Review

Revolutionizing Cardiovascular Health with Nano-Encapsulated Omega-3 Fatty Acids: A Nano-Solution Approach

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Revolutionizing Cardiovascular Health with Nano-Encapsulated Omega-3 Fatty Acids: A Nano-Solution Approach

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Abstract: Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) offer diverse health benefits, such as supporting cardiovascular health, improving cognitive function, promoting joint and musculoskeletal health, and contributing to healthy aging. Despite their advantages, challenges like oxidation susceptibility, low bioavailability, and potential adverse effects at high doses persist. Nanoparticle encapsulation emerges as a promising avenue to address these limitations while preserving stability, enhanced bioavailability, and controlled release. This comprehensive review explores the therapeutic roles of omega-3 fatty acids, critically appraising their shortcomings and delving into modern encapsulation strategies. Furthermore, it explores the potential advantages of Metal-organic framework nanoparticles (MOF NPs) compared to other commonly utilized nanoparticles in improving the therapeutic effectiveness of omega-3 fatty acids within drug delivery systems (DDS). Additionally, it outlines future research directions to fully exploit the therapeutic benefits of these encapsulated omega-3 formulations for cardiovascular disease treatment.

Keywords: Omega-3 fatty acids; cardiovascular disease; Nanoparticle encapsulation; Metal-organic framework; Drug delivery systems

1. Introduction

Cardiovascular diseases (CVD) remain the world's leading cause of mortality, claiming a staggering 695,000 lives in the United States alone in 2021 [1] translating to roughly one death every 30 seconds [2]. According to a 2019 report by the World Health Organization, CVD contributes to 32% of total worldwide fatalities, with 85% of these fatalities attributed to heart attacks or strokes [3]. Major contributors and risk factors for CVD include elevated blood pressure, blood sugar, and cholesterol levels, as well as smoking, unhealthy diet, obesity, and physical inactivity [4].

According to a recent report from the American Heart Association, an intake of approximately 3g of omega-3 fatty acids daily, whether obtained from food or supplements, appears to be the optimal amount for reducing high blood pressure and preventing cardiovascular disease, as indicated by a review of multiple research studies [5]. Omega-3 fatty acids (ω-3 F.A.s) are categorized as polyunsaturated fatty acids (PUFAs) that include a minimum of a single double bond (C=C) between the carbon atoms in the third and fourth position from the methyl end of the fatty acid [6,7]. PUFAs are long-chain fatty acids (LC-FAs) found in oily fish like sardines, tuna, salmon, and other seafood like shellfish, algae, and shrimp, as well as particular plants, and nut-based oils [8]. Most common bioactive ω-3 FAs, eicosapentaenoic acid (EPA) (C20:5 ω – 3), docosahexaenoic acid (DHA) (C22:6 ω – 3), and α-linolenic acid (ALA) (C18:3 ω) [9]. ALA can undergo various elongation and

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desaturation processes within the body to be converted into EPA and DHA [10]. However, the conversion rates of ALA to EPA and DHA may be relatively low, potentially insufficient to confer health benefits. Therefore, it is essential to ensure adequate intake of EPA and DHA for various aspects of health, including cardiovascular health, brain function, and inflammation regulation. PUFAs are essential nutrients that must be obtained from the diet because the body cannot synthesize them.

PUFAs play numerous physiological roles involving cell signaling and transmission, intercellular contact, membrane fluidity, phospholipid membrane maintenance, reduced inflammation [11,12], and improved oxidation [13]. Hence, a deficiency in ω-3FAs can deteriorate bone health [14,15,16], cardiovascular health [17], and skin and neurological health [18] (Figure 1). Along with this, ω-3FA ingestion is associated with a lowered prevalence of inflammation [19] through the lowering of pro-inflammatory cytokines triggered by oxidative stress [20,21]. Various studies have also studied the anti-inhibitory effect of ω-3 FAs on cancers [22,23]. Over the decades various preclinical and clinical studies have been conducted using ω-3FAs to show their efficacy in reducing cardiovascular ailments. This review paper will provide an overview of ω-3FAs with a focus on their effect on the cardiovascular system, along with shortcomings in the delivery of ω-3FAs to which nanoparticles could be potentially a viable solution.

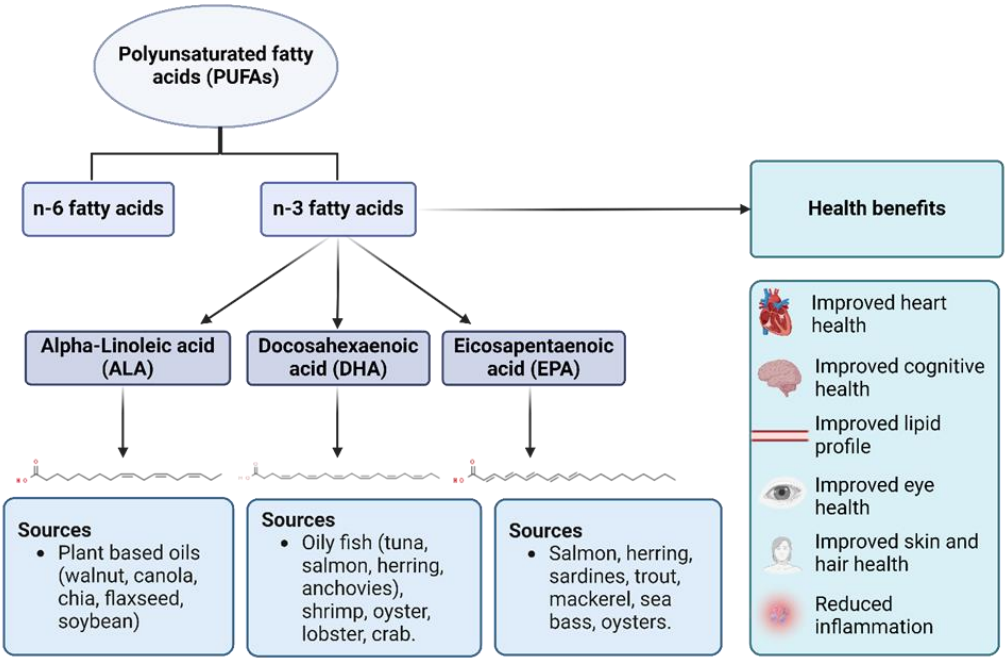

Figure 1. Types, sources, and health benefits of Omega 3 fatty acids.

1.1. Preclinical Studies

Over the years various pre-clinical studies conducted on a range of animal experimental units have proved the effectiveness of ω-3FAs in cardioprotection and decreasing markers of cardiovascular stress as summarized in Table 1**.** Below.

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Table 1. Summary of outcomes of pre-clinical studies published between 1992 and 2022 on cardiovascular health utilizing diets rich in Omega-3 Fatty acids (ω-3 FAs).

Experimental unit	Sample size (n)	Omega-3 FA diet/dose	Treatment period	Outcomes	References
Marmoset monkey	29	22.8%	30 months	↓ in the threshold for fibrillation	[24]
Mongrel dogs	17	5 mL (Intravenous)	1 week	↓ in ventricular flutter-fibrillation	[25]
Mice	3	3%	6 weeks	↓ in loss of Connexin43 (Cx43)	[26]
Mice	14	2.1%	6 weeks	↓ in Endothelin-1 (ET-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1)	[27]
Mice	36	8%	2 weeks	↓ in the expression of the Myosin Heavy Chain 7 (Myh7) gene and Collagen type III alpha 1 chain (Col3a1)	[28]

1.2. Clinical Studies

Several significant meta-analyses of ω-3FAs and their connection to cardiovascular morbidity and mortality have been published in the last four decades. Some of these studies concluded that fish oil supplementation lowers the risk of cardiovascular events and the mortality rates from CVD while others did not support this conclusion as seen in Table 2**.**

Table 2. Summary of outcomes of randomized clinical trials (RCTs) published between 1989 and 2021 on cardiovascular health utilizing diets rich in ω-3 FAs.

Study name	Sample size (n)	Omega-3 FA dose/day	Follow up period	Outcomes	References
DART Clinical Trials	2,033	900mg EPA and DHA	2 years	32% ↓ reinfarction, 29% ↓ in mortality from all causes.	[29]
GISSI-Prevenzione Trials	11,232	850 mg of DHA or EPA	3.5 years	28% ↓ in mortality from all causes, and 45% ↓ in sudden cardiac death.	[30]
JELIS Clinical Trials	18,645	Statin + 1.8 g of EPA	5 years	19% ↓ in mortality, revascularization, MI, and angina.	[31]
DOIT Clinical Trials	563	2.4 g of ω-3 PUFA	3 years	↓ in mortality from all causes.	[32]
OMEGA Trial	3,851	460 mg EPA and 380 mg DHA	1 year	No ↓ in mortality due to unexpected cardiac events.	[33]
Alpha Omega Trial	4837	EPA (400mg), DHA (400mg), ALA(2g)	3.3 years	No ↓ in incidence of serious cardiac events.	[34]
SU.FOL.OM3 Trial	2501	600mg of ω-3 FAs	5 years	No ↓ in incidence of serious cardiovascular events.	[35]
ASCEND Trial	15,480	380 mg DHA and 460 mg EPA	2.5 years	No ↓ in major vascular incidents	[36]
VITAL Trial	25,871	380 mg DHA and 460 mg EPA	5.3 years	No ↓ in risk of cardiovascular diseases	[37]
REDUCE-IT Trial	8179	4g of icosapent ethyl (EPA ethyl ester)	4.9 years	↓ in the incidence of ischemic events.	[38]
STRENGTH Trial	13,078	4g omega-3 carboxylic acid formulation (EPA+DHA) per day	2.6 years	No ↓ in cardiovascular events	[39]
OMEMI Trial	1,027	1.8 g ω-3 FAs (930 mg EPA + 660 mg DHA)	2 years	No ↓ in the frequency of cardiovascular events or deaths from all causes	[40]

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The differences in research findings might be attributed to the various fatty acids employed in these studies, which ranged from Omega-3 CA to ethyl ester of EPA, DHA, and ALA. The omega-3 CA employed in the STRENGTH study is EPA as a free fatty carboxylic acid, that has greater absorption in a diet low in fat than EPA and DHA ethyl esters, comparable to the EPA ethyl ester used in the REDUCE-IT study. Consequently, omega-3 CA increases blood levels of EPA and DHA when combined with a diet low in fat yet not with a standard diet. In the STRENGTH study, omega-3 CA was administered independent of eating habits or dietary fat composition, which might culminate in fluctuation in EPA and DHA levels in the blood and perhaps reduce the impact on cardiovascular events. Icosapent ethyl additionally contains approximately 25% higher EPA in each dose than omega-3 CA, resulting in 61% greater EPA levels in blood in REDUCE-IT versus STRENGTH from comparable baseline values [41].

1.3. Epidemiological Studies

Apart from clinical studies, epidemiological studies were also conducted on the effect of ω-3 FAs on the reduction of cardiovascular events. The results of the studies in Table 3**.** were mixed with some claiming that ω-3FAs decrease cardiovascular events and others claiming no such outcome

Table 3. Summary of outcomes of epidemiological studies published between 2000 and 2021 on cardiovascular health utilizing diets rich in ω-3 FAs.

Sample size (n)	Diet (consisting of ω-3 FA)	Follow up period	Outcomes	References
8,825	1 serving of fish/week	19 years	**No** ↓ in risk of (CVDs) cardiovascular disease	[42]
41,578	40-60 g ω-3 FA /day	9 years	↓ incidence of coronary heart disease (CHDs), ↓ in fatal cardiac events	[43]
48,315	31.3 g ω-3 FA /day	4 years	**No** ↓ risk of myocardial infarction (MI) or stroke	[44]
16,479	> 2 servings of fried fish/week	4 years	↑ in the chance of cardiovascular events	[45]
20,969	> 4 servings of fish/week	4 years	**40%** ↓ in the likelihood of CHD and stroke	[46]
34,033	1 serving of fish/week	18 years	↓ in risk of ischemic stroke	[47]
197,761	1 serving of fish/week	3.3 years	↓ in risk of non-lethal ischemic stroke	[48]
4,067	200 mg ω-3 FA /day	12 years	**30%** ↓ in the possibility of deadly CHD	[49]

1.4. Case-Control Studies

The number of case-control studies measuring EPA and DHA levels in plasma as a biomarker of ω-3 FA after 2004 declined due to the introduction of the new concept of the Omega-3 index (O3I) [50]. The omega-3 index is defined as the proportion of EPA and DHA in a total of 26 distinct fatty acids in the membrane of red blood cells (RBCs) with many studies claiming that an O3I of 8% is required to elicit the cardioprotective effect of ω-3 FA [51]. There are many reasons why measuring EPA and DHA in erythrocyte membranes is a more accurate method of assessing ω-3FA intake in the diet. RBC fatty acid content has relatively little biological variability in comparison to plasma. Erythrocyte lipids are nearly entirely composed of phospholipids and RBC fatty acid content represents tissue fatty acid composition [52]. Table 4**.** below are the results of a few of the earliest case-control studies.

Table 4. Summary of outcomes of case-control studies published between 1990 and 2010 on cardiovascular health utilizing diets rich in ω-3 FAs.

Sample size (n)	ω-3 FA in fish consumption	Study period	Outcomes	References
287	1 serving of fish/weekly	5 years	↓ the likelihood of cardiovascular diseases (CVDs)	[53]
334	5.5g/monthly	6 years	**50%** ↓ in the possibility of first cardiac arrest.	[54]

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78	>1 fish serving/weekly	18 months	↓ in risk of myocardial infarction (MI)	[55]
848	<150 g fish/weekly	12 months	38% ↓ in likelihood of developing acute coronary syndrome (ACS)	[56]
108	2 servings of fish/weekly	2 years	↓ in risk of coronary events	[57]

2. Discussion

2.1. Obstacles in the Administration of Omega-3 PUFA Effectively

There have been concerns regarding the optimal source and route of administration of ω-3 FAs for human consumption. Even though the simplest way of ω-3 FAs intake is through eating fish, decreasing fish stocks worldwide and biomagnification of toxic trace elements due to water pollution are proving to be valid concerns [58]. An alternate method is consuming ω-3 FAs supplements. The issue with supplements is that they may cause undesired side effects such as stomach upsets, stale breath, nausea, etc. (Figure 2). Moreover, the release of ω-3 FAs in supplements occurs rapidly, simultaneously delivering the entire amount [59].

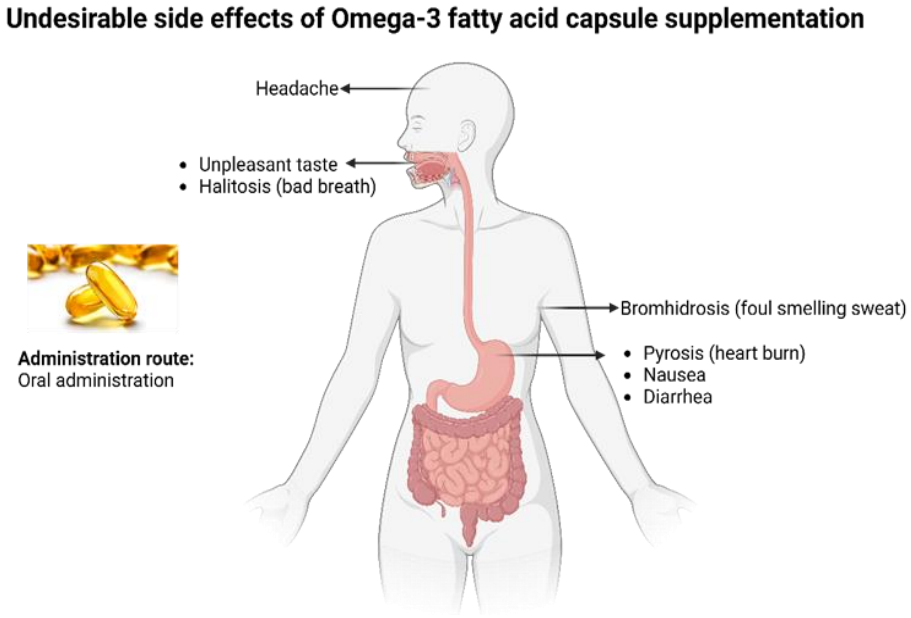

Figure 2. Common undesirable side effects of Omega-3 fish oil capsule supplements.

The bioavailability of long-chain ω-3 PUFA is another complex issue that needs to be tackled. Bioavailability is a subjective phrase that refers to both the rate of absorption and the amount of the substance ingested [60]. The major cause of the limited bioavailability of long-chain n-3 PUFAs is low solubility in the aqueous gastrointestinal fluids of the GI tract, alongside their vulnerability to chemical breakdown during transit through the stomach [61]. Long-chain omega-3 PUFAs are mostly present in fish as triacylglycerides (TAGs), phospholipids (PLs), and free fatty acids (FFAs) [62]. ω-3 PUFAs, when ingested as pure oil, cannot be completely absorbed by the cells in our intestines, resulting in reduced bioavailability [63]. Fish oils are transformed into oil-in-water emulsions within the mouth and stomach, while emulsified oils are colloidal before consumption. Lipases in the stomach and pancreas subsequently attach to the surface of the lipid drop and begin the process of lipid digestion, which converts TAGs into FFAs and monoacylglycerols (MAGs). The digestive products; FFAs and MAGs subsequently combine with bile and PLs to produce blended micelles that transport the lipids across the mucus membrane to the epithelial cell surfaces, from where they are absorbed. Investigations have demonstrated that the bioavailability of ω-3 PUFAs is enhanced when consummated in an emulsified way rather than in a pure form [61]. Widely ingested edible oils and products have less ω -3 PUFA compared to the suggested daily guideline; also, the minimal quantity of PUFA taken is poorly absorbed. The transformation rate of plant-sourced ω -3 FAs, namely, ALA

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into EPA and DHA, the primary -3 PUFAs accountable for the reported benefits, is only 3%-6%, with DHA having an inadequate transformation rate maxing out at 1% [64].

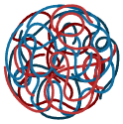
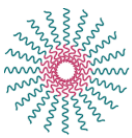
Apart from these complications, lipid oxidation is an additional problem that needs to be addressed. Among the different types of ω-3 FAs, EPA and DHA are extremely vulnerable to the oxidation of lipids due to the presence of numerous double bonds [65]. The oxidative degradation of lipids in fish oil, along with other PUFA-rich and fortified foods is a severe issue that frequently results in a decrease in shelf-life, customer acceptance, performance, nutrient content, and quality [66]. The oxidation of these ω-3 FAs results in aldehydes that are toxic to proteins and nucleic acids in the human body namely; 4-hydroxy-2-nonenal and malondialdehyde [67]. The toxicity stems from their capacity to crosslink proteins and attach covalently to nucleic acids.

Lipid oxidation in fish oils is heightened by exposure to light, oxygen, and heat. Lipid oxidation creates three major issues: (i) it produces disagreeable unpleasant flavors, (ii) It decreases the nutritional content of lipid-containing food items, and (iii) free radicals generated during oxidation may contribute to the occurrence of atherosclerosis in the system [68]. Nevertheless, the low oxidative resistance of PUFA ω-3 FA makes these oil-enriched foods require potent antioxidant defense to avert oxidative degradation and undesirable flavor formation [69]. Some solutions to stabilize ω-3 PUFAs include providing antioxidants for oxidative stability, mixing and blending with other oils, hydrogenation, and interesterification [64]. However, another innovative solution might be ω-3 FAs encapsulation using nanoparticles as part of nanotechnology.

2.2. Nano-Encapsulation of Omega-3 PUFA

Nanoparticles (NPs) are the focal point of nanomedicine, which is a branch of medicine that relies on smart drug delivery technology that can boost the biological action, pharmacological index, and physiological half-life of the drug it is loaded with inside the body [70]. Nanoparticles are increasingly becoming popular as drug delivery systems, especially to treat CVDs [71] and metabolic disorders [72] due to their ability to have a comparatively big surface area that can attach to, adsorb, and transport molecules including drugs, probes, and protein molecules [73] Furthermore, for the administration of medication, not only engineered nanoparticles as well as the drug itself can be synthesized at nanoscale and operate as a carrier for itself [74]. There exists an array of nanoparticles, each having its distinct features, advantages, disadvantages, and applications (Table 5).

Table 5. Characteristics, Uses, and advantages and disadvantages of different classes of nanoparticles.

Nanoparticle type	Characteristics	Advantages	Disadvantages	Application/Use	References
 Polymeric NPs (organic)	Solid particles (colloidal) that range in size from 10 to 1000 nm. Two main types; nanocapsules and nanospheres.	Controlled and sustained drug release, stable, and efficient. biodegradable, good biocompatibility.	Difficult to scale up, lack of toxicological evaluation, can be an environmental hazard and can pose an occupational hazard during production.	Vaccine delivery, cancer treatment, antibiotic delivery, purification of biomolecules and bioimaging	[75–77].
 Polymeric micelles (organic)	Spherical, 10 – 100 nm in diameter. Amphiphilic block copolymers produce nanoscopic core/shell structures via covalent bonding. Hydrophobic core, hydrophilic shell.	Highly stable, high loading efficiency, selective and controlled drug release, and kinetically stable.	Low solubility, low loading capacity, low stability *in vivo*, and can dissociate *in vivo*.	Cancer treatment, food-based technology, drug delivery, photodynamic therapy, and gene delivery.	[78–80].
	Spherical, compact, 1 – 15 nm in diameter. Comprises a central core atom, followed by	High loading capacity, high bioavailability, high	Low water solubility, high nonspecific toxicity, challenging to separate the NPs from	Biomedical applications, targeted delivery, cancer treatment,	[81–83].

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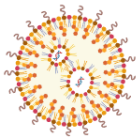
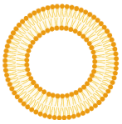
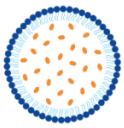
Dendrimer NPs (organic)	repeating branching subunits and terminal groups.	penetrability, high symmetry, and surface groups can be customized easily.	the reactants, and time consuming.	cancer diagnosis, antibacterial therapy.	
 Solid lipid NPs (organic)	Spherical shape, diameter ranging from 50nm - 1µm, big surface area, substantial drug loading capacity, and surfactant on the outer layer.	Controlled and/or targeted medication release, optimized drug stability, higher and improved drug content, and non-toxic.	Drug ejection upon polymeric transformation during storage and high moisture content of the dispersions.	Gene vector transporter, topical drug application, cosmetics, agricultural usage, anticancer medication carrier.	[84,85].
 Liposomes (organic)	Spherical lipid vesicles 50-500 nm in diameter comprised of several lipid bilayers formed by the emulsification of real or artificial lipids in water-based solutions	Improved effectiveness, improved therapeutic value of drugs, improved stability by encapsulation, not toxic, adaptive, and biocompatible.	Poor solubility, transient half-life, oxidation, hydrolysis, leak, coagulation of enclosed molecules and expensive manufacturing.	Anticancer drug delivery, antifungal drug delivery, analgesic delivery, COVID–19 mRNA vaccines, photodynamic therapy.	[86,87].
 Nanoemulsion (organic)	Spherical, 20-500 nm diameter, 10-20% polydispersity, unstable thermodynamically, stable kinetically.	Large surface area, high free energy, manufactured in an array of formulations, not toxic, and non-irritant.	Stabilization requires a high concentration of surfactant, and stability is regulated by pH and temperature.	Cosmetics, food, pharmaceuticals, drug delivery, vaccine delivery, material synthesis, and encapsulation of natural food preservatives	[88,89].
 Gold NP (inorganic)	Spherical, 10-100 nm in diameter, colored orange, brown, red, or purple, and absorbs between 500-550 nm.	High surface area to volume proportion, very stable, good biocompatibility, customizable, steady size and shape.	Gold NPs can be toxic at large doses. Gold NPs entrapped in the liver might impair its function and costly manufacturing.	Imaging, electronic gadgets, material production, colorimetric and electrochemical sensing, drug delivery, and cancer diagnosis.	[90,91].
 Silver NP (organic)	Various shapes (spherical, triangular, hexagonal, octagonal, etc.), 1-100 nm diameter, small size crystalline, high heat conductivity, and high electric conductivity	High surface area, bactericidal, catalytic features, fungicidal, not toxic, anticancer properties, very stable, and high solubility	Limited resolution, numerous light scatterings, sedimentation, and high energy required in preparation	Disease diagnosis, agriculture, cosmetics biotechnology, wound dressing, textile industry, and antiseptic reagents.	[92,93].
 Iron oxide NP (inorganic)	Various shapes (spherical, cubes, hexagonal, rods, etc.), superparamagnetic, 10-20 nm in diameter or less, different forms such as hematite, magnetite, maghemite	High surface area to volume proportion, inexpensive, low toxicity, high binding capability, substantial	Highly reactive, agglomerate, surface oxidation, absence of functional groups, reduced capacity to adsorb molecules, slow kinetics, leach in low pH	Biomedical, magnetic resonance imaging diagnosis, drug delivery, antibody and vaccine manufacture, gene therapy, cancer	[94–97].

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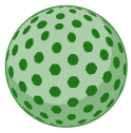
		dispersibility, not toxic		therapy, sensory probes	
 Quantum dots (inorganic)	Various shapes (spherical, cuboidal, conical, etc.), 2-20 nm in diameter, metallic or semi-conductors, can be zero, one, two, or three dimensional, nanocrystals, and have 100 – 10000 atoms and <100 electrons.	Customizable morphology, great biocompatibility, high ability to disperse, magnetic, and great optical features.	Toxic, lacks significant polarization, water insolubility, and needs strong polymer casing.	Photocatalysis, biosensing, bioimaging *in vivo* and *in vitro*, optoelectrical gadgets, and microscopy.	[98,99].
 Mesoporous NP (inorganic)	Spherical or rod-shaped, 30-300 nm in diameter, majorly made up of silicone, highly structured pores, stable porous matrix, 5 different types of nanocomposites	Low toxicity, high biocompatibility, large surface area, big pore volume, heat stable, chemically stable, customizable pore size	Mild toxicity, silanol moieties on the surface can interact with the outermost layer of red blood cell membrane phospholipids causing hemolysis and induction of metabolic alterations promoting melanoma	Cancer treatment, biosensing, bioimaging, targeted illness treatment, radiotherapy, chemotherapy, dynamic therapy, thermal therapy, Immune therapy, gene therapy,	[100–102].

In the past few years, multiple studies have been performed that utilized encapsulated ω-3 FAs within NPs as a drug delivery method. A study by Deshpande et al tested a nanotechnology-focused method for administering ω-3 FAs to the walls of vascular vessels alongside other drugs to avoid occlusive vasculopathy after vascular injury [103]. The researchers created an ω-3-FA-rich oil-in-water nano-emulsion composition using flax seed oil (Jedwards International, Quincy, MA, USA) rich in ALA naturally, that successfully administered 17-βE (Sigma-Aldrich, St Louis, MO, USA) and CER (Avanti Polar Lipids, Alabaster, AL, USA) to cultured vascular cell lines. Combining the administration of 17-βE and CER-laden nano-emulsions had a stronger anti-proliferative impact on vascular smooth muscle cells as compared to endothelial cells [104]. In 2016, the same researchers set out to examine the effectiveness of an ω-3-FA containing 17-βE (Sigma-Aldrich, St Louis, MO, USA) Nano-Delivery setup in treating induced atherosclerosis. The study found that a 3-week 17-βE therapy administered in an ω-3 PUFA-encapsulated nano-emulsion setup improved acute vascular damage with just 30% arterial stenosis [105].

Another study conducted by a separate group in 2019 focused on utilizing Atorvastatin (Caplin Point Laboratories Ltd., Pondicherry, India) nano lipid carriers preloaded with ω-3-PUFA (Triomega, Sanofi India Ltd., Mumbai, India) to lower hyperlipidemia. When compared with the commercial formulation, orally administered ω-3-FA based AT preloaded nano lipid carriers resulted in a substantial decrease in low-density lipoprotein and triglyceride levels in the blood [106]. Through various studies, nanoencapsulation has been shown to increase the bioavailability of ω-3-PUFAs in the body. Through their studies, Wakil et al., 2010 and Sanguansri et al., 2013 proved that clearly, microencapsulation can improve the availability of FAs [107,108].

Nanofibers like zein have also been used to encapsulate ω-3-PUFAs recently such as in one study by Busolo et al., where 85 wt.% DHA-supplemented fish oil (KD-Pür® DHA800 TG, K.D. Pharma Bexbatch GmbH, Bexbach, Germany) was encapsulated in zein (Sigma-Aldrich, Madrid, Spain) through electrospraying assisted by pressurized gas technology (EAPG). The average particle size and encapsulation efficiency were 3.7 ± 1.8 μm and 84%, respectively. The fortified reconstituted milk with zein/DHA-enriched fish oil microcapsules showed no signs of oxidation even after 45 days in an oxidation test [109].

Whey microgels loaded with ω-3-PUFA were also tested in a study in 2022 where 85 wt % DHA-enriched algal oil (Kingdomway Pharmaceutical Co., China) was loaded into whey protein microgels by ball milling. The end product had an average particle size of 250 nm, an average diameter of 380

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nm, and a polydispersity index of 0.26, indicating the zeta potential. These protein microgels loaded with omega-3 PUFA addressed several obstacles in the development and storage of omega-3 PUFA oils, such as long-term oxidative resistance and better sensory and textural qualities [110].

A summary of studies utilizing unique nanoparticles for the encapsulation of ω-3 FAs, their mechanism of production, physiochemical properties, and observed effect is listed below in Table 6.

Table 6. Summary of studies encapsulating Omega-3 fatty acids using different types of nanoparticles between 2013 and 2022.

Omega-3 dose and source	Nanoparticle type	Production Technique	Physiochemical characteristics	Effect	References
Flax seed oil 20%, w/v	Nanoemulsion	Microfluidization	Average diameter =146 nm Surface charge =34 mV Encapsulation efficiency = 93% and 99%%	Strong anti-proliferative impact on vascular smooth muscle cells	[104]
Flaxseed oil 20%, w/v	Nanoemulsion	Microfluidization	Average diameter = 187 ± 7.5 nm and 176 ± 4.8 nm Surface charge = (-54.6 ± 4.1 mV and -56.4 ± 5.1 mV Encapsulation efficiency = 94.6%	Improved acute vascular damage with only 30% arterial stenosis	[105]
Omega-3 FA	Atorvastatin-loaded nano lipid carrier	Melt emulsification and ultrasonication method	Particle size = 87.29 ± 6.68 nm Surface charge = -36.03 ± 1.50 mV Encapsulation efficiency = 86.70 % ± 0.15	Improving Omega-3 FA bioavailability and antihyperlipidemic action	[106]
85 wt.% Docosahexaenoic acid-supplemented fish oil	Nanofiber	Electrospraying assisted by pressurized gas technology (EAPG).	Average particle size = 3.7 ± 1.8 μm Encapsulation efficiency = 84 %	Supplemented reconstituted milk with zein/DHA-enriched fish oil microcapsules showed no signs of oxidation even after 45 days.	[109]
85 wt % DHA enriched algal oil	Oleogel based microgel	Ball milling	Whey protein microgel particle size = 250 nm Polydispersity index = 0.29 Diameter = 380 nm	Protein microgels addressed various obstacles in the development of omega-3 polyunsaturated fatty acid oils, such as long-term oxidative resistance and better sensory and textural qualities.	[110]

The most common mechanism for nanoencapsulation of ω-3 FAs in literature involves physical methods as illustrated below in Figure 3.

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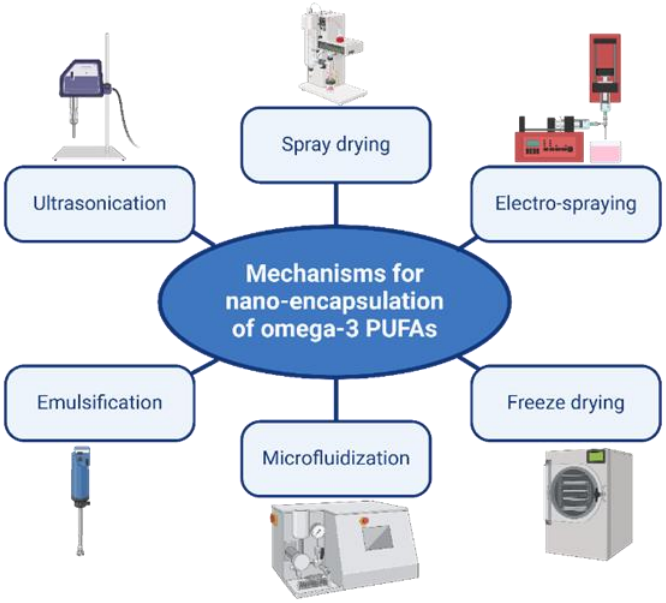

Figure 3. Common physical mechanisms for nano-encapsulation of Omega-3 PUFAs.

However, lipid-based NPs have their drawbacks as well. Due to their precise crystalline form, they display limited drug loading capacity and the likelihood of drug ejection owing to crystallization during storage [111] along with initial burst discharge of drug instead of slow controlled drug release [112]. Other disadvantages during oral administration of lipid-based NPs are the formation of gel of hydrophobic lipid dispersion, restricted loading quantity for hydrophilic formulations, and polymorphic transformation [113]. Liposomes are another type of lipid-based NPs that are employed for drug delivery; however, they tend to have a reduced solubility window [87], problems with drug incorporation and encapsulation, high manufacturing costs, and trouble preserving drug integrity and bioactivity during conjugation [114]. Microgels on the other hand are complicated and time consuming to mass produce on a large scale as the yield and stability of the individual microgels is highly variable using the currently available technology [115]. Nanofibers although super effective in encapsulating omega-3 PUFAS have their shortcomings too. Their disadvantages include quick disintegration, low mechanical durability, and full dissolution. Therefore, such fibers must be cross-linked to limit their solubility [116].

An alternative to avoid this uncontrolled release would be to use metal-organic framework (MOF) NPs, a novel group of composite nanomaterials, consisting of a combination of inorganic and crystalline organic components [117]. A few of the properties of MOF NPs are their extensive surface area (hollowed-out interior structure) [118], a high degree of porosity, configurable pore dimensions, heat resistance, chemical stability [119], and post-synthesis alterations are what elevate MOF NPs over lipid-based N.P.s when it comes of versatility, adaptability, and customizability [120,121]. MOF NPs such as Material Institute Lavoisier 89 nanoparticles (nanoMIL-89) due to their vast list of perks (Figure 4), can mitigate non-specific drug administration to unsuitable sites, pre-activation of therapeutic agents before reaching targeted tissue, ahead of time immune system approval, and, in certain instances, potentially enhance the pharmacokinetics of drugs at the level of permeability, intake, and dispersion of drug in tissue layers [122].

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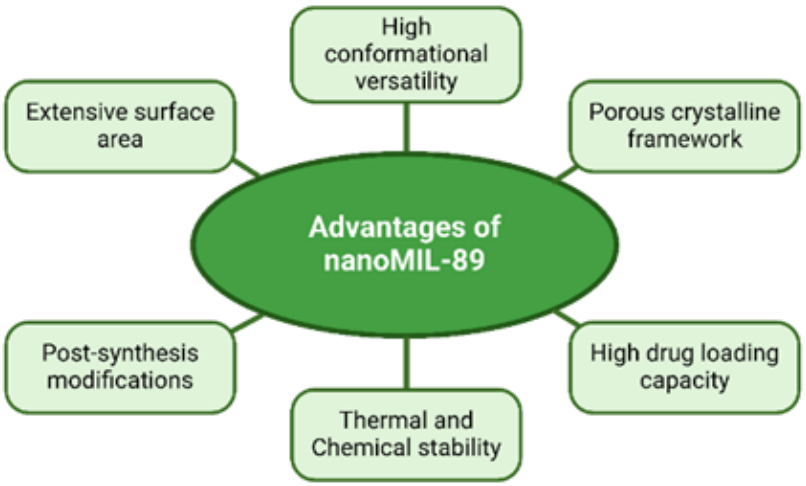
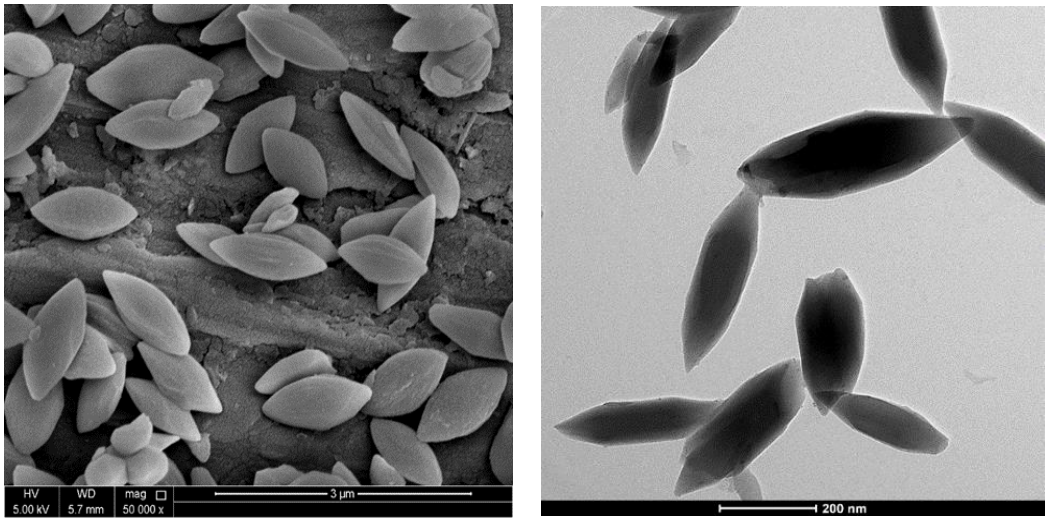


Figure 4. Advantageous features of a type of MOF; Material Institute Lavoisier 89 nanoparticles (nanoMIL-89).

SEM and TEM analysis is commonly used to characterize the shape and size of nanoparticles after production as in the case of NanoMIL-89 below (Figure 5.).



(a) **(b)**

Figure 5. NanoMIL-89 (iron oxide nanoparticles), a subcategory of MOF nanoparticles. (a) Scanning Electron Microscope captured images of nanoMIL-89 (50000x). (b) Transmission Electron Microscope captured image of nanoMIL-89 (5000x).

Studies employing metallic or magnetic NPs have been used for drug delivery in oncology [123], dermatology [124], and cardiology [125]. Mykola Ya Spivak et al. utilized gold NPs loaded with levosimendan (Simdax®) in an in-vivo study with Wistar rats and concluded that conjugated AuNPs-Simdax® had a favorable impact on cardiac contractile capacity [126]. In 2020, Li, Yan, et al. successfully demonstrated that Gold nanorod-based NP that catalyzes continuous NO production safeguards against cardiovascular damage in vitro [127]. Some studies employ a hybrid NP that combines liposomes coated with metal NPs, as in the case of Bejarano et al., who developed a gold NP-based nanosystem and employed it to optimize the distribution of angiotensin-1-9 (Núcleo de Biotecnología de Curauma, Pontificia Universidad Católica de Valparaíso, Valparaíso, Chile), which is a cardio protectant peptide, to the myocardium helping both hypertension and myocardial remodeling [128]. Lastly, another study implied that an administration of 400µg/kg/daily gold NPs (Sigma-Aldrich, St Louis, MO, USA) helps improve myocardial damage induced by isoproterenol

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(Sigma-Aldrich, St Louis, MO, USA) in male albino rats [129]. However, there is still a lack of studies using MOF NPs as drug delivery systems for the treatment of CVDs.

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references.

3. Conclusions

In conclusion, encapsulating omega-3 fatty acids with nanoparticles offers a potential strategy for improving the vital nutrients' durability, bioavailability, and targeted administration. Investigators have effectively mitigated oxidation, undesirable taste, and restricted GI absorption linked to free omega-3 fatty acids using various encapsulating strategies from nanoemulsions to solid lipid and polymeric nanoparticles. Nanoparticle containment has various benefits, including environmental protection, precise release dynamics, and the opportunity to integrate other bioactive substances for synergistic effects. Furthermore, the nanoscale dimension of these delivery methods facilitates effective cellular absorption and transit beyond biological barriers, resulting in better therapeutic effects.

Nonetheless, additional investigation is needed to optimize the formulation characteristics, such as nanoparticle structure, dimension, surface characteristics, and encapsulation efficacy, to maximize the bioavailability and effectiveness of omega-3s. Furthermore, long-term stability trials and in vivo tests are required to evaluate the safety, pharmaceutical kinetics, and medicinal potential of nanoparticle-based omega-3 nanoparticles in a variety of clinical contexts. In summary, applying nanoparticles to encapsulate omega-3 fatty acids shows considerable potential for resolving present problems in omega-3 supplementation while opening up new options for personalized nutrition and preventative healthcare.

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