Nanodelivery Systems and Constituents Derived from Novel Foods

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Novel Food is a new category of food, regulated by the European Union Directive No. 2015/2283. This latter norm defines a food as “Novel” if it was not used “for human consumption to a significant degree within the Union before the date of entry into force of that regulation, namely 15 May 1997”. Due to their natural source, Novel Food can represent another new and not fully exploited reservoir of nutraceuticals. Indeed, Novel Food can also be considered an important source of raw matter to produce a nano-drug delivery system. The application of Novel Foods as new nanoceutical materials or bioactive compounds embedded into nanocarriers is a new research field, as these sources have been employed only in recent decades.

novel food health compounds natural polymers nanoparticles nanocarriers

1. Novel Food Materials for Nanoparticle Production

Polymeric Nanoparticles

Nanoparticle-mediated smart delivery systems (np-DS) can exhibit favorable multifunctional characteristics for the delivery of nutrients or bioactive molecules for successful targeting. In this scenario, the np-DS application is evolving from traditional raw food products to advanced technologies in novel food engineering, which ensure purity and functionality.

Polymeric particles (PNp), intended as nano- and microparticles, are an important class of drug delivery system for the suitable delivery of bioactive compounds. PNp are defined as particles of diameter <1 µm composed of either biodegradable or non-biodegradable biopolymers that have been recently reviewed by M. Elmowafy et al. [1]. The most recent source of polymers for PNp synthesis are Novel Foods, as summarized in **Table 1**.

Table 1. Materials listed in the Novel Food catalog and used for producing nanoparticles.

Material(s) from Novel Foods	Type of Carrier	References
Astragalus membranaceus root extract	Polysaccharide nanoparticles	[2][3]
Cellobiose	Cryoprotectant for liposomes	[4]

Material(s) from Novel Foods	Type of Carrier	References
Chia seed oil from *Salvia hispanica* L.	Liposomes and nanoemulsions	[5]
Chitosan extracted from fungi (*Aspergillus niger*; *Agaricus bisporus*)	Chitosan nanoparticles	[2][6][7]
Chondroitin sulphate (synthetic)	Polysaccharide nanoparticles	[8][9][10]
Coagulated potato proteins	Protein-based nanoparticles	[11][12]
Dextran from *Leuconostoc mesenteroides*	Polysaccharide nanoparticles	Reviewed by [13]
Digitaria exilis	Polysaccharide nanoparticles	[14]
Eggshell membrane protein hydrolysate	Protein-based nanoparticles	[15][16][17]
Fucoidan extracted from the seaweed *Fucus vesiculosus* and *Undaria pinnatifida*	Polysaccharide nanoparticles	[18][19][20]
Guar gum	Polysaccharide nanoparticles	[21]
Lucerne leaf extract from Medicago sativa	Protein-based nanoparticles	[22]
Mung bean seed proteins from *Vigna radiata*	Protein-based nanoparticles	[23][24]
Panax notoginseng root extract	Polysaccharide nanoparticles	[25]
Phytoglycogen	Polysaccharide nanoparticles Polyelectrolyte complex	[26][27][28][29][30] [31]
Phytosterols	Solid lipid nanoparticles Liposomes	[32][33]
Phospholipids from egg yolk	Liposomes	[34][35][36]
Phosphatidylserine from soya and fish phospholipids	Liposomes	[37][38]
Rapeseed protein from *Brassica napus* L. and *Brassica rapa* L.	Protein-based nanoparticles	[12][39]

Material(s) from Novel Foods	Type of Carrier	References
Sacha inchi seed oil from *Plukenetia volubilis*	Nanoemulsions	[40]
Schizochytrium sp. oil	Nanostructure lipid nanoparticles	[41]
Sugar cane fiber	Polysaccharide nanoparticles	[42]
Tenebrio molitor L.	Protein-based nanoparticles	[43]
Tetraselmis chuii microalgae	Extracellular vesicles	[44][45]
Trehalose	Cryoprotectant for liposomes	[4]
Yeast β-glucan	Polysaccharide nanoparticles	[46][47]

Lipid-Based Nanoparticles

Lipid-based nanoparticles are a class of nanocarriers composed of lipids with different characteristics depending on the purpose and the active ingredient to be transported. Among this class, the most used delivery systems are liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid nanoparticles (NLCs).

Liposomes are vesical nanoparticles able to load both hydrophilic and lipophilic compounds. Their spherical 3D structure is composed of an internal aqueous core surrounded by phospholipid bilayers usually stabilized by cholesterol. The use of phytosterols in the place of cholesterol for stabilizing liposome membranes is widely investigated to avoid its negative effects, such as the increased risk of cardiovascular disease. Phytosterols are naturally occurring lipids extracted from natural sources (such as rice, vegetable oils, and soybeans) included in the Novel Food list. They are expected to exhibit the same unique features of cholesterol due to their close chemical structure.

Extracellular Vesicles

Extracellular vesicles (EVs) are lipid membranes in a nanosized range that can be produced by different cell types. In order to promote the use of sustainable material, the natural metabolites of microalgae, such as nanoalgosomes, a type of EVs secreted with high yields by microalgae, isolated by a tangential flow filtration technique, have been proposed as a new delivery system. The marine chlorophyte *Tetraselmis chuii* and its metabolites are intended as Novel Food [45].

Nanoemulsion Systems

The emulsions are a mixture composed of two different phases that are normally immiscible. With the addition of surfactants or particular techniques, a delivery system can be produced. In particular, nanoemulsion is a colloidal

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suspension that contains oil and surfactants to obtain a stable formulation and is transparent in appearance with a droplet size less than 200 nm, which is usually obtained using a high-speed disperser.

Different types of oils can be used for the production of nanoemulsion systems. Concerning the Novel Food list, chia seeds contain the highest amount of α-linolenic acid (ALA), an essential fatty acid precursor of omega-3 and phospholipids. The use of ALA for the preparation of a nanoemulsion was investigated by Kuznetcova et al., who obtained a stable formulation of about 100 nm with a negative surface charge [5]. Moreover, sacha inchi oil was exploited by Echeverri et al. to prepare a nanoemulsion with good stability over time, unlike the coarse emulsion [40].

Protein-Based Nanoparticles

Proteins or peptides are bioactive molecules that are gaining importance in the drug delivery field. As a matter of fact, they are attractive alternatives to synthetic polymers. Protein nanoparticles can be obtained with chemical (emulsion or complex coacervation), physical (spray drying), or self-assembly methods [48]. The advantages of using these biomacromolecules in nanoparticle formulations rely on their high safety, biocompatibility, and biodegradability. Moreover, the amphiphilic properties make the protein highly water-soluble. Therefore, the production of protein nanoparticles does not require the employment of any toxic chemical or organic solvents.

Proteins can be extracted from animal or plant sources. Those extracted from plants are gaining interest for their low allergenicity and sustainability, and are being extracted from agri-food wastes in most cases [49].

Coagulated potato, rapeseed, and mung bean proteins are listed in the Novel Food Directive No. 2017/2470. These natural peptides facilitate the endosomal escape and the release of the active compound in the cytosol, and were thus proposed as excipients for formulating nanoparticles suitable for a magnitude of applications [39].

2. Compound Derived from Novel Foods Embedded into Nanocarriers

The European list of Novel Foods in Regulation No. 2017/2470 covers foods traditionally used in non-EU countries as nutritional or medical sources, new substances to be used in foods, food from new sources, as well as new ways and technologies for producing food.

Consequently, numerous Novel Foods listed in the Directive are well-known substances commonly employed in the food industry but obtained via a new industrial process, for which applicants requested authorization because it was more convenient or eco-friendly, such as the processes from agri-food wastes. The European Commission authorizes the use of a Novel Food at the moment in which its consumption is not nutritionally disadvantageous. As an example, the stilbene resveratrol extracted from Japanese knotweed (*Fallopia japonica*) has been largely used in food supplements before 1997. The *trans* isomer of resveratrol obtained from microbial sources or via synthetic processes is considered a Novel Food. Also, epigallocatechin-3-gallate can be found in the Novel Food list as a purified extract from green tea (*Camellia sinensis*) leaves, even though other green tea extracts have been used

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prior to 1997. Nanotechnology can be considered an important platform for favoring and increasing the beneficial effects of bioactive compounds.

Starting from resveratrol and epigallocatechin-3-gallate, their effects on health might be impaired by their low bioavailability or high instability in the physiological environment. The encapsulation of resveratrol and epigallocatechin-3-gallate in different nanocarriers was investigated in order to increase their beneficial activity, such as their antioxidant, antimicrobial, and anti-aging effects, as recently reviewed by Bohara et al. and Salehi et al., respectively [50][51].

The same beneficial activities were also reported for other phytochemicals belonging to phenolic acid, flavonoid, lignan, stilbene, alkaloid, and anthraquinone classes; however, the bioavailability of phytochemicals is quite low after oral intake. Indeed, these bioactive compounds are easily metabolized at the intestinal level by digestive enzymes and microbiota, and degraded because of the low-pH stomach environment [52]. From the Plantae kingdom, taxifolin extract from Dahurian Larch (*Larix gmelinii*) wood, *Magnolia officinalis* bark, Korean Angelica (*Angelica gigas*) roots, noni and bush mulberry (*Morinda citrifolia*), and blue honeysuckle (*Lonicera caerulea*) fruits were proposed as new sources of nutraceuticals in Europe by the Novel Food Directive No. 2017/2470. These plants were exploited for centuries in traditional medicine because of the beneficial properties of their phytochemicals (taxifolin, magnolol, pyranocoumarins, anthraquinones, and anthocyanins, respectively), and innovative delivery strategies were recently proposed to enhance their antioxidant, antimicrobial, and anti-cancer activities [53][54][55].

Another relevant class of plant-derived nutraceuticals is represented by phytosterols. As mentioned before, phytosterols display a similar chemical structure to cholesterol. This feature contributes to the lipid-lowering effects of phytosterols. On the other hand, the steroidal structure impairs their bioavailability and bioactivity. The same *Achilles* heel has been noticed for carotenoids and liposoluble vitamins together with a marked photo instability. The poor water solubility and chemical degradation have been easily counteracted by several nanodelivery strategies. The carotenoids lycopene and zeaxanthin are inserted in the food additive list (E160 and E161h) and have been authorized in food supplements for decades for their antioxidant properties. The European Commission allowed the employment of these nutraceuticals obtained via synthetic or microbial processes.

From the kingdom Animalia, eggshell membrane proteins, Antarctic krill (*Euphausia superba*) oil, and bovine lactoferrin are cited in the Novel Food list as new sources of foods. The eggshell membrane proteins display an important biological activity in addition to interesting delivery properties. Mucoadhesive polymeric nanoparticles were demonstrated to increase the local delivery of eggshell membrane proteins, emphasizing their antioxidant and anti-inflammatory properties and simultaneously preventing their intestinal degradation. Antarctic krill is rich in omega-3 fatty acids (docosahexaenoic and eicosapentaenoic acids) and the carotenoid astaxanthin. These nutraceuticals are active in reducing blood lipid and sugar levels, and their encapsulation in lipid-based nanocarriers demonstrated an ability to efficaciously protect them from light and thermal oxidation.

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3. Nanoceutical Application in the Food Sector: Safety Issues and Regulations

Nanocarriers loaded with bioactive compounds or produced using materials derived from foods for influencing human health or condition can find application in different fields, such as pharmaceutical, health, cosmetic, and food. In this latter case, nanoceuticals can be designed for fortifying foods or obtaining dietary supplements to increase the total nutrient profile of a diet. Besides the advantages and benefits, the employment of nanoparticles has raised concerns regarding the safety of their intake, which has not been fully elucidated. Even though a material is considered safe, its physicochemical properties at a nanoscale are completely different. The oral intake of nanoparticles might alter the normal functions of the gastrointestinal tract [56] and gut microbiota [57] or increase the risk of accumulation within tissues and cells depending on their dimensions, shape, and surface charge, as discussed in depth by other authors [58][59][60].

The first advantage of using Novel Foods as materials for obtaining ingredients for the production of nanoceuticals or bioactive compounds is related to the reuse of agri-food wastes. In March 2020, the European Commission adopted the "new circular economy action plan" within the "European green deal" for more sustainable growth. Thus, the recovery of compounds from waste (e.g., lycopene from tomato peel or eggshell membrane proteins) is fundamental for achieving the goal set out by the European Union. Another advantage can be represented by the employment of new sustainable sources in light of the dramatic foreseen scenario alerted by the Food and Agriculture Organization, as mentioned in the introduction. The exploitation of algae, microorganisms, or insects are a few examples [61].

EFSA has recently drafted two guides on the risk assessment of nanomaterials that outline (i) the technical requirements for establishing the presence of small particles and (ii) the scientific risk assessment and the necessary testing for evaluating the safety to protect consumers [62][63]. The regulatory safety assessment of nanoparticles in foods has been recently discussed in depth by Schoonjans and co-workers [64].

Briefly, the EFSA Scientific Committee has considered specific studies that provide the key information useful for hazard characterization, exposure assessment, and physico-chemical properties of nanomaterials. The first step for the risk assessment is the physico-chemical characterization of the material. In particular, particle size is the most important feature. As a matter of fact, the scientific literature underlined that particles up to 250 nm have a high chance of translocation from the gastrointestinal tract to the tissues. Thus, the Scientific Committee established that particles with a size equal to or larger than 500 nm with less than 10% of particles with a smaller size (number-based particles) are not engineered nanomaterials and can be approved with a conventional risk assessment. If these particles are composed of ingredients present in the lists of Novel Foods (Regulation (EC) No. 2015/2283), substances for the fortification of foods (Regulation (EC) No. 1925/2006), foods for specific groups (Regulation (EU) No. 609/2013), or food additives (Regulation (EC) No. 1333/2008), they are considered as safe and can be used without any risk assessments.

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According to EFSA guidelines, if the material displays nanomaterial features after physico-chemical characterization, the second step of the nano-specific risk assessment involves in vitro digestion by reviewing the existing information or generating new data, including genotoxicity and cell toxicity. Subsequently, if the material is persistent or there are indications of toxicity, step 3 comprises in vivo testing for determining pharmacokinetic profiles and the histopathology of gastrointestinal sites and organs [62][63].

4. Conclusions

Undoubtedly, nanoparticles naturally occur in food because numerous food and feed constituents consist of inherent proteins, carbohydrates, and fats, which span a range of sizes from large biopolymers (macromolecules) down to the nanoscale. The primary concern, however, revolves around whether synthetic nanoparticles and other nanomaterials may pose any potential risks. EFSA has recently produced guidelines, which can deeply help the development of robust, integrated, and acceptable testing methods; however, a harmonized and detailed approach is not yet available to assess their adequate safety profiles. Critical points are probably related to the biodegradation of the nanocarriers and their biocompatibility—mainly related to their nature (GRAS nanosystems) and their production—which should avoid the use of hazardous chemical reagents and also create systems (nanovectors) mimicking natural exosomes, which cannot be recognized by our body as harmful vectors that induce immunological reactions or other adverse events.

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