Nanonutraceuticals

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Over the last few years, the application of nanotechnology to nutraceuticals has been rapidly growing due to its ability to enhance the bioavailability of the loaded active ingredients, resulting in improved therapeutic/nutraceutical outcomes. The focus of this work is nanoprebiotics and nanoprobiotics, terms which stand for the loading of a set of compounds (e.g., prebiotics, probiotics, and synbiotics) in nanoparticles that work as absorption enhancers in the gastrointestinal tract. In this manuscript, the main features of prebiotics and probiotics are highlighted, together with the discussion of emerging applications of nanotechnologies in their formulation. Current research strategies are also discussed, in particular the promising use of nanofibers for the delivery of probiotics. Synbiotic-based nanoparticles represent an innovative trend within this area of interest. As only few experimental studies on nanoprebiotics and nanoprobiotics are available in the scientific literature, research on this prominent field is needed, covering effectiveness, bioavailability, and safety aspects.

Keywords: nutraceuticals ; health ; nanotechnology ; probiotics ; prebiotics ; synbiotics ; safety ; supplements ; nanonutraceuticals

1. Nutraceuticals

Beside the emerging need for natural origin alternatives to pharmaceuticals, the interest is focusing more and more on possible applications of food derived products that can be used as tools to prevent (and in some cases also cure) or delay the onset of a health issue. Nutraceuticals, are a novel toolbox not completely explored so far for its full potential in medicine. Nutraceuticals, a portmanteau of the words ‘nutrition’ and ‘pharmaceutical’, have been defined as “the phytocomplex if they derive from a food of vegetal origin, and as the pool of the secondary metabolites if they derive from a food of animal origin, concentrated and administered in the more suitable pharmaceutical form”. Examples of substances that have nutritional and nutraceutical interest are antioxidants, vitamins, polyunsaturated fatty acids, dietary fibres, prebiotics, and probiotics. Nutraceuticals reside nowadays in a gray area between pharmaceuticals and food; their safety and efficacy in health conditions and safety must be substantiated by clinical data; moreover, there is lack of a shared regulatory system for them.

2. From Nanopharmaceuticals to Nanonutraceuticals

2.1. Characteristics of Nanoparticles and General Classification

Within the different definitions of nanomaterials, these can be described as the products of nanotechnology, characterized by at least one dimension within the size range below 100 nanometers. Due to their remarkable properties and versatility, nanomaterials are being exploited in different fields, e.g., agriculture, health, electronics, cosmetics, representing a great challenge, in particular, in food science and technology, environment, and human health. The progress in pharmaceutical nanotechnology has led to a new class of products, the so-called nanopharmaceuticals, defined as pharmaceutical drug molecules formulated in nanomaterials . Different types of nanoformulations are being exploited for the treatment of neurodegenerative diseases, cancer, infectious diseases, and others. Besides, nanomaterials are also succeeding in offering new advanced tools for imaging and diagnosis which, combined with therapy, have been proposed as nanotheranostics. These formulations are also being tailored for personalized medicine.

Nanoparticles can be produced from natural (e.g., proteins, polysaccharides, lipids) and from synthetic (e.g., polymers) sources. Ideally, materials should be biocompatible, biodegradable, and biotolerable, namely the way by which designed materials are tolerated by the body, and of generally recognized as safe (GRAS) status, in order to be used in pharmaceutical and nutraceutical products. Among the available options, and if the nanoparticles are intended for oral administration (as happens with nanonutraceuticals), lipid nanoparticles are of special interest. Lipids are known for their role as absorption enhancers in the gut, which contribute to improving the oral bioavailability of several drugs and biomolecules. Besides this, the loading of poorly soluble drugs into lipid nanoparticles overcome the limitations

encountered in their formulation into final products. Lipid nanoparticles can be produced from well-known lipids existing both in the human body and in foodstuff (e.g., fatty acids, triglycerides, phospholipids, waxes, cholesterol) thereby enhancing their biodegradability, and biocompatibility profiles.

Among polysaccharides, chitosan, and alginate, have been frequently used in the production of nanoparticles for oral delivery. Being a mucoadhesive polysaccharide, chitosan is able to increase cellular permeability and improves the bioavailability of orally administered drugs and proteins. Moreover, the molecule itself exhibits antimicrobial properties, and has a low toxicity. The molecule has chemical functional groups that can be modified for site specific targeting. Alginate is also a versatile mucoadhesive natural polymer with very low toxicity *in vivo*. Alginate nanoparticles have a hydrophilic character with improved loading capacity for hydrophilic drugs, being able to modify their release profile. Alginate nanoparticles are reported as adjuvants in vaccinations and can be produced conjugated with dextran to modify the release profile of proteins and other macromolecules intended for oral administration.

Nanopharmaceuticals and nanonutraceuticals are obtained, respectively, when a pharmaceutical or a nutraceutical is formulated in nanoparticles. The rationale for their development is mainly addressed to improve the physicochemical properties (e.g., solubility) and pharmacokinetic parameters (t_{max}, C_{max}, area under the plasma drug concentration–time curve (AUC)), with the ultimate aim to reduce the dose required to observe the therapeutic/nutraceutical outcome and thus the possible risk of toxicity. Parameters, such as efficiency, quality, and safety should therefore be considered. Nevertheless, regulatory issues related to nanopharmaceuticals still need further developments.

2.2. Emerging Area of Applications

Nanopharmaceuticals and the great change of the pharmaceutical industry have a great impact also on nutraceuticals. Recent researches give the patented and approval scenario of nanopharmaceuticals with regards to biomedical application, manufacturing procedure, and safety aspects.

Some Authors highlighted how nanotherapeutics and nanopharmaceuticals could lead to a more precise individual diagnosis, improve targeted therapies, reduce side effects, and enhance therapeutic monitoring. The same review also underlines that the field of nanomedicine is at its early stage and that further efforts to translate their potential into clinical trials and medical practice are still needed.

A growing number of studies are addressed towards the application of nanotechnologies to nutraceuticals in order to obtain improved bioavailability, delivery, and effect. This leads to the development of an emerging area of innovative products: the nanonutraceuticals.

Nanotechnology can be used to improve absorption, bioavailability, stability, and controlled release of nutrients and nutraceuticals, thereby increasing health benefits; some examples of potential advantages of applications of nanotechnology on the nutraceuticals are (i) efficient encapsulation; (ii) smart delivery and release from a nanoformulation. For example, research on encapsulation of nutraceuticals into biodegradable, environmentally friendly nanocarriers, is ongoing to increase their absorption and their therapeutic potential.

The nanonutraceutical formulations represent a valuable and promising strategy to maintain nutraceutical health beneficial properties at a nano level, to guarantee safety and efficacy, when used in managing health conditions, particularly for patients who are not eligible for a conventional pharmacological therapy. Follow-up studies, as reported by recent works, and communication strategies, are needed for both the nanopharmaceuticals and nanonutraceuticals, in view of expanding the area of interest to different health conditions. For instance, it has been described the current status of the various delivery systems that are used for the delivery of hydrophilic bioactive compounds and discuss future prospects to be explored for the delivery of hydrophilic bioactive compounds, e.g., niosomes, bilosomes, cubosomes.