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Review article

Docosahexaenoic acid-loaded nanoparticles: A state-of-the-art of preparation methods, characterization, functionality, and therapeutic applications

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A B S T R A C T

Docosahexaenoic acid (DHA, C22:6 n-3), an omega-3 polyunsaturated fatty acid, offers several beneficial effects. DHA helps in reducing depression, autoimmune diseases, rheumatoid arthritis, attention deficit hyperactivity syndrome, and cardiovascular diseases. It can stimulate the development of brain and nerve, alleviate lipids metabolism-related disorders, and enhance vision development. However, DHA susceptibility to chemical oxidation, poor water solubility, and unpleasant order could restrict its applications for nutritional and therapeutic purposes. To avoid these drawbacks and enhance its bioavailability, DHA can be encapsulated using an effective delivery system. Several encapsulation methods are recognized, and DHA-loaded nanoparticles have demonstrated numerous benefits. In clinical studies, positive influences on the development of several diseases have been reported, but some assumptions are conflicting and need more exploration, since DHA has a systemic and not a targeted release at the required level. This might cause the applications of nanoparticles that could allow DHA release at the required level and improve its efficiency, thus resulting in a better controlling of several diseases. In the current review, we focused on researches investigating the formulation and development of DHA-loaded nanoparticles using different delivery systems, including low-density lipoprotein, zinc oxide, silver, zein, and resveratrol-stearate. Silver-DHA nanoparticles presented a typical particle size of 24 nm with an incorporation level of 97.67 %, while the entrapment efficiency of zinc oxide-DHA nanoparticles represented 87.3 %. By using zein/Poly (lactic-*co*-glycolic acid) stabilized nanoparticles, DHA's encapsulation level reached 84.6 %. We have also highlighted the characteristics, functionality and medical implementation of these nanoparticles in the treatment of inflammations, brain disorders, diabetes as well as hepatocellular carcinoma.

1. Introduction

Omega-3 polyunsaturated fatty acids (ω-3 PUFA) have been utilized for the treatment and prevention of several health issues including inflammations, brain diseases, hepatocellular carcinoma and diabetes. It has been stated that ω-3 PUFA-supplemented intakes have the potential to decrease the risks of hepatocellular carcinoma growth in organisms with known hepatitis infections [1]. The preventive roles of ω-3 PUFA in hepatocarcinogenesis have been also confirmed [2]. Among these PUFA, DHA is an ω-3 FA found in various natural sources, particularly in marine oils [3,4]. DHA is liable to oxidation because of its six unsaturation (Fig. 1) leading to loss of its bioactivity. Hence, DHA encapsulation is recommended to protect it from several environmental influences, such as oxygen, humidity, light, gastric acid, etc. [5,6] In the body, this fatty acid is produced from α-linolenic acid (C18:3) through elongations and desaturations reaction series. However, the bioconversion level is very low (about 2–10 %) [7], and even lower (0.01 %) [8]. Thus,

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DHA-enriched food products and DHA dietary sources are considered the two major exogenous supplies to acquire further DHA required for several biological activities in the body. Seafood and its by-products contain considerable amounts of ω-3 PUFA, comprising DHA. Conventionally, cold-water fish species, for instance salmon, mackerel, herring, and trout are considered as the major diet sources for DHA. The amount of DHA in these types of fish represents around 0.68–1.43 g/100g meat. Furthermore, milk, meat, and egg from animals fed with seafood by-products or PUFA-producing algae have been reported as DHA sources [9].

Omega-3 PUFA have neuroprotective effects towards different neurological syndromes, for example depression and Alzheimer's disease, and the way *via* which these fatty acids efficiently amended those neurological syndromes was by obstructing the expression CD11b, a microglia M1 phenotypic marker and down-regulating pro-inflammatory cytokines IL-1β, TNF-α and IL-6 levels, whereas elevated microglia M2 phenotype marker naming CD206, and the anti-inflammatory cytokine IL-10 [10]. Moreover, ω-3 PUFA exhibited cytoprotective effects towards 7 KC-prompted cell death in murine neuronal N2a cells: 7 KC-prompted reactive oxygen species excess mitigation, mitochondrial transmembrane hypothetical drop, and escalated the permeability of the plasma membranes [11]. *In vitro* investigations have revealed that DHA demonstrated a dose-dependent cytotoxicity towards hepatocellular carcinoma cells [12,13]. However, required toxic levels exceed those attained through dietary supplements [14]. An alternative could be considered as an efficient delivery system for prospective claims of DHA to hepatocellular carcinoma's patients [15]. DHA demonstrated a dose-dependent inhibition of *in vitro* growth of *Hepatocellular* pylori strains. Notably, treatment by using free DHA caused a 50 % decline in gastric colonization of H. pylori by 50 % in mice with gastric infections [5,16].

Among various delivery systems available including emulsions, nanoparticles, liposomes, microcapsules and gels, nanoparticles stand out due to their advantages [17,18]. Indeed, nanoparticles have been widely implemented in diverse applications, including medicine, food, and cosmetic industries [19–21]. Regarding therapeutic and diagnostic nanoparticles, two major groups are known; organic nanoparticles, such as liposomes, micelles, polymeric and other inorganic nanoparticles, such as gold, iron oxide. Organic nanoparticles have many clinical applications, such as diagnostics, imaging and photothermal therapies [22] and inorganic nanoparticles exhibited beneficial roles in preclinical researches, including cancer imaging and therapy [23], incorporation of drugs, peptides, and proteins for *in vitro* and/or *in vivo* applications, along with therapeutic molecules delivery, magnetic targeting, anemia and hyperthermia treatment, and thermal ablation cure of tumors [24]. Alongside the wide medical and industrial applications of nanoparticles, they exhibited definite toxicities [25] and basic understanding is essential to accurately encounter these toxic properties [26].

Several studies have assessed DHA-loaded nanoparticle properties [27–29]. These materials can be synthesized by dissolving DHA in ethanol and adding it into casein solution. Theses nanoparticles have demonstrated significant protective effects on DHA, and exhibited better bioactivity and stability [30]. When prepared with low-density lipoprotein (LDL), DHA-loaded nanoparticles exhibited superior physical properties and oxidative stability than free DHA and native LDL [31]. DHA-loaded nanoparticles prepared using polylactic acid and chitosan showed higher water solubility and better encapsulation level (80.45 %) than free DHA [27]. Using stable nanoparticles like zein/Poly (lactic-*co*-glycolic acid), DHA encapsulation level reached 84.6 %, with a good stability until one month of storage. DHA-loaded nanoparticles improved 750 times in water solubility than free DHA due to hydrophilic carboxyl and hydroxyl groups in polylactic acid [28].

While some individual studies have touched upon various aspects of DHA delivery, there is limited information on comprehensive reviews that delve into the various strategies for delivering DHA effectively. In this context, our review aimed to spotlight specifically on synthesis methods employed for DHA-loaded nanoparticles, their distinctive characteristics, and potential therapeutic applications. The criteria used to select the cited literature was the comparison of certain treatments and experimental design of these studies.

2. Preparation methods of DHA-loaded nanoparticles

Different types of DHA-loaded nanoparticles are prepared by using various delivery systems and preparation methods (Table 1). DHA nanoparticles could be synthesized as triglycerides, phospholipids or ethyl esters. The ethyl ester forms of DHA had another absorption rate in the human body as compared to the triglyceride-based DHA forms, but the plasma lipids level seem to be equivalent; nevertheless, the triglycerides form could be better exploited in the body [32]. In another study, plasma level of DHA was higher when provided in monoacylglycerols than ethyl esters form [33]. The preparation of DHA-loaded nanoparticles in primarily are sorted into two main groups; bottom-up methods and top-down approaches. Furthermore, these processes are subdivided into various subcategories depending on reactions' conditions, operations, and approved procedures. Bottom-up methods are further subdivided into two main classes; the first class includes biological synthesis employing plants and microorganism, while the second class comprises spinning, template support formulation, plasma or flame spraying formulation, atomic or molecular condensation, and laser pyrolysis [34]. Top-down methods include chemical etching, laser ablation, electro-explosion, sputtering, and mechanical milling [26,35]. In top-down methods, nanoparticles are prepared through a size reduction approach where the bulk material is converted into tiny

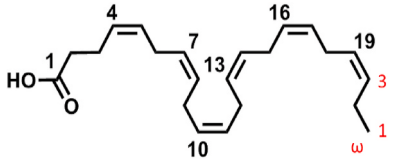

Fig. 1. Chemical structure of docosahexaenoic acid. Draw using ChemDraw (Pro 12.0, Cambridge Soft Corporation).

Table 1
Preparation methods and characterizations of DHA-loaded nanoparticles.

DHA-Carrier	Preparation method	Target	Particle size	Zeta potential	Incorporation level of DHA	Reference
LDL	Homogenization and ultrasonication	Study DHA activity against *Helicobacter pylori*	260, 302, and 323 nm for DHA synthesized using 1, 2, and 2.5 % of DHA, respectively	−28 mV	A maximum incorporation of 66 ± 7 % was achieved when 2 % v/v of DHA was utilized	Seabra et al. [39]
LDL	Reconstitution	Transarterial locoregional of DHA delivery to the liver	24.5 nm	−21.6 mV	2000 molecules of DHA per LDL particle	Li et al. [40]
LDL	Core replacement	Localized delivery of DHA to the brain	An average particle size of 22.4 ± 0.71 nm	−25.5 ± 1.31 mV	LDL-DHA nanoparticles contained an average of 596 phospholipids molecules	Mulik et al. [41]
LDL	Core replacement	Elucidating the structural organization of DHA	22.4 ± 0.71	−22 mV	LDL-DHA nanoparticles were able to include more than1100 DHA molecules/ particles	Mulik et al. [42]
LDL	Reconstitution	Tumor cell death in hepatocellular carcinoma bearing rats	A diameter of 30.1 ± 0.5 nm	−23.4 ± 0.9 mV	Each LDL nanoparticle carried around 1672 ± 219 DHA molecules	Wang et al. [43]
LDL	Reconstitution	Hepatic arterial infusion of DHA	A particle size of 20 nm,	−25 mV	DHA loading approximating 1152 molecules/LDL particle	Wen et al. [44]
ZnO and gum Arabic	One-step solid-state reaction and sonication	Study DHA as an antidiabetic agent in rats	~90 nm compared to pure ZnO nanoparticles (30 nm)	−35 mV	–	Hussein et al. [45]
Silver nanoparticles	Nanoprecipitation	Improving the endothelial dysfunctions	An average particle size of 24 nm	–	Inclusion efficiency of 97.67 %	Hussein et al. [46]
ZnO	Homogenization and ultrasonication	DHA nanoparticles role in diabetic rats	–	–	Entrapment efficiency of 87.3 %	Hussein et al. [47]
ZnO and silver	Solid state	Expression of glucose transport pathway	16–22 nm for ZnO nanoparticles and 3–14 nm for silver nanoparticles	–	–	El-Daly et al. [48]
Zein/poly(lactic-*co*-glycolic) acid	Antisolvent precipitation	Fabrication and characterization of DHA nanoparticles	319.9 nm	−55.1 mV	64–84.6 %	Liu et al. [28]
Resveratrol stearate	Microemulsion	Antineoplastic activity in colorectal cancer cells *in vitro*	A particle size of 1000 ± 1.8 nm	–	Encapsulation efficiency of 100 %	Serini et al. [49]
Transferrin-conjugated phospholipid	Solvent evaporation and emulsification	Treatment of human immunodeficiency virus reservoir in brain	90–140 nm	−35 mV	Nanocarriers contained 5–15 % DHA	Guo et al. [50]
Polyethylene glycol	DHA liposomes	Targeting chronic inflammatory diseases and cancer	99 ± 16 nm	−15.7 ± 2.5 mV	81.35 ± 3.24 %	Alaarg et al. [51]

LDL, low-density lipoproteins; DHA, docosahexaenoic acid; ZnO, zinc oxide.

materials by using ultrasonic generators at higher frequencies about 1,200,000 rpm [36]. In the bottom-up methods, nanostructures are synthesized atom by atom or particle by particle to produce nanostructure, using a high supersaturation with nuclei growth [37]. In spite of that top-down methods have been greatly successful on the commercial scale, they have inherent disadvantages that require the development of other methods. The bottom-up methods have not yet been recognized as an effective commercial approach [38]. The advantages, disadvantages, and influencing factors of various top-down and bottom-up methods applied for nanomaterials production have been reported [34].

2.1. Low-density lipoprotein-DHA nanoparticles

Lipoproteins serve as endogenous carriers within the circulatory system, facilitating transportation of triacylglycerol and cholesterol within body tissues. They could be extracted from the plasma, adjusted with pharmaceutical drug or imaging agents, and subsequently reintroduced into preclinical studies. The significance and adaptability of lipoprotein-based nanoparticles in medical applications have been demonstrated [52,53]. Among these, LDL, spherical nanosize molecules with a diameter of 18–25 nm, offered active nanoparticle targeting potential [54]. The external layer of LDL comprises a hydrophilic phospholipid monolayer together with free cholesterol and apolipoprotein-B100, while its internal layer contains a hydrophobic core comprising esterified cholesterol and triacylglycerols (Fig. 2).

LDL-based nanoplatforms are well-sited as vehicles for DHA delivery, since many tumors actively taken up these lipoproteins to get the required cholesterol and lipids to support rapid cells proliferation [55]. LDL does not tend to provoke immune reactions and contributes to reducing excessive stress in the body due to its status as an endogenous molecule [56]. The application of synthetic and natural LDL-based delivery systems in nanomedicine, employing various targeting mechanisms, has been extensively reviewed [57]. Several studies employed various techniques to incorporate non-esterified DHA into LDL. Ou et al. isolated human LDL from individuals with a history hypercholesterolemia [58]. The reconstitution method, reported by Reynolds et al. [31] was subsequently followed to incorporate non-esterified DHA into LDL. Wen et al. used the same method to isolate human LDL from apheresis plasma [44,59], and DHA was incorporated into LDL *via* reconstitution approach. Moreover, Seabra et al. reported that nanoparticles were formulated *via* hot homogenization and ultrasonication [39].

Moss et al. reported that human serum albumin was dissolved in potassium chloride solution [60]. DHA solution in ethanol was mixed with human serum albumin solution, vortexed, and kept for 1 h at 37 °C. DHA bound to human serum albumin was purified and stored under nitrogen. Li et al. isolated human LDL from apheresis plasma, and non-esterified DHA was incorporated into LDL through reconstitution procedure [40]. LDL freeze-dried with starch, were subjected to numerous organic extraction circles to eliminate non-polar lipids from LDL. The residue was mixed with DHA and kept at 4 °C. Finally, solvent was vaporized under nitrogen, and the sample was resuspended in tricine buffer and kept at 4 °C.

2.2. Zinc oxide-DHA nanoparticles

Looking to countless applications of zinc oxide (ZnO)-DHA nanoparticles in cosmetics, drugs delivery, and biosensors, ZnO nanoparticles attracted a significant interest compared to other metal nanoparticles. These nanoparticles have been widely studied in several fields due to their anti-diabetic, anticancer, and antimicrobial properties [61]. ZnO nanoparticles can be prepared in a solid-state, dry process, offering eco-friendly benefits, cost-effectiveness, scalability, and high production yields as its primary advantages [62]. Comprehensive details regarding ZnO nanoparticles characteristics have been covered in previous literatures [63,64].

Hussein et al. developed nanoparticles coated with gum Arabic, employing a straightforward synthesis method allowing size control and reveals cytocompatibility [45]. ZnO nanoparticles were prepared using one-step solid-state reaction. Gum Arabic was grinded and mixed with sodium hydroxide powder. Then, zinc acetate was added to the powder and grinded for 20 min. A number of deionized water and alcohol intervals were used to rinse the solid mixture through sonication to eradicate extra sodium hydroxide and

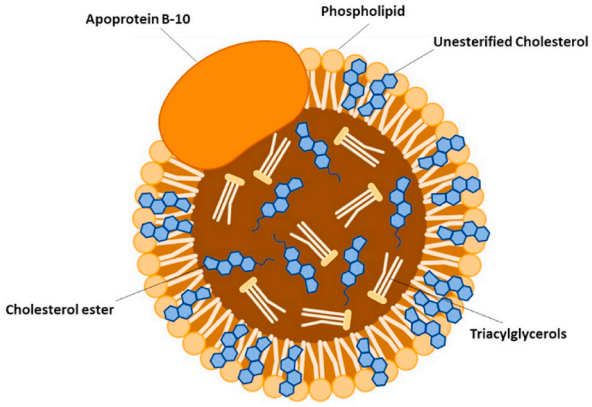

Fig. 2. Low-density lipoprotein structure. The figure is drawn using biorender.com.

gum Arabic. The product was filtered, dried, calcined for 4 h at 600 °C, resulting in decomposition of zinc hydroxide to form pure ZnO nanoparticles. The calcined nanoparticles were re-dispersed in ultrapure water. DHA solution was added into ZnO nanoparticles aqueous suspension, serving as the ideal drug carrier. Then, ZnO and DHA mixture was stirred for 30 min, and sonicated to guarantee a comprehensive entrapment of DHA. The solution was stored in dark overnight to create nanocomposites of DHA-loaded ZnO nanoparticles.

According to Hussein et al., ZnO nanoparticles were prepared by dissolving cellulose nanocrystals in deionized water [47]. Zinc nitrate was added to cellulose nanocrystals then the mixture was vortexed for 30 min. Sodium hydroxide was added to the mixture, and ZnO nanoparticles were formulated from zinc hydroxide precipitate that was enclosed by cellulose nanocrystals chains *via* calcination for 3 h at 900 °C. The calcined nanoparticles were suspended in water and stirred for 120 min. DHA was suspended in water followed by homogenization to disperse DHA particles. The solution was dropwise added to ZnO nanoparticles, and the obtained mixture was blended for 60 min followed by sonication to guarantee encapsulation.

Cellulose nanocrystals were utilized as stabilizing agents to synthesize DHA-ZnO nanoparticles [48]. Nanocrystals were grinded with zinc acetate dehydrate, and sodium hydroxide was added to the obtained powder. Then, the powder was washed by distilled water to eradicate unprocessed composites. The wet powder was calcined at 700 °C to induce zinc hydroxide layered by cellulose nanocrystals to pure ZnO nanoparticles through water removal. The nanoparticles were dispersed in water and Tween 60 mixture, and DHA solution was dropwise added, afterwards mixing for 60 min. The mixture was centrifuged at 20,000 rpm, and dehydrated at 50 °C [48].

2.3. Other DHA-loaded nanoparticle carriers

Silver nanoparticles have found extensive applications in the medical field [65,66]. Their effectiveness is largely attributed to their nanoscale sizes, which provide elevated surface area-to-volume ratios [67]. Hussein et al. prepared silver nanoparticles using the nanoprecipitation method [68,69]. Soluble starch was dispersed in deionized water comprising sodium hydroxide. The temperature was increased to 60 °C following whole dissolution. Tween 80 in water comprising silver nitrate was added drop by drop to the solubilized starch, followed by mixing for 30 min. The formulated nanoparticles were utilized as DHA carriers through the addition of 0.5 g DHA/5 mL water to the nanoparticles suspension, followed by stirring for 30 min. Nanoparticles-encapsulated DHA solution was precipitated with ethyl alcohol, followed by centrifugation. The powder was rinsed with ethanol to eliminate other unreacted compounds, and then centrifuged again. Finally, the upper phase was retained to evaluate the incorporation efficacy for silver nanoparticles concerning DHA.

Zein, a natural protein polymer found in corn, has been stated to self-assemble into structures diversity because of its amphiphilic features [70]. Besides, conjugates and complexes shaped by zein and composites are easy to accumulate, which presents larger assemblies to zein-constructed colloidal systems [71]. Zein nanoparticles offer several advantages over other colloidal systems. Indeed, they originate from natural sources, avoid using toxic synthetic agents, allow for straightforward efficient large-scale industrial production under mild conditions, and exhibit biocompatibility and biodegradability [72,73]. Zein nanoparticles and microparticles have proven to be effective delivery systems for various non-polar compounds, such as vitamin D, curcumin, and thymol [74–76]. These vehicles exhibited an ability to protect the loaded molecules from stomach severe conditions and provide an instrument for controlled release of target compounds [77,78].

Liu et al. [28] synthesized zein/poly (lactic-*co*-glycolic acid), stable nanoparticles, *via* antisolvent precipitation approach reported by Yuan et al. [79] Diverse zein amounts were dissolved in ethanol using magnetic stirring for 120 min. After 5 min of stirring, different amounts of poly-D, L-lactide-*co*-glycolide acid/DHA were mixed with the ethanol to obtain a final concentration of 1 %, followed by ultrasonication. Later, the solutions were poured into the formulated zein mixture in dark. The aforementioned solutions underwent an additional 6-h stirring phase at the same speed while kept in darkness. This extended stirring duration was employed to remove ethanol from zein/poly (lactic-*co*-glycolic acid) nanoparticle dispersions. To complete the lost ethanol, deionized water was mixed, subsequently centrifuging to remove nonencapsulated DHA.

Anti-inflammatory and anti-irritant properties of DHA encapsulated in resveratrol-based solid lipid nanoparticles were evaluated [80]. Free and DHA-loaded resveratrol-stearate solid lipid nanoparticles were prepared with an encapsulation value of 100 % using the microemulsion method. Resveratrol-stearate either with or without DHA were liquefied at 60–65 °C. Then, a warm solution of butanol, sodium taurocholate, and Tween-80 were supplemented to get a visual clear system. One volume of microemulsion was directly dispersed in 20 volume of cold water at high-speed homogenization. Ultrafiltration was applied to clean the obtained dispersions twice.

3. Characterization of DHA-loaded nanoparticles

The different characteristics of DHA-loaded nanoparticles including the particle size, zeta potential, and incorporation level are presented in Table 1. Notably, the particle size distribution and zeta potential values exhibited variations depending on the chosen carriers and preparation's methods. The stability of DHA-zein loaded nanoparticles was shown to be influenced by numerous factors, for instance pH, temperature, and ionic intensity [28].

One important finding was enhanced thermal stability and salt tolerance of these nanoparticles, which could be attributed to the incorporation of long-chain molecule poly(lactic-*co*-glycolic) acid restricted the space for zein to enlarge by raising the temperature, making the structure of nanoparticles more compact [28]. Nanoparticles molecules gathering could be prevented at low levels of salt by the electrostatic interactions [81]. Compared to free DHA, DHA-loaded nanoparticles exhibited 750-fold higher water solubility

[28]. DHA nanoparticles loaded within poly-D, L-lactide-*co*-glycolide and chitosan displayed higher water solubility as compared to free DHA with an encapsulation level of 80.45 %. Moreover, under gastrointestinal fluid model, both nanoparticles showed a controlled-release behavior [27].

DHA-loaded nanoparticles characteristics can be evaluated through several techniques, including Ultraviolet–Visible (UV–visible) spectroscopy, Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscope (SEM), X-ray diffraction, and Circular Dichroism (CD) spectroscopy. Hussein et al. stated that DHA-silver nanoparticles exhibited a small spherical size when examined with UV–visible spectroscopy, DLS, TEM, and SEM analysis [46]. The morphological structure of freeze-dried DHA nanoparticles became a little smoother, and simultaneously the particle size had improved to ~25 μm, which might be attributed to that DHA was endangered in nanoparticles core-shell assembly due to hydrophobic interactions energy [82]. It has been also reported, through TEM examination, that the DHA-loaded ZnO nanoparticles exhibited a spherical structure as in the parent ZnO nanoparticles ensuring that particles surface properties were not affected by the incorporation process [45]. The peaks of DHA spectrum were detected at 1442.18 and 928.33 cm^{-1} through FTIR analysis. These peaks correspond to the absorptions of dimethyl bond and unsaturated bonds [83].

4. Functionality and therapeutic applications of DHA nanoparticles

Nanoparticles can be applied for drugs delivery in different ways, including targeted drugs delivery, improved solubility, controlled release, drugs protection, vaccine delivery, cancer therapy, imaging and diagnostics, and gene delivery. Their extensive application in medical sector features their potential as promising delivery systems for diagnostic and therapeutic mediators [84,85]. It is assumed that nanoparticles might be capable to conquer definite physical and biological barriers where traditional medications fail. For biological applications, nanoparticles should be synthesized in a manner retaining their beneficial properties when applied to tissues, cells, or serum [86].

Fig. 3 shows different types of nanoparticles (lipid-based, polymeric, and inorganic) used for DHA delivery in medical applications. As a result of their small size, nanoparticles integrally possess a higher surface area: volume ratio. This causes a natural affinity to collect and act together with the plasma proteins after intravenous injection, resulting in a prompt allowance by the reticuloendothelial system. Therefore, nanoparticles are regularly covered with biocompatible hydrophilic polymers. The bioactive profile and level of released drugs could be affected by manipulating the coating materials and size of nanoparticles [74].

4.1. DHA-loaded nanoparticles for inflammations treatment

The anti-inflammatory activities of DHA were observed by experimental inflammation models [75]. The mechanism of DHA employing its anti-inflammatory properties is remaining a matter of debate; however, it is expected that DHA-derived oxygenated

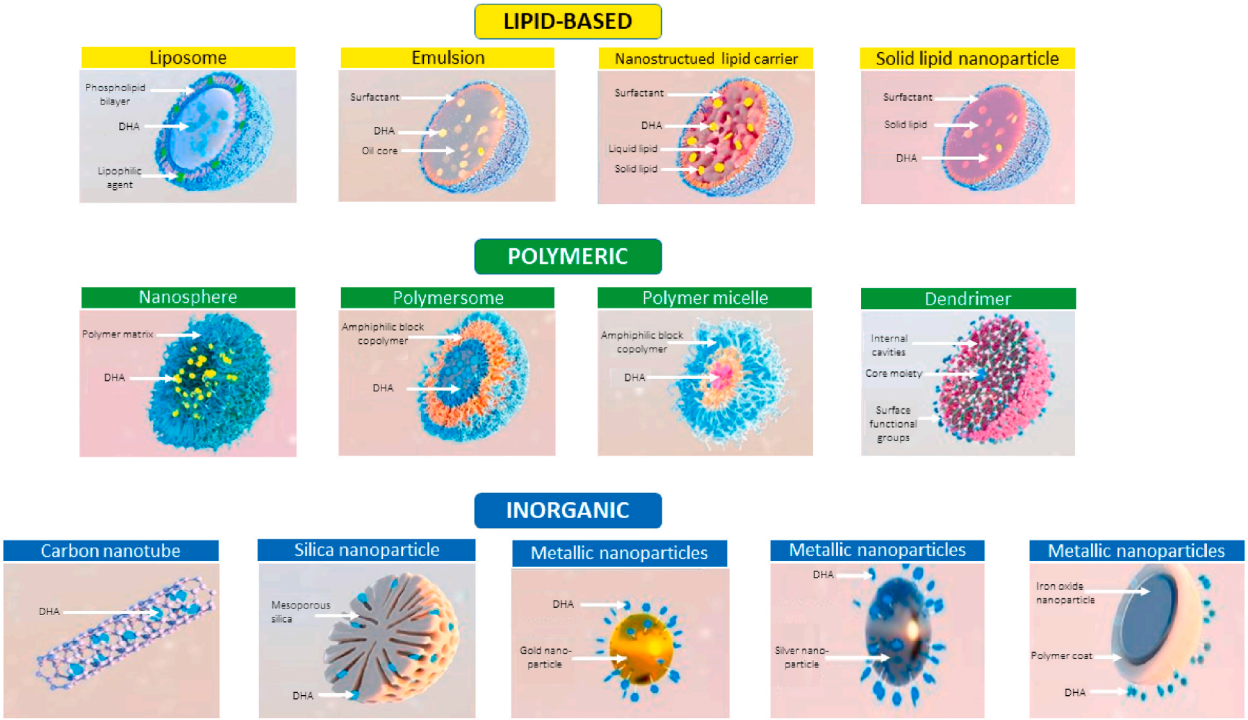

Fig. 3. Different forms of nanoparticles used for DHA delivery in medical applications.

metabolites, specifically protectins, resolvins, and macrophage mediators in determining inflammation could be responsible for these properties [76]. Although resolvins are the most well-recognized DHA-derived mediators, another pro-resolving mediator originating from DHA, known as maresins, has demonstrated substantial efficacy in experimental models for the treatment and prevention of intestinal inflammations [87]. It has been reported that after immune cells treatment with DHA, pro-inflammatory cytokines interleukin-1β, interleukin-6, in addition to tumor necrosis factor α decreased [88].

Seabra et al., assessed microbial growth curves for 24 h in the existence of diverse DHA levels either free or nanoparticles-loaded [39]. Nanoencapsulation process improved the bactericidal impact of DHA, as DHA-loaded nanoparticles exhibited a higher capability to restrain the growth of H. pylori in much lower levels (25 μM) as compared to free DHA (more than100 μM). Through SEM, TEM and imaging flow cytometry, it was recognized that DHA-loaded nanoparticles interacted with cell membrane of H. pylori. This interaction increased the bacterium's periplasmic space, membrane disruption, and subsequent leak of its cytoplasmic contents. The formulated nanoparticles did not show cytotoxicity to the gastric adenocarcinoma cells of human, even at levels effective against *H. pylori*. Thus, DHA-loaded nanoparticles hold promise as a potential substitute for H. pylori infections treatment.

Targeting cancer cells with LDL-DHA nanoparticles creates a phenomenon often referred to as the "typical storm" in which PUFA, substantially effective substrates toward lipids peroxidation [89], are introduced into the cellular environment with irregular iron and redox metabolisms [90]. The consequent reduction of glutathione and suppression of glutathione activity directs the set ferroptotic tumor cell death. Additionally, an effective anti-tumor regulation was reached by LDL-DHA-induced ferroptosis, since tumor expansion suppression was persistent after termination of the treatment. The results showed innovative visions into the molecular mechanisms leading the tumor cytotoxicity of LDL-DHA. Thus, LDL-DHA nanoparticles might be involved in expanding therapeutic agent lists, such as sorafenib, erastin, and artesunate that have the ability to provoke anticancer properties through ferroptosis [58].

4.2. DHA-loaded nanoparticles for brain functions

It has been reported that DHA content can be doubled within hours using focused ultrasound/LDL-DHA nanoparticles. Based on previous studies of ω-3 PUFA functions in the central nervous system (CNS) disorders, LDL-facilitated administration of DHA to the brain is expected to have several positive effects, such as reducing neuroinflammations [91], increasing cognition [92], and providing protection against strokes [93] and seizures [94].

DHA has been reported to have anticancer properties [93] suggesting its potential function in treatment of the brain tumors. A critical aspect of this methodology is the neurological significance related to recurrence opening of the blood-brain-barrier (BBB) through ultrasonication. For LDL-DHA treatment, the persistent character of neurodegenerative syndromes requires repetitive opening of BBB. Previous studies suggested safety of repeat BBB opening; however, additional investigations are required [95]. The approach might be better used in severe brain injury conditions where one single intervention of focused ultrasound/LDL-DHA treatment might provide protection to the brain by simplifying the resolution at injury regions and preventing neuroinflammatory flow [91].

Mulik et al. revealed that stereotactic-guided focused ultrasound was able to non-invasively mediate LDL nanoparticles delivery into ordinary mice brain [41]. LDL nanoparticles were transferred selectively into neuronal cells in the targeted section of focused ultrasound exposure. Once LDL-DHA nanoparticles were endocytosed, DHA was freely integrated in phospholipids' bilayers of brain cells. Besides esterification, LDL-carried DHA was likewise favorably oxidized to resolvin D1 pro-resolving lipids mediator, instead of going through lipids peroxidation to malondialdehyde. Targeting the brain with DHA has several medical concerns since DHA is involved in various neurological functions [96]. More importantly, DHA's accumulation in the brain from diverse dietary sources is comparatively low representing 4 mg/day [97]. Accordingly, in cases where DHA's content in brain (a regular average of 5 g) is lacking by around 20–30 %, it would require several months up to one year to compensate DHA content through dietary ingestion.

Indeed, effective and safe conveyance of drugs through BBB is vital for treatment of human from immunodeficiency virus, which involves adequately high levels of anti-retroviral in CNS section for annihilation of the suppressed and occasionally drugs-resistant human immunodeficiency virus strains [98]. Given its significance as a vital brain nutrient, DHA is an intriguing candidate for the enhancement of secure and effective lipid-based nano-carriers tailored for this purpose. Guo et al. investigated the effect of DHA incorporation into nano-delivery systems for anti-retroviral drugs across BBB [50]. The study revealed several benefits to this approach. Comparing DHA incorporation transferrin-receptor targeting, both approaches improved the accumulation of nano-carriers in brain and their uptake by brain cells. However, DHA proved to be more effective in enhancing BBB permeability and increasing the accumulation of the anti-retroviral drug darunavir in brain. By using another oil as DHA replacer remarkably decreased the cellular uptake of nano-antiretroviral. The study validated the advantageous of combining DHA in nano-carriers as an applicable, simple and prospective safe approach to improve the administration of darunavir and possibly other lipophilic components to brain [50].

4.3. DHA-loaded nanoparticles for the management of diabetes

Several research have confirmed that DHA has a synergistic impact on diabetes, and this effect could be further improved through its encapsulation into nano-carriers. Shoji et al. revealed that using DHA for the pre-incubation of placental trophoblast cells delivered a protection for the cells from oxidative damage of DNA [99]. Barden et al. stated that 4 g daily of fish oil-enriched group showed considerably lower cord plasma F2-isoprostanes compared to those observed in olive oil-enriched group [100]. Hussein et al. revealed that DHA-loaded ZnO nanoparticles displayed a superior antioxidative impact than the free form of DHA proved by a noticeable decline of DNA impairment, malondialdehyde and advanced oxidation protein product and increase in superoxide dismutase levels [45]. ZnO nanoparticles antioxidant properties could be attributed to their capability in destructive management of inflammatory cytokines gene expression that were approved to produce reactive oxygen species [101]. Various biochemical analyses, including

insulin, insulin resistance, blood glucose, fatty acids factors, oxidant and antioxidants, triacylglycerols and cholesterol, and phosphoinositide 3-kinase quantities confirmed the effective research of diabetes in investigational rats. Afterwards the oral administration of rats using free DHA or DHA-loaded ZnO nanoparticles, data confirmed DHA nanoparticles advantages than free molecules. The physicochemical properties and biocompatibility of ZnO nanoparticles had a vital function in diabetes treatment [102].

The improvement in insulin sensitivity was attributed to improved insulin signaling mediated by PUFA. The administration of DHA up-regulated proliferator-activated receptors, further enhancing insulin sensitization [103]. These nuclear receptors have a vital role in adipocyte diversity, carbohydrates and lipids metabolism over diverse genes transcriptional regulation [104]. Hussein et al. revealed that the DHA-loaded ZnO nanoparticles demonstrated a superior anti-diabetic influence than DHA verified by an obvious blood glucose reduction, insulin resistance, in addition to increasing levels of insulin [45]. Glucose metabolism is regulated through the interaction of zinc with numerous constituents of insulin signaling reaction. ZnO nanoparticles increased insulin gene mRNA expression levels and steadily detected elevated insulin gene receptor expression concentrations in the hepatic tissue of ZnO nanoparticles-treated diabetic groups [105].

According to El-Gharbawy et al., ZnO nanoparticles prompted a substantial decrease in the non-esterified fatty acids, triacylglycerols and total cholesterol contents in diabetic group, and this was mainly due to the production of leptin stimulated by zinc, which is recognized to increase fatty acids release from adipocytes [106]. PUFA use probable hypocholesterolemic influence through inhibiting main enzymes involved in cholesterol' synthesis. PUFA selectively decrease triacylglycerols level by increasing the fluidity of glucose to glycogen, increasing the β-oxidation of the mitochondria, and reducing triacylglycerols production, an influence that is facilitated to some extent by proliferator-activated receptors activation [45]. Malondialdehyde and advanced oxidation protein product were declined and superoxide dismutase was noticeably increased in treated rats than diabetic rats. Besides, DNA graphics appeared normal DNA in control groups as compared to diabetic groups, in which DNA destruction was raised to 80.6 %. DNA damage decreased and returned to 51 % when diabetes treated with DHA compared to DHA-loaded ZnO nanoparticles treatment, and it was found that DNA damage was greatly declined to 18.3 %, indicating that DHA nanoparticles displayed superior anti-diabetic performance than free DHA [45].

Hussein et al. investigated DHA-silver nanoparticles efficacy in alleviating diabetic complications and endothelial dysfunction in empirical diabetes albino rats [46]. The study revealed that cell membranes cholesterol and triacylglycerols displayed a substantial promotion in diabetic groups than the control. The management with silver nanoparticles and DHA-silver nanoparticles casued a significant enhancement in nitric oxide reduction in asymmetric dimethylarginine content in comparison to the diabetic group. The

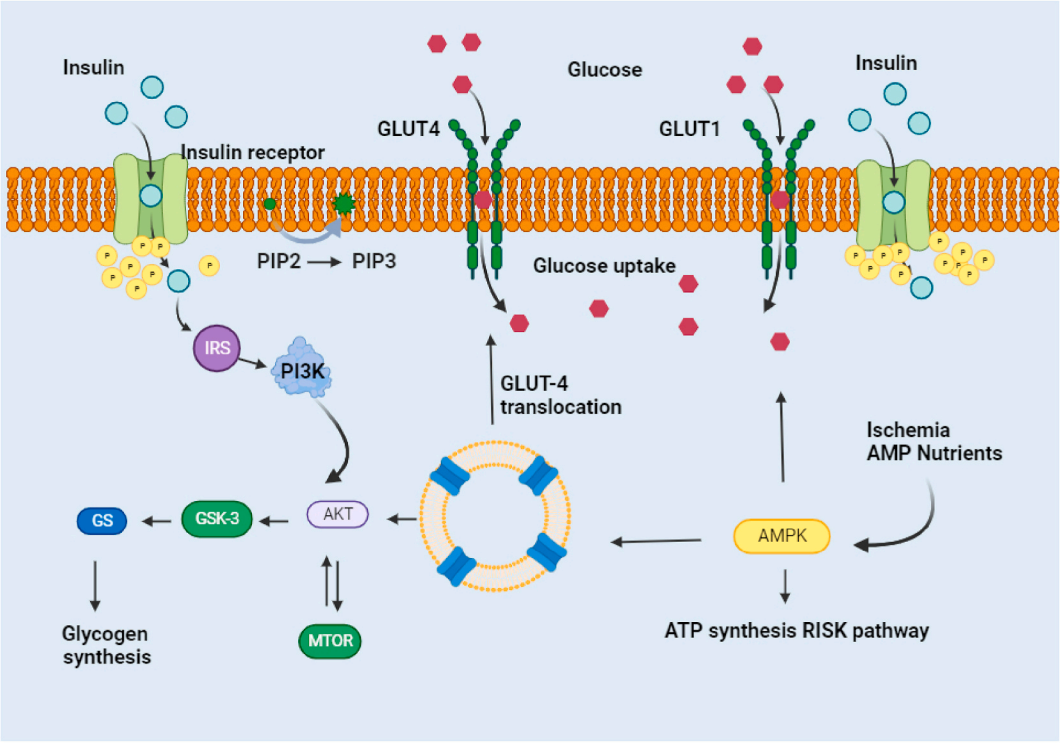

Fig. 4. Insulin signaling pathways were redrawn based on the concepts from previously published literatute [111] using biorender.com (Agreement number: JR25VYABGN). Abbreviations: GLUT4, Glucose transporter type 4; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, hosphatidylinositol 3,4,5-triphosphate; PI3K, Phosphoinositide 3-kinase; IRS, Insulin receptor substrate 1; AKT, Protein kinase B; GSK-3, Glycogen synthase kinase 3; MTOR, Mammalian target of rapamycin; AMP, Adenosine monophosphate; ATP, Adenosine triphosphate; AMPK, Adenosine monophosphate-activated protein kinase. The figure was drawn using Biorender.com (Agreement number: JR25VYABGN).

cell membranes FA analysis revealed that ω-3 PUFA content significantly reduced, while ω-6 PUFA's content increased in diabetic group than control group. After DHA, silver or DHA-silver nanoparticles treatment, there was a noteworthy progress in fatty acid levels in all groups.

In another study, Hussein et al. showed that there were no substantial variations among the two treated groups excluding for homocysteine that was considerably reduced in DHA-loaded ZnO nanoparticles compared to DHA-treated group [47]. While DHA-treated groups vary from control in majority of determined biochemical measurements; however, these constraints became more or less close to the control group in groups treated with DHA-loaded ZnO nanoparticles. ZnO nanoparticles have the ability to improve insulin signaling through diverse ways, for instance increasing the phosphorylation of insulin receptors and phosphatidylinositol 3-kinase activity [102]. ZnO nanoparticles roles may be associated to preventing protein kinase C isozyme elevation, which by the way increased insulin sensitivity. Hussein et al. reported a positive relationship between protein kinase C isozymes and insulin resistance [107].

Previous studies indicated that ZnO nanoparticles can enhance insulin biosynthesis and secretion of insulin, while improving insulin through increased phosphorylation of insulin receptors [102]. DHA nanoparticles exhibited an important influence in raising the secretion of insulin and adjusting blood sugar by improving glucokinase expression, insulin receptor isoform A, in addition to glucose transporter-2. El-Daly et al. investigated the applications of ZnO nanoparticles, silver nanoparticles or free DHA or DHA loaded in ZnO nanoparticles or silver nanoparticles. These nanoparticles showed a significant ability to decrease insulin level either in pancreatic tissue sections or in serum, and accordingly controlled insulin resistance in treated rats as compared to untreated groups signifying that these administrations particularly DHA-silver nanoparticles could reinstate the deficiency in PI3k/AKT pathway [48].

Fig. 4 illustrates the process where insulin molecules bind to their receptors, initiating glucose delivery to the target tissues. This binding triggers receptor autophosphorylation, setting off a signaling cascade involving phosphorylation of insulin receptors-1 or insulin receptors-2 tyrosine residues and PI3K, Akt1, Akt2 and PKC-α and -γ phosphorylation [108]. Insulin receptor-1, serving as a substrate material of insulin receptor tyrosine kinase has a vital role in stimulating insulin signaling transduction reaction pathway. Insulin receptor-1 is an ameliorating indicator in the cure of human metabolic several disorders [109]. It has been established that insulin receptor-1 gene disruption developed an insulin resistance state but not hyperglycemic in rats [110]. Treatment with various nanoparticles, particularly DHA-silver nanoparticles, caused regulated glucose transporter expression, enhanced phosphoinositide 3-kinase activation, increased insulin receptor-1 expression, and a significant reduction in insulin resistance.

The improvement of DHA activity by incorporation in ZnO nanoparticles or silver nanoparticles could increase the production of insulin and control glucose transporters expression in diabetic mice throughout which insulin linking to its receptor results in reactions sequence causing glucose transporters translocation from an intracellular section and setting into the plasma membranes. Two mechanisms; (i) PI3K/AKT and (ii) CAP/Cb1/TC10 control glucose transporters induction by insulin (Fig. 4). The use of ZnO nanoparticles, silver nanoparticles, DHA loaded in ZnO or silver nanoparticles led to a restoration of glucose homeostasis. This was achieved by increasing insulin levels, which in turn suppressed hepatic glucose production, facilitated the translocation of glucose transporter-4, and ultimately improved insulin sensitivity through enhanced utilization of available glucose [48].

4.4. DHA-loaded nanoparticles for liver diseases treatment

LDL-DHA nanoparticles exhibited targeted cytotoxicity against hepatoma cells and reduced the expansion of orthotropic liver tumors in mice. LDL-DHA nanoparticles induced tumors-definite necrosis *via* selectively unsettling redox balance in cancer cells [44]. After 3 days of LDL-triolein administration or imitation surgery, control group displayed large, exceedingly vascularized tumor in which proliferating cells were contained. Nonetheless, LDL-DHA-treated groups exhibited pale, smaller tumor that were lacking of vascular supply and more that 80 % of the tumor tissues were necrotic. After 4–6 days of LDL-DHA injection, the tumor was 3-folds smaller than that of the control group. Liver tissues surrounding tumors displayed no biochemical or histologic signs of injury. LDL-DHA injection into hepatic artery selectively released redox responses in the tumor tissue *via* raising reactive oxygen species levels and lipids peroxidation, reducing and oxidizing glutathione and nicotinamide adenine dinucleotide phosphate, and considerably down-regulating the antioxidant enzyme glutathione peroxidase-4. DHA reconstruction into LDL nanoparticles increased PUFA efficacy, facilitating its application as an anticancer. LDL nanoparticles transarterial injection delivered DHA to the tumor cells at adequately high levels to persuade substantial tumoricidal properties [44].

LDL-DHA nanoparticles have been stated to accelerate hepatocellular carcinoma cell death and decrease tumors size *in vivo* [44]. Conversely, extra investigation of tissues resulting from these trials revealed that epithelial cellular adhesion molecule positive cells may be more resistant to such treatment compared to epithelial cellular adhesion molecule negative cells. The justification for this obvious inconsistency between *in vivo* and *in vitro* results needs further investigation. As cancer stem cells have a tendency to be positioned in the central sections of tumor where blood stream is more restricted, nanoparticles transport to the comparatively small cancer stem cells inhabitants of the tumor might explains that finding [112]. Also to be taken in consideration are variances in the types of hepatocellular carcinoma cells employed. The effect of tumors microenvironment, such as fibroblasts, extracellular matrix, and inflammatory cells. All of these factors might affect tumor cells sensitivity to chemotherapy, explaining the *in vivo* results [113].

Increasing hepatic arterial infusion doses of LDL-DHA was reliable and effectively endured in regular mice [40]. Histological analysis of treated mice showed slight portal inflammations; nevertheless, since these fluctuations were not dose-dependent this result might reveal hepatic artery infusion practice instead of LDL-DHA infusion. LDL-DHA nanoparticles administration resulted in similar hepatic DHA levels in various lipid fractions with increasing dosage. However, the liver metabolic profile exhibited noticeable changes. Higher level of saturated fatty acyl chains was monitored in neutral lipids pool of the treated mice's liver. Saturated lipids accumulation suggests that PUFA, like DHA, may inhibit stearoyl-CoA desaturase activity. DHA can suppress stearoyl-CoA desaturase

expression at both transcriptional and mRNA stability levels [114]. The livers of treated group exhibited lower contents of oleic acid and DHA, which might be attributed to the suppressed activity of stearoyl-CoA desaturase [40,115]. Along with enzyme-facilitated oxidation of DHA delivered by LDL, non-enzymatic oxidation could happen. This issue should be considered since free radicals attack of the PUFA could stimulate lipids peroxidation, which might had harmful outcomes on the tissues. After hepatic arterial infusion of LDL-DHA, particular DHA obtained aldehydes nor any additional types of lipids aldehydes accrued in the treated rat liver [40]. Peroxidation of lipids did not raise in the normal liver after LDL-DHA treatment, relatively the entry of LDL supplied DHA was favorably directed *via* lipoxygenase-protectin biosynthesis mechanism (Fig. 5).

DHA oxidized derivatives showed a proof for its voracious metabolism [40]. Di-hydroxylated DHA derivative (PDX) exhibited a dose-dependent increase in intensity with the treatment, while mono-hydroxylated DHA levels did not vary. PDX is protectin/neuroprotection D1 isomer resulted by double lipoxygenases of DHA [116]. These bioactive molecules have anti-aggregator and anti-inflammatory activities [117]. PD1/PDX had the ability to decrease the inflammations and prevent the liver injury [118]. PD1/PDX hindered pro-inflammatory cytokines formation, immune cells permeation, endoplasmic reticulum stress, NF-κβ activation, cyclooxygenase-2 expression, in addition to necroinflammatory injury in the liver. One single management of PDX at a quantity of 1 ng/rat induced substantial anti-inflammatory activities [119]. The basic level of protectin DX in rodents liver was assessed to be about 100 pg/g of the tissue [120], 3.6, 8, and 11 folds increase in PDX after the treatment with 2, 4, and 8 mg/kg of LDL-DHA would hypothetically depiction 9 g rat liver to 2.3, 6.3, and 9 ng raise in the PDX, respectively. Accordingly, the level of PDX derived from LDL-DHA could positively afford anti-inflammatory defensive advantages to the liver [40].

Murine non-cancer (TIB-73) and liver cancer cells (TIB-75) were studied to validate differential LDL-DHA nanoparticles roles in ordinary as opposed to cancerous cells [60]. Normal TIB-73 cells and malignant TIB-75 cells exhibited substantially higher basal oxidative stress level. When LDL-DHA nanoparticles entered the malignant cells, DHA underwent rapid oxidation, leading to increased lipid peroxidation and lysosomal permeability. This resulted in lipids peroxidation products release and lysosomal contents, triggering subsequent nuclear damage and mitochondrial dysfunction. The progression of LDL-DHA-facilitated lipids peroxidation and organelle injury was moderately inverted by using iron chelators like deferoxamine or antioxidants like N-acetylcysteine. In contrast, treatment of ordinary TIB-73 cell with LDL-DHA was well-endured and did not induce cellular or organelle damages [31].

5. Conclusion and future prospective

Numerous studies have evaluated the functional roles of DHA in different physiological processes. DHA delivery in suitable levels not only enhances diabetes and cardiovascular diseases, but also obstructs obesity and other related inflammations, as well as benefits neurological/brain and vision. Nevertheless, DHA has several disadvantages, such as high oxidation sensitivity, weak water solubility, low bioavailability, and odd smell, which limit its applications. Significant developments have been accomplished in the delivery systems to transport DHA effectively and enhance its bioavailability with arrays of applications. Different delivery systems, including emulsions, liposomes, microcapsules, gels, and nanoparticles are reported to increase DHA protection, encapsulation, release, and bioavailability. Natural components, such as polysaccharide and dairy proteins are considered to be safe and eco-friendly, making them valuable for expanding DHA delivery systems rooted in natural constituents, offering enhanced performance and multifaceted functionality. When selecting and formulating the appropriate delivery system of DHA, several critical considerations come into play. These include addressing DHA's susceptibility to variability of DHA during handling, storage, and carrying, improving DHA bioavailability, and emerging profitable values in various fields. The findings of the deliberated studies clearly exemplify that by using diverse nanodelivery approaches, DHA can be efficiently advanced, and therefore positively managed to provoke the mandatory therapeutic effects. The targeted delivery of formulated DHA nanoparticles would facilitate the incorporation of traditional medication with up-to-date pharmaceutical approaches.

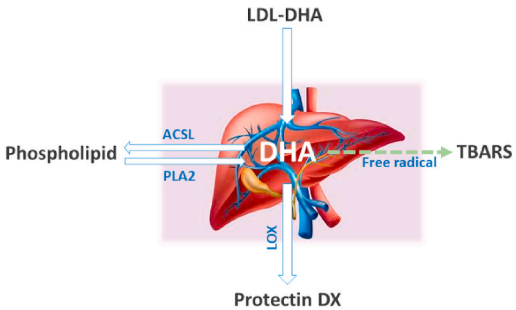

Fig. 5. Metabolism of LDL-DHA nanoparticles in the liver. DHA is released from nanoparticle after intracellular uptake by LDL receptor. Free DHA could be: activated by the long-chain-fatty-acid-CoA ligase (ACSL) for esterification into phospholipids or triacylglycerols of the membrane; undergo auto-oxidative lipids peroxidation producing aldehyde end products; or be successively metabolized through lipoxygenase enzyme reaction to the pro-resolving protectin DX mediator. DHA delivered to the liver cells through LDL nanoparticles favorably undergoes enzyme-induced oxidation through lipoxygenase reaction instead of free radicals degradation. 15/5-LOX, 15-lipoxygenase and 5-lipoxygenase; PLA2, phospholipase A2 [40].

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Abdelmoneim H. Ali: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Conceptualization. **Mayssa Hachem:** Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Mirja Kaizer Ahmmed:** Writing – review & editing, Visualization, Validation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests Mayssa Hachem reports financial support was provided by Khalifa University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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