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REVIEW

Nanoencapsulation of unsaturated omega-3 fatty acids as protection against oxidation: A systematic review and data-mining

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ABSTRACT
The chemical structure of unsaturated fatty acids makes them highly prone to oxidation, which decreases their nutritional properties. Nanocarriers have the ability to protect unstable nutraceuticals and take them to their specific targets. Thus, the aim is to determine the effectiveness of nanoencapsulation of omega-3 unsaturated fatty acids as protection against oxidation, as well as to apply data-mining approach to identify nanoencapsulation profiles. Three databases were used to search for studies focused on comparing omega-3 encapsulation to the active compound in its raw form. Studies without oxidation test or no use omega 3-rich oil as active ingredient in nanoformulations were excluded. Twenty-three studies were included in the systematic review. The qualitative analysis indicated that the main evaluated parameters were encapsulation efficiency (%), physical-chemical parameters and oxidation (analyzed at different storage temperatures), oil type, and whether the formulation was added to food. With regard to quantitative analysis, studies that did not perform oxidation tests focused on comparing free oil to the encapsulated one were excluded. Data-mining indicated that encapsulation efficiency and particle size were the main characteristic defining nanocarrier's effectiveness in protecting the oil against oxidation. Nevertheless, it is important to note the main characteristics associated with oil protection in nanocarriers.

KEYWORDS
Essential fatty acids; n-3 oils; nanotechnology; systematic reviews as topic; computer-assisted decision making

Introduction

Polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), are the most abundant omega-3 fatty acid enabling many health benefits such as providing protection against cardiovascular diseases and to the nervous system, improving blood pressure and mitigating inflammatory diseases (Ojagh and Hasani 2018). According to dietary recommendations by World Health Organization (WHO), the minimum intake of omega-3 fatty acids necessary to induce primary prevention of cardiovascular diseases in adult individuals corresponds $0.5-2\%$ energy (%E)/day of EPA/DHA combination (Food and Agriculture Organization of The United Nations 2010; World Health Organizations 2019). Food products enriched with these fatty acids have been developed by industries to help minimizing the effects of low omega-3 PUFA intake by Western populations (Hardy et al. 2018). However, the main challenge for omega-3 fatty acids intake is associated with its high susceptibility to oxidation (and autoxidation) and with the resulting undesirable taste (Mohammadi, Assadpour, and Jafari 2019). Nowadays, encapsulation is considered an effective technique capable of increasing the intake of bioactive compounds through food in order to delay oxidation, as well as to increase the solubility and avoid the unpleasant taste of ingredients (Cheong, Tan, and Nyam 2017). Omega-3 fatty acids are unstable and very prone to autoxidation and to oxidation induced by environmental conditions such as the presence of oxygen and/or pro-oxidants, temperature and exposure to light; generation of lipid hydroperoxides and free radicals due to the primary oxidation of double bonds, mainly for EPA and DHA (Melgosa et al. 2019).

Therefore, PUFAs degradation due to autoxidation reactions during extraction, storage or processing induces the formation of primary oxidation products such as peroxides and volatile compounds associated with rancid flavor, such as 3-hexanal, which changes the acceptability of food products' texture, flavor and color. In addition, secondary by-products such as substances reactive to thiobarbituric acid (TBARS) and p-anisidine can be formed (Cheong, Tan, and Nyam 2017; He et al. 2017). Oxidative degradation products have negative impact on compound properties, since they also have potentially cytotoxic, carcinogenic and mutagenic effects on them (Uluata, McClements, and Decker 2015).

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However, despite the relevance of this topic, the literature still lacks studies focused on investigating nanoencapsulation efficiency in protecting unsaturated fatty acids from oxidation (and autoxidation) and on identifying the main analysis parameters. Lack of systematic approaches adds uncertainty and variability to the literature in the field and limits the generalization of existing studies. Data-mining techniques are acknowledged as one of the most promising tools to extract valuable knowledge from different databases, a fact that makes them important to help making more accurate decisions (Du 2020; Groenhof et al. 2020). Knowledge resulting from the data-mining process is mainly categorized as predictive models or standards; thus, this knowledge must be valid, authentic, innovative, understandable and based on significant associations among large amounts of data (Liu et al. 2019). The classification task, algorithm J48 and random tree, available in the WEKA tool, was adopted. This choice was made in function of classifying from the decision tree (Gorunescu 2011; Patel and Upadhyay 2012), due to the possibility of identifying the variables most strongly related to the one selected as the focus of analysis, such as the size of the particle for example.

The nanoencapsulation of unsaturated fatty acids plays a key role in conserving their functional properties, since it improves their bioavailability and, consequently, therapeutic effectiveness. Thus, the aim of the present study is carried out a systematic review followed by data-mining approach in order to determine the effectiveness of omega-3 unsaturated fatty acid nanoencapsulation as protection against its oxidation, as well as discerning trends of data indicating the main characteristics associated with oil protection in nanocarriers.

2. Methodology

2.1. Experimental design

A systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) statement (Moher et al. 2009). The research question was formulated and the study selection criteria were defined using the PICO strategy where (omega-3 [P]; oxidation tests [I]; nanoencapsulated oil × free oil, [C]; oil protection [O]).

2.2. Search

The search for articles was carried out in the ScienceDirect, PubMed, and Web of Science databases. Studies focused on evaluating the effectiveness of omega-3 fatty acids nanoencapsulation in protecting against oxidation, in comparison to their crude or free form, were taken into consideration. Studies published in English from 1985 and September 2020 were evaluated. The search strategy was based on the following terms: ((nano*) and (stability) and ((UFA) or (omega 3) or (unsaturated fatty acids))). Manual search was performed in the reference list of the included articles in order to find potential additional articles. Studies that did not perform any oxidation assessment test (e.g. peroxide value (PV), p-anisidine value, TBARS), or did not use omega 3-rich oil or compound as the active ingredient in nanoformulations, or that presented particle size greater than 500 nm (or if smaller, it was referred to by the authors as microparticles were excluded. Only studies with comparison between oil free and oil-loaded nanoformulation were included.

2.3. Studies' selection

Two independent reviewers (MCV and CRB) initially checked the titles of the articles found in the investigated databases and conducted the first exclusions based on search criteria. Subsequently, the remaining articles had their abstracts evaluated to enable identifying the eligible articles. In case of doubts about the exclusion of a specific article, it was included for full text evaluation. Full article reading and analysis have defined studies inclusion in, and exclusion from, the current review. Articles independently included in the study were compared in pairs. In case of disagreement between reviewers, a third reviewer was in charge of making the decision about including or excluding the article from the study (JAS).

2.4. Data extraction and tabulation

Data were extracted by the two reviewers in a standardized way, based on a table previously defined by all authors (supplementary information). Similar variables were classified and grouped in order to be evaluated based on results recorded for the following physical-chemical parameters: particle or droplet size, zeta potential and polydispersity index (PDI) at 4, 15, 25, and/or 40 °C (when temperature test was different but near criteria, the data was included into classification); encapsulation efficiency (%); oxidation data, such as analysis of oxidation products, atmosphere (presence or not O_2), temperature, analysis period (days), and applied tests of oxidation; food application; additive incorporation into the nanoformulation. With respect to the quantitative analysis, all studies included compare nanoformulation to free compound or oil, without added surfactants or antioxidants to the free oil.

2.5. Risk of bias

The Review Manager Cochrane tool (RevMan Version 5.3., The Cochrane Collaboration, 2014) was used to analyze the risk of bias. The selection of parameters was according guideline by Cochrane. The following parameters were considered important for results' quality and reliability: encapsulation efficiency measurement, particle size distribution calculation, temperature during oxidation, control oil without additives, and number of replications. Studies were evaluated in separate by taking into consideration each of the analyzed parameters; they were classified as "low risk" when the parameter was measured, or "high risk" when it was not measured. Parameters in studies failing in presenting clear or accurate information were classified as "unclear."

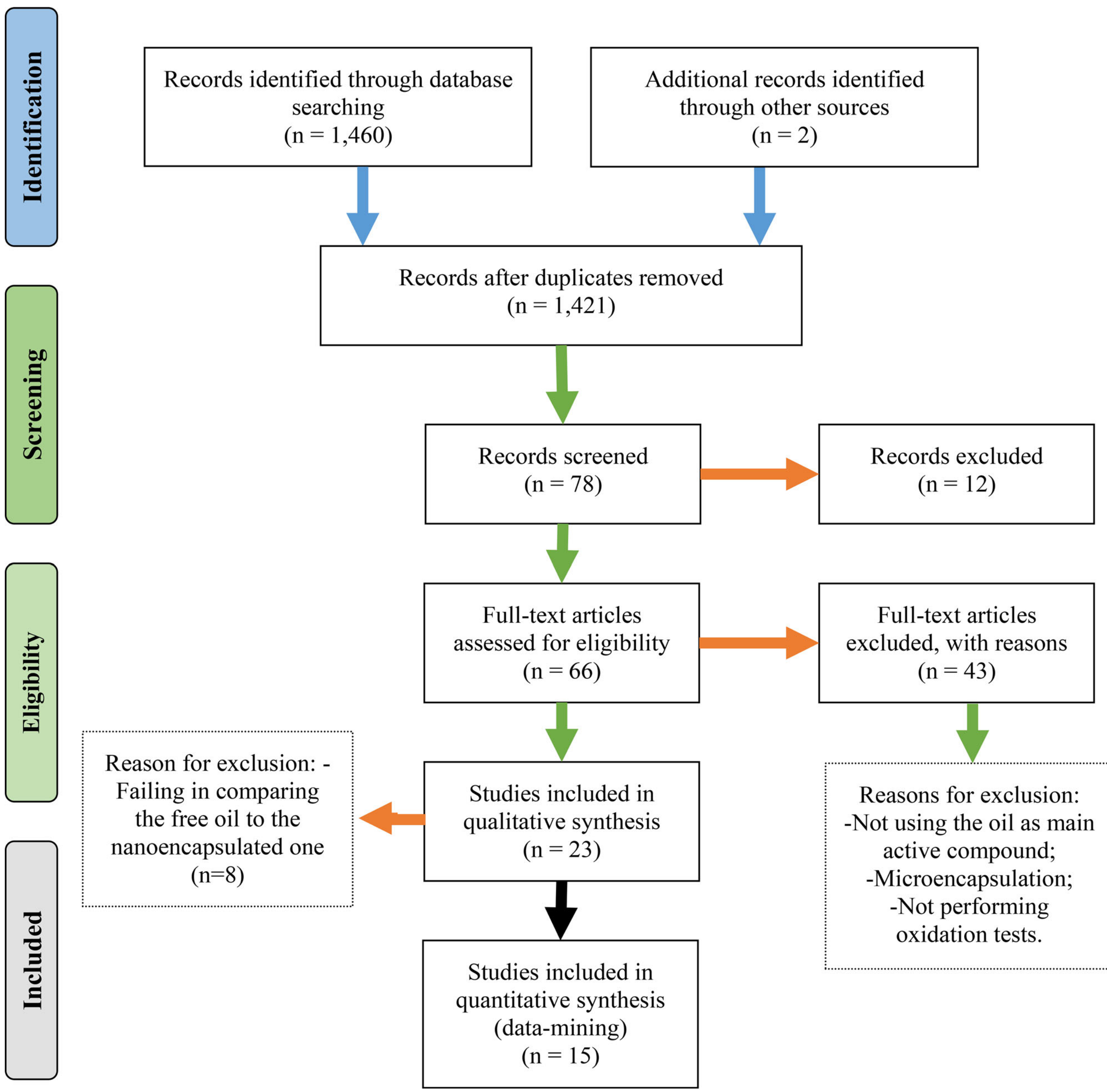

Figure 1. Selection procedures according to PRISMA declaration (based on Moher et al. (2009)).

2.6. Experimental datasets

Data were processed to enable data-mining based on a file in ARFF format, which is the input file format used by the WEKA data-mining software (University of Waikato, New Zealand). It allows to apply algorithms to the data already incorporated in the tool as well as to develop some specific algorithm for this task. Eight (8) attributes were selected to create the data file, namely: formulation (nanoformulation type); particle size at 25 °C (nm); encapsulation efficiency (%); oxidation data such as analysis of oxidation products, atmosphere, temperature, analysis time, and applied tests used to determine oxidation; and 38 instances referring to the types of analyzed data as formulation and oxidation – instances refer to their occurrence in the analyzed articles (number of times) (see supplementary information). The selection of attributes was based on the main parameters to be considered in the characterization of a nanoformulation, combined with the common parameters observed by eligible studies. J48 decision tree and Random trees were the algorithms applied to clean and adjust data in order to get more adequate results.

3. Results

In total, 66 articles were fully evaluated and 2 articles were found in reference lists; articles included in the current review were accepted by all reviewers. Figure 1 presents the framework selection of the articles in detail.

3.1. Qualitative analysis

Twenty-three studies (Table 1) were included in the systematic review because they assessed the nanotechnology efficiency in protecting omega-3 fatty acids from oxidation.

Table 1. Articles included in the systematic review.

Ref.	Author/Year	Title	Comparison	Tests	Results	Outcome
Belhaj, Arab-Tehrany, and Linder (2010)	Belhaj, Arab-Tehrany, and Linder (2010)	Oxidative kinetics of salmon oil in bulk and in nanoemulsion stabilized by marine lecithin	Crude salmon oil vs. nanoemulsion with, or without, antioxidants (marine lecithin, α-tocopherol, quercetin)	Particle size; oxidation analysis based on the index of polyenes and diene conjugates under O_2 or N_2 atmosphere; presence of H_2O, ROH and ROOH based on FT-IR	Marine lecithin (extracted from salmon head) presented higher oxidative stability than free oil samples. Lecithin-based nanoemulsion increased free oil stability due to its high LC-PUFA levels (measured at 30 °C)	Nanoemulsion containing salmon's natural antioxidant (marine lecithin) was effective in protecting crude salmon oil from oxidizing
García-Moreno et al. (2016)	García-Moreno et al. (2016)	Encapsulation of fish oil in nanofibers by emulsion electrospinning: Physical characterization and oxidative stability	Free fish oil vs. oil in poly (vinyl alcohol) (PVA) nanofibers blended with emulsion	Droplet size; encapsulation efficiency; oxidation analysis based on PV and analysis of secondary products based on CG-MS	PVA-emulsion fish oil nanofibers presented higher PV and volatile compound content than unprotected fish oil (measured at 40 °C)	PVA presented negative influence as oil carrier, even it had pro-oxidant potential. Although most of the fish oil was encapsulated inside the fibers as small droplets, these fibers showed poor oxidative stability, likely due to traces of metals such as Fe
Ghorbanzade et al. (2017)	Ghorbanzade et al. (2017)	Nano-encapsulation of fish oil in nano-liposomes and its application in yogurt fortification	Yogurt fortified with free fish oil or with nanoliposomes (lecithin and sunflower oil)	Particle size; PDI; encapsulation efficiency; Yogurt oxidation analysis based on PV	Yogurt fortified with free oil presented higher PV incidence than the one fortified with nanoliposomes added with oil (measured at 4 °C)	Different from what was observed for yogurt fortified with free fish oil, fish oil addition to yogurt nanoliposomes provided features closer to the non-fortified samples
Ha, Lee, and Lee (2018)	Ha, Lee, and Lee (2018)	Oxidative stability of DHA in β-lactoglobulin/oleic acid-modified chitosan oligosaccharide nanoparticles during storage in skim milk	Free DHA vs. DHA in β-lactoglobulin/oleic acid-modified chitosan oligosaccharide nanoparticles	Particle size; PDI; zeta potential; encapsulation efficiency; oxidation analysis based on PV and by-product analysis based on CG-MS	Skimmed milk presenting nanoparticles added with DHA recorded lower PV and p-anisidine values than milk with free DHA. The unpleasant taste in milk was mitigated by the presence of nanoparticles (measured at 4 °C)	Nanoparticles led to increased oxidative stability and reduced DHA self-oxidation.
Haider et al. (2017)	Haider et al. (2017)	Formation of chitosan nanoparticles to encapsulate krill oil (*Euphausia superba*) for application as a dietary supplement	Free krill oil vs. oil in chitosan-tripolyphosphate (TPP) nanoparticles	Particle size; PDI; zeta potential; encapsulation efficiency; oxidation analysis based on PV and by-product analysis based on FT-IR (ROOH, CO and diene conjugates)	Nanoparticles presented lower hydroperoxide formation, even after two weeks of krill oil storage (measured at 45 °C)	Nanoparticles have shown oxidative protection of krill oil
Karthik and Anandharamakrishnan (2016a)	Karthik and Anandharamakrishnan (2016a, 2016b)	Fabrication of a nutrient delivery system of docosahexaenoic acid nanoemulsions via high energy techniques	Free DHA vs. DHA of algae oil in nanoemulsion prepared with Tween-40	Particle size; PDI; zeta potential; oxidation analysis based on TBARS and by-product	Nanoemulsion has shown the highest TBARS value in the first analysis. There was increased oxidation in	The combination of homogenization techniques resulted in better physical-chemical properties and stability

				analysis based on CG-MS	free DHA over 30 days. Nanoemulsion prepared with DHA at 4 °C has shown lesser TBARS formation than the ones stored at 28 °C or 40 °C	over 100 storage days than other emulsification techniques for DHA encapsulation. The high-pressure production process resulted in the most stable nanoformulation, which presented the most efficient protection against oxidation
Nejadmansouri et al. (2016a)	Nejadmansouri et al. (2016a, 2016b)	Physicochemical properties and oxidative stability of fish oil nanoemulsions as affected by hydrophilic lipophilic balance, surfactant to oil ratio and storage temperature	Free fish oil vs. oil in conventional emulsions and nanoemulsion (with Tween-80 and Span80)	Particle size; polydispersity (span); oxidation analysis based on TBARS	Conventional emulsions have shown lower TBARS values than nanoemulsions. Both formulations have shown more oxidation products than free fish oil (measured at 4 and 25 °C).	Nanoemulsion did not protect fish oil from oxidizing. However, α-tocopherol incorporation increased the chemical stability of unsaturated fatty acids for up to two weeks; after this time, values were similar to the ones recorded for the antioxidant-free nanoemulsion
Nejadmansouri et al. (2016b)	Nejadmansouri et al. (2016a, 2016b)	Physicochemical properties and storage stability of ultrasound-mediated WPI-stabilized fish oil nanoemulsions	Free fish oil vs. conventional emulsions and nanoemulsion (with whey protein)	Particle size; polydispersity (span); zeta potential; oxidation analysis based on TBARS	Nanoemulsions and conventional emulsions have shown more oxidation products than free fish oil (measured at 4 and 25 °C). Formulations were prepared in greater volume for stability tests; however, physical-chemical parameters were not repeated	The oxidation rate of whey protein-stabilized nanoemulsions was lower than that of conventional emulsions, likely due to the size of larger particles, which were influenced by temperature
Ojagh and Hasani (2018)	Ojagh and Hasani (2018)	Characteristics and oxidative stability of fish oil nano-liposomes and its application in functional bread	Free fish oil vs. oil in nanoliposome (with lecithin and sunflower oil).	Particle size; PDI; encapsulation efficiency; oxidation analysis based on PV and TBARS	Fish oil in nanoliposomes has shown lower lipid oxidation product values than the free fish oil (measured under refrigeration)	Fish oil in nanoliposomes was protected from oxidation; bread enriched with fish oil did not present undesirable odor and taste, likely due to greater oxidative stability
Rasti, Erfanian, and Selamat (2017)	Rasti, Erfanian, and Selamat (2017)	Novel nanoliposomal encapsulated omega-3 fatty acids and their applications in food	Free fish oil vs. oil in microparticles and nanoliposomes added to bread and milk	Particle size; PDI; oxidation analysis based on PV and p-anisidine	The lowest oxidation product values were observed in bread and milk enriched with nanoliposomes in comparison to free oil or microparticle	Based on sensory evaluation results, milk and bread enriched with nanoliposome have shown high stability during storage (3 and 7 days for milk and bread, respectively)

(continued)

Table 1. Continued.

Ref.	Author/Year	Title	Comparison	Tests	Results	Outcome
					samples (measured at 4 and 25 °C)	and did not present any detectable unpleasant fish flavor
Rasti et al. (2012)	Rasti et al. (2012)	Comparative study of the oxidative and physical stability of liposomal and nanoliposomal polyunsaturated fatty acids prepared with conventional and Mozafari methods	Free DHA and EPA vs. nanoliposomes and conventional liposomes added with DHA and EPA	Particle size; PDI; encapsulation efficiency; oxidation analysis based on TBARS and diene conjugate analysis based on CG-MS	There was not significant change in physical-chemical stability over 10 months of cold storage at 4 °C in the dark	PUFAs recorded lower conjugated diene and TBARS values, which indicated that liposomal formulation production made unsaturated fatty acids more exposed to oxidation. However, among the formulations, the physical and oxidative stability of liposomal PUFAs increased as liposome size decreased
Yang et al. (2017)	Yang et al. (2017)	Enhancing oxidative stability of encapsulated fish oil by incorporation of ferulic acid into electrospun zein mat	Free fish oil vs. oil in zein nanofibers with, or without, polyphenol and ferulic acid	Fiber diameter; encapsulation efficiency; oxidation analysis based on PV	The oil incorporated to zein nanofibers presented lower oxidation than free oil under O_2 or N_2 atmosphere, at 25, 45, and 60 °C	Antioxidant ferulic acid addition increased the oxidative stability of zein nanofibers and reduced the oxidation of oil products
Zimet and Livney (2009)	Zimet and Livney (2009)	Beta-lactoglobulin and its nanocomplexes with pectin as vehicles for ω-3 polyunsaturated fatty acids	Free DHA vs. DHA in β-lactoglobulin and pectin nanoparticles	Particle size; zeta potential; encapsulation efficiency; oxidation analysis based on DHA stability measurement through RP-HPLC	Electrostatic nanocomplexes consisting of β-lactoglobulin and pectin have encapsulated DHA molecules, showed very good colloidal stability and effectively protected DHA from oxidation during the accelerated shelf-life stress test (measured at 40 °C)	The nanocomplex provided high protection to DHA, with maximum loss of 10% over an extended period-of-time, unlike free DHA, which recorded 8% loss in the same period
Zimet, Rosenberg, and Livney (2011)	Zimet, Rosenberg, and Livney (2011)	Re-assembled casein micelles and casein nanoparticles as nano-vehicles for ω-3 polyunsaturated fatty acids	Free DHA vs. DHA in casein nanoparticles	Particle size; encapsulation efficiency; oxidation analysis based on DHA stability measurements through RP-HPLC	Nanoparticles have shown remarkable protective effect against DHA oxidation (measured at 4 °C)	Nanoparticles have shown good colloidal stability and enabled excellent DHA protection against oxidation, since casein has partial antioxidant activity
Walker, Decker, and McClements (2015)	Walker, Decker, and McClements (2015)	Physical and oxidative stability of fish oil nanoemulsions produced by spontaneous emulsification: Effect of surfactant concentration and particle size	Nanoemulsion spontaneously prepared with fish oil vs. high homogenization speed. It was not compared to free oil	Particle size; PDI; zeta potential; oxidation (Peroxides and TBARS)	Nanoemulsions have shown similar oxidative stability at 55 °C, for 14 days. Neither particle size nor surfactant concentration had major impact on lipid rate	Nanoemulsion preparation does not promote lipid oxidation. Overall, this study has shown that low-energy homogenization methods (spontaneous emulsification) can be

						used to produce fish oil emulsions capable of strengthening transparent food or beverage systems
Salminen et al. (2017)	Salminen et al. (2017)	Tuning of shell thickness of solid lipid particles impacts the chemical stability of encapsulated ω-3 fish oil	Comparison among nanoemulsions presenting lecithin of different molecular weights. The comparison did not include free oil	Particle size; PDI; zeta potential; oxidation (Peroxides)	Lipid particles presenting higher tristearin ratio have shown better oxidative stability	Minimum capsule thickness ranging from 10 to 20 nm of crystalline tristearin in lipid particles is essential to enable its stabilization against lipid oxidation
Cheong, Tan, and Nyam (2017)	Cheong, Tan, and Nyam (2017)	Physicochemical, oxidative and anti-oxidant stabilities of kenaf seed oil-in-water nanoemulsions under different storage temperatures	Nanoemulsions at different temperatures, without free oil values	Particle size; PDI; zeta potential; oxidation (Peroxides and p-anisidine)	Nanoemulsions stored at 4 °C maintained the highest stability over 12 storage weeks	Kenaf seed-based nanoemulsions maintained the best physical-chemical and oxidative stability at 4 and 25 °C for up to 8 weeks, in comparison to nanoemulsions stored at 40 °C
Azizi et al. (2018)	Azizi et al. (2018)	Improvement of physicochemical properties of encapsulated echium oil using nanostructured lipid carriers	Nanostructured lipid carriers incorporated in echium oil droplets and whey protein isolates in oil-in-water emulsions were analyzed Lipid carriers, such as lauric, palmitic and stearic acids, were used	Encapsulation efficiency; particle size; zeta potential; oxidation (TBARS)	Lipid carriers, mainly lauric acid, improved physical stability of droplets. TBARS assay has indicated that lauric acid was more effective in protecting Echium oil from oxidation than palmitic and stearic acids	Different lipid carriers with different chain lengths affected the physicochemical properties of echium oil Lipid carriers' addition to echium oil emulsions can improve their stability
Salminen et al. (2013)	Salminen et al. (2013)	Formation of solid shell nanoparticles with liquid ω-3 fatty acid core	Comparison between nanoemulsions with fish oil and different surfactants, without free oil values	Particle size; PDI; zeta potential; oxidation (Peroxides)	Results have shown that saturated high-melting lecithin played a key role in the development of physically and oxidatively stable lipid nanoparticles	It could increase the storage time of omega-3 fatty acids in food products and enable using them to supplement a greater variety of food at higher concentrations
Wang et al. (2016)	Wang et al. (2016)	Colloidal complexation of zein hydrolysate with tannic acid: Constructing peptides-based nanoemulsions for alga oil delivery	Zein nanoemulsion and zein/tannic acid nanoemulsion added with different oil proportions, without free oil	Encapsulation efficiency; particle size; zeta potential; oxidation (Peroxides)	Zein's emulsifying activity has improved after tannic acid complexation. Emulsions stabilized by the zein/tannic acid complex have shown remarkable physical stability and high seaweed oil encapsulation efficiency	Seaweed oil nanoemulsions stabilized by the zein/tannic acid complex have shown increased oxidative stability in comparison to nanoemulsions only stabilized with ZH
Dey et al. (2018)	Dey et al. (2018)	Designing of ω-3 PUFA enriched biocompatible nanoemulsion with sesame protein isolate as a natural surfactant:	Fish oil nanoemulsions presenting different surfactant and sesame protein (sesame)	Particle size; zeta potential; PDI; oxidation (TBARS)	The nanoemulsion formulation presenting sesame protein isolate – at 0.5% (w/v) concentration –	The sesame protein isolate incorporated to the formulation as natural surfactant has substantially increased

(continued)

Table 1. Continued.

Ref.	Author/Year	Title	Comparison	Tests	Results	Outcome
		Focus on enhanced shelf-life stability and biocompatibility	proportions, without free oil		combined with Tween 20 and Span 80 (1: 1) – has minimized particle size and substantially increased the shelf-life stability of nanoemulsions over an 8-week storage period.	the shelf-life stability of nanoemulsions
Karthik and Anandharamakrishnan (2016b)	Karthik and Anandharamakrishnan (2016a, 2016b)	Enhancing omega-3 fatty acids nanoemulsion stability and in vitro digestibility through emulsifiers	Comparison among different formulations (nanoemulsions with different Tween-40 emulsifiers, sodium caseinate and soy lecithin) without free oil	Particle size; PDI; zeta potential; oxidation (Peroxides)	The Tween-40 nanoemulsion presented greater physical stability than sodium caseinate and soy lecithin when it was stored at $28 \pm 1\,°C$; at $40 \pm 0.2\,°C$ it presented lesser lipid oxidation than other emulsions	Nanoemulsion can improve storage stability and bioavailability
Nunes et al. (2020)	Nunes et al. (2020)	Lactoferrin-based nanoemulsions to improve the physical and chemical stability of emoga-3 fatty acids	Free mixed DHA (25%) and EPA (35%) vs. omega 3 mix in lactoferrin nanoemulsions at different concentrations	Droplet size; PDI; zeta potential; encapsulation efficiency; release profile; oxidation (DPPH and peroxides)	Nanoemulsions stored at $4\,°C$ maintained the highest stability over 69 storage days, however, the oxidative stability was loosen at day 36	Oil free showed increased peroxide values at the final of experiment, at $4\,°C$, 36th day. Nanoemulsion-loaded DHA/EPA mix did not protect the oxidation and showed similar values to the control at day 8, indicating that nanoformulations were worst to the oil oxidation profile

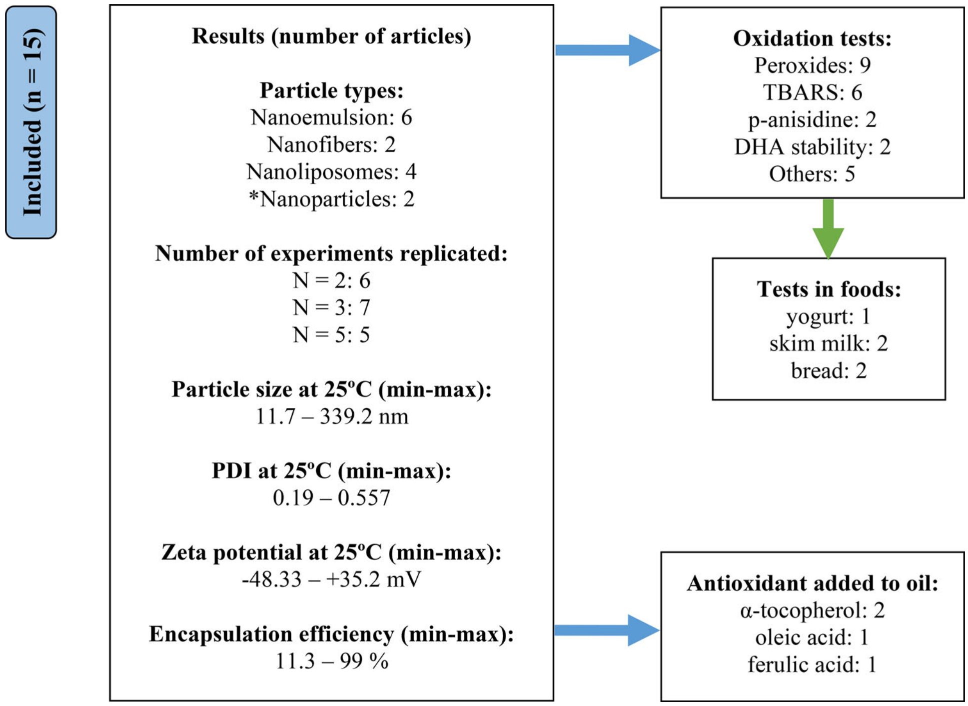

Figure 2. Flowchart of the selection descriptor and validation protocol for data mineralization purposes.

Twelve articles (52%) used fish oil (Belhaj, Arab-Tehrany, and Linder 2010; Salminen et al. 2013; Walker, Decker, and McClements 2015; García-Moreno et al. 2016; Nejadmansouri et al. 2016a, 2016b; Ghorbanzade et al. 2017; Rasti, Erfanian, and Selamat 2017; Salminen et al. 2017; Yang et al. 2017; Dey et al. 2018; Ojagh and Hasani 2018), seven (30%) reported using omega-3 polyunsaturated fatty acids (EPA and/or DHA) as major active (Zimet and Livney 2009; Zimet, Rosenberg, and Livney 2011; Rasti et al. 2012; Karthik and Anandharamakrishnan 2016b, 2016a; Ha, Lee, and Lee 2018; Nunes et al. 2020) and four articles (17%) used different oils such as kenaf seed (Cheong, Tan, and Nyam 2017), echium (Azizi et al. 2018), seaweed (Wang et al. 2016), and krill oils (Haider et al. 2017).

From articles included in the systematic review, five studies (≈22%) have assessed the oxidation of fatty acids in food products such as: bread (Rasti, Erfanian, and Selamat 2017; Ojagh and Hasani 2018), milk (Rasti, Erfanian, and Selamat 2017; Ha, Lee, and Lee 2018) and yogurt (Ghorbanzade et al. 2017). Nanocapsules and liposomes were the nanotechnologies most used in these studies for fatty acids incorporation. Formulation efficiency in carrying the oil was subjected to stability tests – such stability was evaluated for 3–69 days. Comparison between formulation and free oil has shown decreased omega-3 fatty acid oxidation in most of studies.

Thirty (56.5%) studies focused on testing encapsulation efficiency were observed (Zimet and Livney 2009; Zimet, Rosenberg, and Livney 2011; Rasti et al. 2012; García-Moreno et al. 2016; Wang et al. 2016; Ghorbanzade et al. 2017; Haider et al. 2017; Rasti, Erfanian, and Selamat 2017; Yang et al. 2017; Azizi et al. 2018; Ha, Lee, and Lee 2018; Ojagh and Hasani 2018; Nunes et al. 2020), whereas one study (Ha, Lee, and Lee 2018) presented the physical-chemical parameters featuring nanoformulations, namely: particle or droplet size; zeta potential; PDI at different storage temperatures 4, 15, 25, and/or 40 °C; encapsulation efficiency (%); and oxidation tests at different analysis times.

The systematic review has found six articles using the following milk proteins as fatty acid encapsulation material: whey protein isolate (Nejadmansouri et al. 2016b; Azizi et al. 2018; García-Moreno et al. 2018) β-lactoglobuline (Zimet and Livney 2009; Ha, Lee, and Lee 2018) and casein (Zimet, Rosenberg, and Livney 2011). None of the studies has evaluated the addition of synthetic antioxidants as active ingredient protection in the formulation, but two studies used antioxidants such as α-tocopherol and ferulic acid in combination with encapsulated omega-3. Yang et al. (2017) have developed zein nanofibers (corn protein) added with fish oil and ferulic acid; the acid addition to the active compound in the nanofibers has significantly improved the oxidative stability of the encapsulated oil, without changing the fish oil release profile.

Five studies (≈22%) did not show protective effects of nanoencapsulation on the oxidation of omega-3 fatty acids. García-Moreno et al. (2016) have encapsulated fish oil in nanofibers based on emulsion electrospinning with, or without, emulsifiers isolated from whey protein isolate or fish protein hydrolysate. According to Nejadmansouri et al. (2016a), fish oil nanoemulsions were stabilized with different mixtures of nonionic surfactants (Tween 80, Span 80) – based on the high-intensity ultrasound method – or with whey protein (Nejadmansouri et al. 2016b). Conventional emulsions were more stable against oxidation than nanoemulsions. Incorporation of α-tocopherol to the active compound in nanoemulsions added with surfactants has increased the chemical stability of unsaturated fatty acids; however, such efficiency was lost after two weeks. Based on

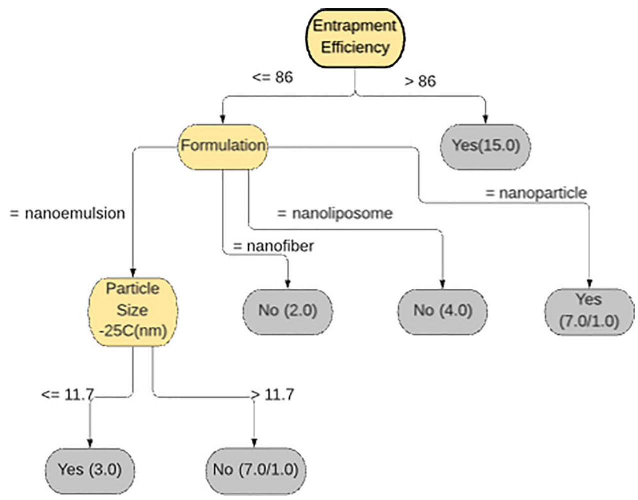

Figure 3. Representative branches resulted from Decision tree 1-J48 learnt based on nanoparticles features. Eight attributes were carried out from 38 instances (see Methodology).

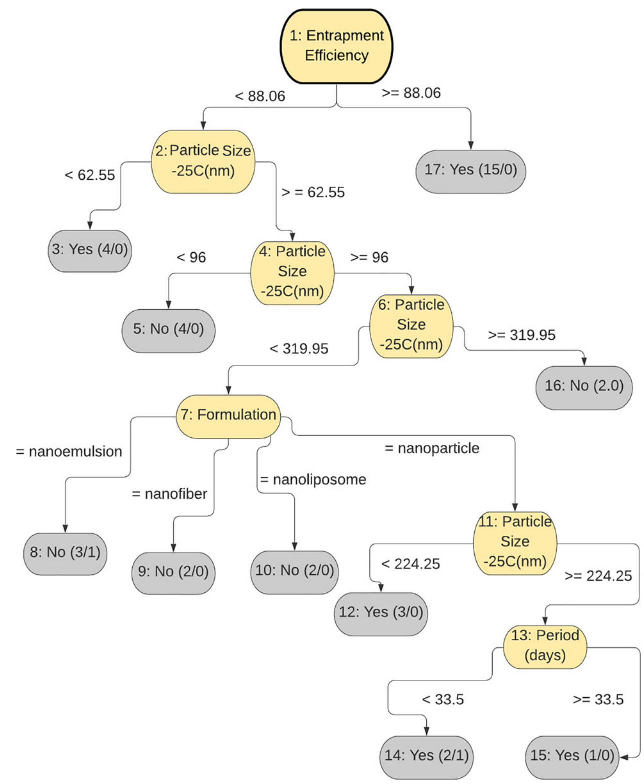

Figure 4. Representative branches resulted from Decision tree 2 – Random trees learnt based on nanoparticles features. Eight attributes were carried out from 38 instances (see Methodology).

another study, nanoliposomes added with DHA and EPA were more efficient in protecting PUFAs from oxidative degradation than conventional liposomes; however, TBARS values were higher than free PUFAs' (Rasti et al. 2012). Recently, one study demonstrated increased values of peroxides in nanoemulsions added with DHA and EPA, indicating fragile preparations probably due the high energy methods applied during nanoformulation, ultra turrax and high-pressure homogenizer, even temperature had been controlled (Nunes et al. 2020).

Based on the formulation safety viewpoint, the toxic potential of omega-3 nanoencapsulation in the included studies, only one investigated through experiments conducted with cells in vitro as alternative tests (Nunes et al. 2020), not even articles that added the nanoformulation to food.

3.2. Data-mining

Common attributes among the ones available in the articles included in the present research were selected for data-mining purposes. These 15 articles compared the oxidation of free oil to that of nanoencapsulated oil based on the following parameters: primary oxidation (PV), secondary oxidation (TBARS and/or p-anisidine), or DHA stability evaluation (Figure 2).

The analyzed studies used different nanoparticle and oxidation test types; degradation analysis days; nanoformulation constituents; additive (surfactants or antioxidants) incorporated, or not, to the oil to analyze any food product. Of the 15 selected studies (supplementary material), eight (≈53%) conducted PV tests (Belhaj, Arab-Tehrany, and Linder 2010; García-Moreno et al. 2016; Ghorbanzade et al. 2017; Haider et al. 2017; Rasti, Erfanian, and Selamat 2017; Yang et al. 2017; Ojagh and Hasani 2018; Nunes et al. 2020), four (≈27%) conducted TBARS tests (Rasti et al. 2012; Karthik and Anandharamakrishnan 2016a; Nejadmansouri et al. 2016b, 2016a), one (≈7%) investigated PV and p-anisidine levels (Ha, Lee, and Lee 2018) and two (≈13%) conducted DHA stability assessment tests (Zimet and Livney 2009; Zimet, Rosenberg, and Livney 2011).

The main question for analysis was whether nanoencapsulation was able to protect omega-3-rich oil from oxidation. Decision trees are machine learning approaches capable of predicting the value of a given target attribute (oxidation of nanoencapsulated omega-3) by learning through simple decisions and inferring rules based on datasets (e.g., encapsulation efficiency, particle size and type, among others). Each of these measurable or observed parameters is called "attributes." Selecting a set of informative and discriminatory resources is a crucial step to enable algorithm effectiveness in recognizing and classifying patterns.

Eight (8) attributes were analyzed in order to check whether nanoencapsulation was able to protect omega-3 from oxidation. Decision Tree 1 (DT1-J48) seen in Figure 3, showed interesting results due to DT1 use. Encapsulation efficiency was the most important discriminator used to assess whether nanoencapsulation can protect omega-3 from oxidation; 10 (≈67%) studies have evaluated this parameter (Zimet and Livney 2009; Zimet, Rosenberg, and Livney 2011; Rasti et al. 2012; García-Moreno et al. 2016; Ghorbanzade et al. 2017; Haider et al. 2017; Yang et al. 2017; Ha, Lee, and Lee 2018; Ojagh and Hasani 2018; Nunes et al. 2020). However, values must be equal to, or greater than, 86% in order to enable the most efficient protection. Particle type was the second analyzed attribute - nanoparticles appeared as decisive attribute. Two studies (≈13%) have investigated nanoparticles (Zimet, Rosenberg, and Livney 2011; Ha, Lee, and Lee 2018), six (36%) have

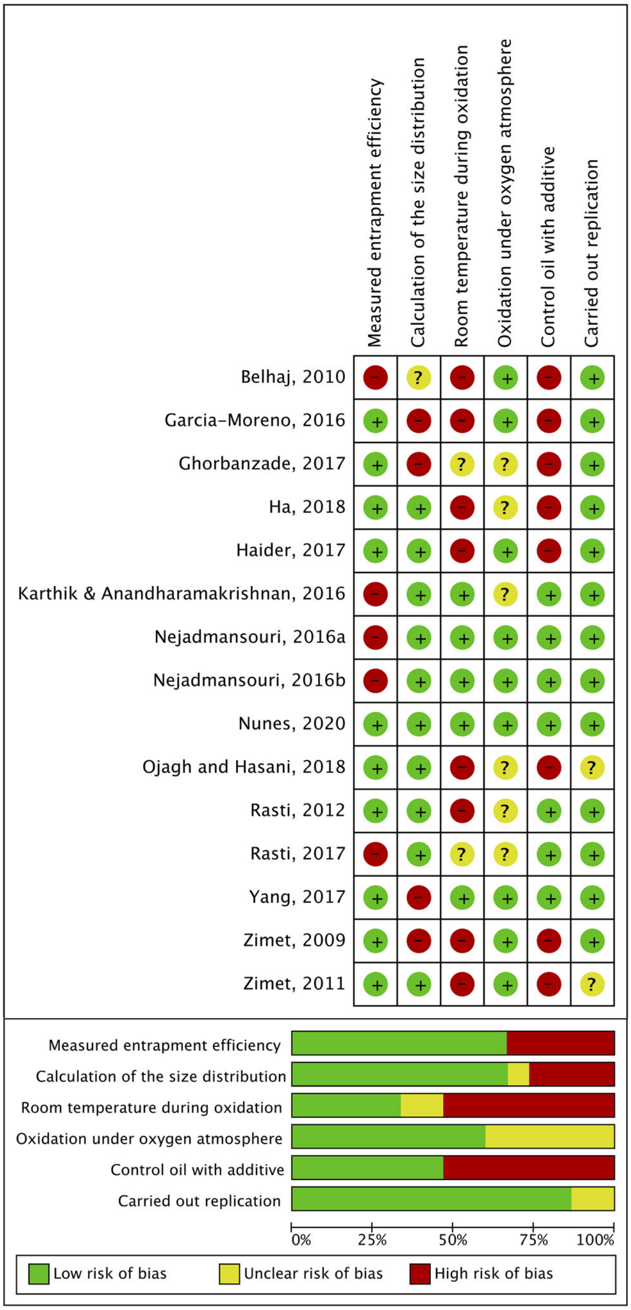

Figure 5. Risk of bias considering aspects reported in the materials and methods section. (Top) Risk of bias for each included study based on parameters established by the authors. (Bottom) Risk of bias for each parameter analyzed in separate. Symbols and color: (+) or green = parameter is present; (–) or red = parameter is not present; (?) or yellow = determination is unclear.

analyzed nanoemulsion (Belhaj, Arab-Tehrany, and Linder 2010; Karthik and Anandharamakrishnan 2016a; Nejadmansouri et al. 2016b, 2016a; Haider et al. 2017; Nunes et al. 2020), two (≈13%) used nanofibers (García-Moreno et al. 2016; Yang et al. 2017), four (≈27%) presented liposomes (Rasti et al. 2012; Ghorbanzade et al. 2017; Rasti, Erfanian, and Selamat 2017; Ojagh and Hasani 2018) and only one study (≈7%) analyzed casein nanocomplex (Zimet and Livney 2009). Particle size was the third attribute taken into consideration when the formulation comprised nanoemulsion, which must be greater than 11 nm.

Of the 15 studies, only four (≈27%) used additives in the formulation to improve oxidation (Belhaj, Arab-Tehrany, and Linder 2010; Nejadmansouri et al. 2016a; Yang et al. 2017; Ha, Lee, and Lee 2018). The very same eight attributes used in DT1 were analyzed in order to check whether additives added to nanoencapsulation were capable of improving omega-3 oxidation.

The Decision Tree 2 (DT2) has its results presented in Figure 4. Encapsulation efficiency was again the optimal descriptor used to assess whether antioxidant addition to nanoencapsulation was capable of improving protection against omega-3 oxidation; however, values must be equal to, or greater than, 88% to enable the most efficient protection. Particle size was the second descriptor – particles must be smaller than, or equal to, 62.55 nm. According to this parameter, particle size should be smaller than, or equal to, 96 nm up to maximum size 319.95 nm in order to assure efficiency. Particle type was the next important descriptor pointed out, which must be analyzed again when the formulation comprises nanoparticles – particle size must be smaller than, or equal to, 224.25 nm. Finally, the number of test days – which was not analyzed in DT1 – must be larger than, or equal to, 33.5 days. However, similar to DT1, it was also not possible stating that a single attribute can define omega-3 oxidation stability in encapsulated oil.

3.3. Risk of bias

Risk of bias indicates was analyzed based on a previous study (Sarkis-Onofre et al. 2014). Articles reporting one or two attributes were classified as having high risk of bias, the ones reporting three or four attributes were classified as having unclear risk, whereas those reporting five or six attributes were classified as having low risk of bias. Thus, of the 15 studies included in the current research, four presented low risk of bias (one of them show all parameters), eight presented unclear risk and three presented high risk of bias (Figure 5). Most articles presented sample repetition ($n = 2$–3) for oxidation tests; however, temperature control during oxidation was the least reported and variable parameter.

4. Discussion

This systematic review has shown that nanotechnology is efficient in protecting unsaturated fatty acids from oxidation, since data analysis based on mineralization enabled identifying the most important parameters of a given nanoformulation to make it efficient in protecting oil from oxidation. These data were the first to show that parameters such as encapsulation efficiency and particle size are the most significant descriptors for the success of formulations containing omega-3 as active compound. Thus, decision trees have highlighted critical variables of a complex dataset observed in studies included in the review, which accurately selected the descriptors. Of the eight attributes analyzed in the datasets, three have showed substantial results, namely: encapsulation efficiency, particle size and particle type were pointed out as optimal descriptors. Nanoemulsion was analyzed as a great oil carrier, since it can be produced without synthetic components and additives, as well as present absorption and bioavailability potential (Bush, Stevenson, and Lane 2019).

Particle size is an important attribute to evaluate oxidation based on data mineralization. In addition, particles' mean diameter and dispersity are used to show the homogeneity of suspended particles, which is an important factor to assure homogeneity in particle diameter distribution, besides being an indicator of formulation stability when its values range from 0.15 to 0.3, depending on the material used for encapsulation (Danaei et al. 2018). Based on the bias analysis, it was possible seeing that ≈33% of evaluated studies did not present data about particle size distribution. Multiple nanoemulsions (MNE) consisting of particle size ranging from 20 to 200 nm may have visible benefits to the protection of bioactive compounds and to improve product stability during food production and storage processes in comparison to conventional multiple emulsions (Qian et al. 2012; Rao et al. 2013). In comparison to conventional multiple emulsions, the smallest particle size of MNEs can increase the interfacial area of emulsions and improve the bioavailability of encapsulated hydrophilic and/or hydrophobic bioactive compounds (Sessa et al. 2014; Hwang et al. 2017). Zeta potential is also an indication of colloidal system stability, since it reflects nanoparticles' surface charge, which can be influenced by particle composition, dispersing medium, pH, and ionic strength in the solution. Nanoparticles presenting zeta potential values close to ± 30 mV often have good stability (Jeevanandam et al. 2018). Studies did not seem to be concerned with the purpose of the developed formulation, since not all of them have evaluated physical-chemical parameters at room temperature, or the temperature the formulation will potentially be used at when applied - these conditions can change the particle load if it is exposed to a new environment, under varying temperature or pH conditions (Vijeth, Heggannavar, and Kariduraganavar 2019).

Based on food quality and safety viewpoint, it is essential controlling oil oxidation in food products to prevent food deterioration and protect human health. Therefore, PV determination is one of the most important quality control measures in food systems, mainly in edible oils. This indicator measures the concentration of unstable hydroperoxides, which can easily decompose to form low molecular weight oxygenated constituents such as alcohols, aldehydes, free fatty acids, ketones, and ultimately lead to rancid flavor (Mohammadi et al. 2016). Despite the similarity of oxidation tests performed in the analyzed studies, the mining analysis did not confirm whether the oxidation products are important descriptors capable of defining the results. Incorporate omega-3 oil rich in foods is a good strategy for human and animal health, however the unsaturated fatty acids oxidation process encompass autoxidation kinetics and heterogeneous catalysis may occur in bulk oil depending on the environment and reactional conditions (Ghnimi, Budilarto, and Kamal-Eldin 2017). The oxidation kinetic of lipid oxidation involves the complex reaction steps characteristic in classical free radical chain: initiation, propagation, and termination (Cadenas and Sies 1998). These steps are in the induction period, or lag phase, which its duration may reflect the antioxidant status or true protection evoked by nanoparticle. Following, the lipid oxidation enters to the exponential phase, when hydroperoxides (primary products) may form micellar structures and are decomposed to free radicals generating secondary products (some of them are volatiles) (Brimberg and Kamal-Eldin 2003; Melgosa et al. 2019). One strategy when measuring lipid oxidation on unsaturated fatty acids in nanoformulations is keep up with oxidation kinetic along time, at controlled temperature, time, considering the presence of oxygen and/or pro-oxidants, water, metals, and eventually antioxidants. Probably herein, some studies did not observed protection induced by nanotechnology on lipid oxidation due to the methodology of nanoformulations production and/or the period of fatty acid oxidation evaluated.

The use of proteins in formulations was an interesting datum observed in the analyses, since they enabled active compound absorption and low toxicity at the end of product degradation, as well as improved the nutritional and functional value of the formulation. Milk proteins have important functional chemical properties such as the ability to bind to hydrophobic molecules, to interact with other biopolymers, to stabilize emulsions, to form gels and to delay oxidation (Livney 2010; Elzoghby, Abo El-Fotoh, and Elgindy 2011). Several studies produced whey protein nanoemulsion (with or without combination with carbohydrates or glycoproteins) and investigated how whey protein isolate or its proteins concentration can affect the physicochemical properties and oxidative stability of oil in nanoemulsions. Here, whey protein was used as emulsifiers to load fish oil in the nanoemulsion, demonstrating lower lipid oxidation, PV value and volatile compounds than free fish oil (García-Moreno et al. 2016; Nejadmansouri et al. 2016b). In similar way, β-lactoglobulin (Zimet and Livney 2009; Ha, Lee, and Lee 2018) casein (Zimet, Rosenberg, and Livney 2011) and lactoferrin (Nunes et al. 2020) provide colloidal stability at 4 or 25 °C, maintaining the particle size during several days.

Chemical compounds known as antioxidants are used to inhibit or delay lipid oxidation. Butylhydroxyanisole (BHA), Butylhydroxytoluene (BHT), Propyl Gallate (PG), and TBHQ are the synthetic antioxidants most often used in the food industry (Freire, Mancini-Filho, and Ferreira 2013). Although synthetic antioxidants have been successfully used to prevent the oxidation of edible oils for more than 50 years, they are seen as possible health risks (Morsy et al. 2019). Based on DT2, it is possible assuming that antioxidant addition to the formulation is not enough to protect the oil, unlike encapsulation efficiency higher than 88% in particles smaller than 300 nm. Morsy et al. (2019) have compared the antioxidant activity of spirulina nanoparticles (Sp-NPs) to the whole spirulina cell (Sp-WC), α-tocopherol and butylated hydroxytoluene (BHT). They also evaluated the effects of Sp-NPs on olive oil stability and showed that different Sp-NPs concentrations presented effective antioxidant action, which was significantly lower in primary and secondary oxidation products than in the control. However, formulations must be carefully developed when it comes to encapsulation efficiency and particle size, and such statement confirms the result presented in DT1. Based on data-mining results, the parameters pointed as more important should be those used in studies evaluating stability and biological efficiency. Additionally, some parameters (attributes) were excluded because was evaluated at extreme temperature ($\approx$ 4 or $\geq$40 °C) or was not evaluated for all studies (e.g. PDI).

The present study suggested the need of developing a basic protocol focused on confirming the effectiveness of a given formulation and its safety, according to international recommendations (Mansfield, Hartshorn, and Atkinson 2017), mainly when formulation's goal is the potential use of nanoparticles in food. There is strong need of investigating other protocols in order to set a definitive one, so that all studies can evaluate the physical-chemical characteristics and oxidation products of the active compound, as well as the physical-chemical characteristics of nanoformulations, namely: particle size, zeta potential, and polydispersity index at standard evaluation temperature, encapsulation efficiency (%), oxidation temperature, standard analysis time, types of test focused on evaluating PV oxidation, p-anisidine value, and TBARS. It would help reducing the risk of bias and developing protocols capable of mitigating the oxidation of unsaturated fatty acids in order to increase the development of food enriched with omega-3 and the intake of these fatty acids by the population.

5. Conclusion

So far, nanotechnology seems to be the best alternative to protect unsaturated fatty acids from oxidizing, the encapsulation efficiency, particle, and type of particles are important factors used to evaluate when oxidation is measured. However, it was not possible identifying the most efficient among the different methodologies used. Nevertheless, that nanoformulations should follow international protocol guidelines in order to present more standardized and, consequently, efficient particles to protect lipid oxidation.

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