vol. 149, no. 2020, pp. 165–177, 2020, doi: 10.1016/j.ijbiomac.2020.01.243.
- [46] Haung H.-Y., Wang Y.-C., Cheng Y.-C., Kang W., Hu S.-H., Liu D., Xiao C., Wang H.-M. D., Ali D., "A novel oral astaxanthin nanoemulsion from *Haematococcus pluvialis* induces apoptosis in lung metastatic melanoma," *Oxidative Medicine and Cellular Longevity*, vol. 2020, no. 2647670, pp. 1–13, 2020, doi: 10.1155/2020/2647670.
- [47] Cho N. H., Williams R., "IDF diabetes atlas," 2019. doi: 10.1016/S0140-6736(55)92135-8.
- [48] Shanmugapriya K., Kim H., Kang H. W., "A new alternative insight of nanoemulsion conjugated with κ -carrageenan for wound healing study in diabetic mice: In vitro and in vivo evaluation," *European Journal of Pharmaceutical Sciences*, vol. 133, no. 2019, pp. 236–250, 2019, doi: 10.1016/j.ejps.2019.04.006.
- [49] Liu C., Zhang S., McClements D. J., Wang D., Xu Y., "Design of astaxanthin-loaded core-shell nanoparticles consisting of chitosan oligosaccharides and poly(lactic-co-glycolic acid): enhancement of water solubility, stability, and bioavailability," *Journal of Agricultural and Food Chemistry*, vol. 67, no. 18, pp. 5113–5121, 2019, doi: 10.1021/acs.jafc.8b06963.
- [50] Gu J., Chen Y., Tong L., Wang X., Yu D., Wu H., "Astaxanthin-loaded polymer-lipid hybrid nanoparticles (ATX-LPN): Assessment of potential otoprotective effects," *Journal of Nanobiotechnology*, vol. 18, no. 1, pp. 1–17, 2020, doi: 10.1186/s12951-020-00600-x.
- [51] Zanoni F., Vakarelova M., Zoccatelli G., "Development and characterization of whey protein-based nanoparticles," *Marine Drugs*, vol. 17, no. 11, pp. 1–16, 2019, doi: 10.3390/md17110627.
- [52] Wang T., Hu Q., Lee J. Y., Luo Y., "Solid lipid-polymer hybrid nanoparticles by in situ conjugation for oral delivery of astaxanthin," *Journal of Agricultural and Food Chemistry*, vol. 66, no. 36, pp. 9473–9480, 2018, doi: 10.1021/acs.jafc.8b02827.
- [53] Kim E. S., Baek Y., Yoo H. J., Lee J. S., Lee H. G., "Chitosan-tripolyphosphate nanoparticles prepared by ionic gelation improve the antioxidant activities of astaxanthin in the in vitro and in vivo model," *Antioxidants*, vol. 11, no. 3, pp. 1–12, 2022, doi: 10.3390/antiox11030479.
- [54] Li C., Song Q., Yin X., Song R., Chen G., "Preparation, characterization, and in vitro anticancer activity evaluation of broccoli-derived extracellular vesicle-coated astaxanthin nanoparticles," *Molecules*, vol. 27, no. 12, p. 3955, 2022, doi: 10.3390/molecules27123955.
- [55] Oh H., Lee J. S., Sung D., Lim J. M., Choi W. II, "Potential antioxidant and wound healing effect of nano-liposomal with high loading amount of astaxanthin," *International Journal of Nanomedicine*, vol. 15, no. 2020, pp. 9231–9240, 2020, doi: 10.2147/IJN.S272650.
- [56] Chen Z., Li W., Shi L., Jiang L., Li M., Zhang C., Peng H., "Kidney-targeted astaxanthin natural antioxidant nanosystem for diabetic nephropathy therapy," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 156, no. 2020, pp. 143–154, 2020, doi: 10.1016/j.ejpb.2020.09.005.
- [57] Nurdianti L., Rusdiana T., Sopyan I., "Antidiabetic activity of thin film containing astaxanthin-loaded nanoemulsion using carboxymethylcellulose sodium polymer on alloxan-induced diabetic rabbit," *Journal of Advanced Pharmaceutical Technology and Research*, vol. 11, no. 4, pp. 189–193, 2020, doi: 10.4103/japtr.JAPTR_55_20.
- [58] Chang X., Xing L., Xing L., Xing L., Xing L., Wang Y., Yang C. X., He Y. J., Zhou T. J., Gao X. D., Li L., Hao H. P., Jiang H. L., Jiang H. L., Jiang H. L., Jiang H. L., "Monocyte-derived multipotent cell delivered programmed therapeutics to reverse idiopathic pulmonary fibrosis," *Science Advances*, vol. 6, no. 22, pp. 1–16, 2020, doi: 10.1126/sciadv.aba3167.
- [59] Narayan D. S., Wood J. P. M., Chidlow G., Casson R. J., "A review of the mechanisms of cone degeneration in retinitis pigmentosa," *Acta Ophthalmologica*, vol. 94, no. 8, pp. 748–754, 2016, doi: 10.1111/aos.13141.
- [60] Cullen A. P., "Photokeratitis and other phototoxic effects on the cornea and conjunctiva," *International Journal of Toxicology*, vol. 21, no. 6, pp. 455–464, 2002, doi: 10.1080/10915810290169882.
- [61] Harada F., Morikawa T., Lennikov A., Mukwaya A., Schapper M., Uehara O., Takai R., Yoshida K., Sato J., Horie Y., Sakaguchi H., Wu C. Z., Abiko Y., Lagali N., Kitaichi N., "Protective effects of oral astaxanthin nanopowder against ultraviolet-induced photokeratitis in mice," *Oxidative Medicine and Cellular Longevity*, vol. 2017, no. 1956104, pp. 1–13, 2017, doi: 10.1155/2017/1956104.
- [62] Chik M. W., Affandi M. M. M., Singh G. K., "Detection of astaxanthin at different regions of the brain in rats treated with astaxanthin nanoemulsion," *Journal of Pharmacy & BioAllied Sciences*, vol. 14, no. 1, pp. 25–30, 2022, doi: 10.4103/jpbs.JPBS.
- [63] You Z. Q., Wu Q., Zhou X. M., Zhang X. S., Yuan B., Wen

- L. L., Xu W. D., Cui S., Tang X. L., Zhang X., "Receptor-mediated delivery of astaxanthin-loaded nanoparticles to neurons: An enhanced potential for subarachnoid hemorrhage treatment," *Frontiers in Neuroscience*, vol. 13, no. 2019, pp. 1–13, 2019, doi: 10.3389/fnins.2019.00989.
- [64] Cai W., Wu Q., Yan Z. Z., He W. Z., Zhou X. M., Zhou L. J., Zhang J. Y., Zhang X., "Neuroprotective effect of ultrasound triggered astaxanthin release nanoparticles on early brain injury after subarachnoid hemorrhage," *Frontiers in Chemistry*, vol. 9, no. 2021, pp. 1–13, 2021, doi: 10.3389/fchem.2021.775274.
- [65] Gu J., Wang X., Chen Y., Xu K., Yu D., Wu H., "An enhanced antioxidant strategy of astaxanthin encapsulated in ROS-responsive nanoparticles for combating cisplatin-induced ototoxicity," *Journal of Nanobiotechnology*, vol. 20, no. 1, pp. 1–17, 2022, doi: 10.1186/s12951-022-01485-8.