Review Article

Emerging Applications of Nanotechnology in Phytonutraceuticals: A Review of Characterization and Product Development

ABSTRACT

Nanotechnology refers to the branch of science and engineering devoted to designing, producing, and using structures, devices, and systems by manipulating atoms and molecules at nano-scale, having one or more dimensions of the order of 100 nanometres (100 millionth of a millimetre) or less Nanotechnologies exhibit significant potential in the field of medicine, including in imaging techniques and diagnostic tools, drug delivery systems, tissue-engineered constructs, implants and pharmaceutical therapeutics. Nano-formulations are widely used for phyto-nutraceuticals and drug delivery systems. These substances are generally having low solubility, leading to their poor absorption and bioavailability in the human body. In this regard, one of the most important applications of nanotechnology in food sector has been the formulation of novel neutraceutical compounds with improved properties viz., enhanced solubility, stability, bioavailability and efficacy. This is achieved by encapsulation of neutraceutical by nanoparticles, which modifies their pharmacokinetics (PK) and biodistribution (BD). Nano-formulations widely used for the purpose are nanoliposomes, nanoemulsions, nanoparticles, nanofibresThe particles are characterized by scanning probe microscope (SPM), Ultraviolet-visible spectroscopy (UV-Vis spectrophotometer, SEM, TEM, Dynamic light scattering (DLS).

Key words: Bioavailibility, Characterization, Nanoformualtios, Nutraceutical delivery, Phytonutraceuticals.

Introduction

The term "nutraceutical" refers to a food substance, or a part of it, which possesses health benefits in terms of therapeutic or preventive effects Khorasani *et al*., 2018. Nutraceuticals include antioxidants, prebiotics, probiotics, herbal products, spices, polyunsaturated fatty acids, and many other compounds of natural and represent natural ways to achieve therapeutic goals Shinde *et al.*, 2014. In the last few years, there was an increase in nutraceuticals consumption among the consumers due to an increase in natural-derived compounds interest; to date, an increasing interest in the development of novel functional food is pushing towards the incorporation of nutraceuticals within food products. The changes in lifestyle that have occurred in recent years have led to an increase in some diseases, such as type-2 diabetes and cardiovascular diseases Gruss *et al*., 2019. At the same time, the awareness among consumers of the close correlation between these dangerous diseases and eating habits has increased. For this reason, consumers are increasingly attentive to the quality of the consumed food and increasingly interested in food that can also have beneficial effects on their health and prevent the onset of dangerous diseases Gonearese*et al.*, 2018. All these aspects prompted researchers to study the potential beneficial effect on human health of nutraceuticals and their mechanism of action; at the same time, the industry was stimulated to develop innovative products capable of attracting consumers’ interest.Nanotechnology, based on structures with sizes in the order of nanometers is a revolutionary technology that has allowed researchers to overcome numerous limitations related to the use of nutraceuticals following their encapsulation into these structures, such as their stability, low solubility, and poor bioavailability Ting *et al*., 2013. It is noteworthy that the bioavailability, that is the fraction of a taken compound which is absorbed and available for physiological functions, is a key aspect for nutraceutical compounds, because their effectiveness is strictly related to their bioavailability. Unfortunately, different endogenous and exogenous factors can compromise the bioavailability of nutraceuticals, such as the biochemical transformations they may undergo into the epithelial cells, their physicochemical features, the food storage, and so on Leonard *et al*., 2000. For this reason, many innovative strategies have been thought to exert their beneficial effects when introduced into the organism. Among them, different nano-formulations have been designed to enhance the beneficial effects of nutraceuticals. Food nanotechnology could revolutionize the scenario of the food industry and agriculture by offering numerous advantages not only in increased bioavailability, but also promoting a controlled-release and targeted delivery of encapsulated bioactive natural compounds, which led to an increase in their biological efficacy representing exciting opportunities for the nutritional supplement industries. In particular, in the design of nutraceutical delivery systems, it must be taken into account that the formulation must have adequate chemical-physical properties, sustainable production costs, and food-grade materials must be used Huang *et al*., 2010.

Nanotechnology has also major role in agriculture as is the backbone of most of the developing countries in which a major part of their income comes from agriculture sector and more than half of the population depends on it for their livelihood. The current global population is nearly 6 billion with 50% living in Asia. A large proportion of those livings in developing countries face daily food shortages as a result of environmental impacts or political instability, while in the developed world there is a food surplus. For developing countries, the drive is to develop drought and pest resistant crops which also maximize yield. In developed countries, the food industry is driven by consumer demand which is currently for fresher and healthier foodstuffs (Anonymous, 2009)’ Nanotechnology helps agricultural sciences and reduce environmental pollution by production of pesticides and chemical fertilizers by using the nano particles and nanocapsules with the ability to control or delayed delivery, absorption and more effective and environmentally friendly and production of nano-crystals to increase the efficiency of pesticides for application of pesticides with lower dose. Nano means one-billionth, thus nanotechnology deals with materials measured in a billionth of a meter. A nanometer is 1/80,000 the diameter of a human hair or approximately ten hydrogen atoms wide. Nanotechnology is the science of very small things. But nanotechnology is not just involved with small things. Nanotechnology is a multi-disciplinary science. It includes knowledge from biology, chemistry, physics and other disciplines. Joseph and Morrison (2006) defined Nano technology as the manipulation or self-assembly of individual atoms, molecules or molecular clusters into structures to create materials devices with new or vastly different properties. Two principal factors cause the properties of nanomaterials to differ significantly from other materials increased relative surface area and quantum effects. Morphology-aspect ratio/size, hydrophobicity, solubility-release of toxic species, surface area/roughness, Surface species contaminations/adsorption, during synthesis/history, Reactive Oxygen Species (ROS) O_2 / H_2O, capacity to produce ROS, structure/composition, competitive binding sites with receptor and dispersion/ aggregation are the important properties of nanoparticles (Somasundaran *et al*., 2010)

Uniqueness in Nanotechnology:

Nanoparticles as the word suggest small size, owing to this small size nanoparticles have large surface area to volume ratio when compared with bulk material. This feature enables them to possess different physical, chemical and optical properties as they have small space to confine their electrons and produce quantum effects. Nanoparticles are highly reactive because of their large surface area they have more surface energy. So more the energy with any particle more unstable it will be to share its energy. The size of nanoparticles ranges from 1-100nm. Nanoparticles surface is coated with PEG (Polyethylene Glycol), it provides the function of adhesion, stabilization etc. Nanoparticles are surface charged (positive as well as negative) and they have also functional groups on surface such as –SH, -COOH, -NH_2. Their surface is decorated with lipids and polymer chains of different molecular weights to provide them stealth properties and conjugated with different targeting ligands such as aptamers, peptides, antibodies to enhance the specific recognition of target cells. Nanoparticles can be of different shapes like rod shaped, cuboidal, spherical, star shaped etc.

A **Synthesis of Nanoparticles**

There are two broad approaches for synthesis of nanoparticles:

Top-down approach: As the word suggests, it is breaking down of larger particles in small sized particles. Different methods adopted in this approach are chemical etching, Laser ablation, Mechanical milling, Sputtering, Electro-explosion.

Bottom-up approach: This is an alternate approach, which has the potential of creating less waste and hence more economical. Bottom-up approach refers to build-up of material from the bottom, atom by atom, molecule by molecule or cluster by cluster. Different methods adopted in bottom-up approach are chemical vapour deposition, sol-gel process, laser pyrolysis, spray pyrolysis, atomic/molecular condensation and Green synthesis. Green synthesis is the synthesis of nanoparticles from living organisms such as plant parts like fruits, flowers, seed, root, and from microorganisms such as fungi, bacteria, algae etc.

Nanotechnology to control plant diseases

About 20–40% of crops are lost due to plant pests and pathogens each year worldwide (Flood, 2010). In modern farming practices, pest management relies heavily on the application of pesticides, such as insecticides, fungicides, and herbicides. The development of cost-efficient, high-performing pesticides that are less harmful to the environment is crucial. The new concepts such as nanotechnology can offer advantages to pesticides, like reducing toxicity, improving the shelf-life, and increasing the solubility of poorly water-soluble pesticides, all of which could have positive environmental impacts. The significance of agricultural nanotechnology, mainly for controlling diseases and safety has been reported elsewhere. Nano-based conventional herbicides and pesticides assist in the slow and continued supply of nutrients and agricultural chemicals in a controlled amount to the plants (Duhan *et al*., 2017). Nanoparticles may have also a key role in the control of insect pests and host pathogens. Type of polysaccharides such as chitosan, alginates, starch, and polyesters have been considered for the synthesis of nano-insecticide. In general, the use of nanoparticles to protect plants can occur via two different mechanisms: (a) nanoparticles themselves providing crop protection, or (b) nanoparticles as carriers for existing pesticides and can be applied by spray (Worrall *et al.*, 2018). However, the suse of nanomaterials in plant protection and production of food is under-explored (Prasad *et al.*, 2017).

B) **Nanotechnology to improve quality of soil and fertilizer distribution**

Nanotechnology for the management of crops is used as an essential technology for enhancing crop productivity. Nanomaterials and nanostructures, such as carbon nanotubes, nanofibers, and quantum dots are now exploited in agriculture research as biosensors for evaluating the quality of soil and fertilizer distribution. The purpose of nanoparticles is to minimize the spread of chemicals amount, reduce the nutrient loss during fertilization, and increase the quality and yield with proper nutrient (Sangeetha *et al.*, 2021). The development and use of vermiculite, nanoclay, and zeolite could improve fertilizer efficacy and crop production for ecological agriculture in coarse-textured. Amending sandy loam soils with inorganic amendments reduce NH_4–N passage and increasing the yield of N fertilizer in ecological agriculture systems (Mazloomi and Jalali, 2019). Nanoclay is systematized into a number of modules such as montmorillonite, bentonite, kaolinite, hectorite, and halloysite on the basis of chemical composition and nanoparticle morphology.

Most of the productivity of agricultural practices is heavily dependent on fertilizer use. Studies show that crop production is linearly determined by exhaustive application of fertilizers to increase soil fertility (Rehmanullah*et al.*, 2020). The use of nano fertilizer is crucial to enhance crop production. Nano fertilizer is a material with nanometer-size which improves the delivery to plants and managed the slow release of nutrients into the soil gradually in a highly controlled way, hence stopping eutrophication and contamination of water (Davari *et al.*, 2017). Nanotechnology makes the exploitation of nanostructured or nanomaterials for fertilizer transport or limited release routes to construct smooth fertilizer as new opportunities to modify nutrient usage efficacy and reduce charges for environmental safety (Hai*et al.*, 2011). Nano-fertilizer could improve nutrient efficiency through encapsulation within nanoparticles which is conducted by three methods. (a) Nutrient encapsulation within nanoporous structures, (b) Coating of thin polymeric film, or (c) Delivery in the form of particle or suspensions with nanoscale sizes (Davari *et al.*, 2017). Nanoscale fertilizers could lead to the more effective delivery of nutrients as their small size may allow them access to plant surfaces and transport channels (Mastronardi *et al.*, 2015). Nano-fertilizer extracted and prepared from banana peels were used in the growth of tomatoes, peppers, or flowers. Nano fertilizers were used for the growth and improvement of different crops, for instance, nanoparticles of ZnO for chickpea, silicon dioxide and iron slag powder for maize, colloidal silica and NPK for tomato, TiO_2 for spinach, gold and sulfur fertilizers were used for the growth of grapes. Fertilizer usage with nanoscale transporters may be subjected in a way so that they anchor the roots of the plant with the surrounding soil contents and organic material hence decreasing chemical loss and lessening environmental issues (Dasgupta *et al.*, 2015). Nanoscale fertilizers can decrease the toxicity of soil and hence the potential undesirable impacts accompanied by high dosage are reduced (Davari *et al.*, 2017). Such nano fertilizers slow down the nutrients release and extend the duration of fertilizer impact. TiO_2 nanoparticles have shown a major effect on the growth of maize crop; moreover, SiO2 plus TiO2 nanoparticles elevated the action of nitrate and increased plant absorption potential, by controlled use of water and fertilizer with the efficient outcome.

C) Nano-sensors in food and agriculture

The use of biosensors combined with improved technologies in the field of molecular biology, nanomaterials, and microfluidics have enormous applications for the productivity of crops. These are also applied to monitor the activity of microorganisms in the soil and able to predict the likely incidence of soil infections. The basic principle related to soil examination with the biosensor is to find out the comparative action of positive and negative microorganisms in soil depends upon variation on oxygen usage during their breathing. They also offer many opportunities in sensing contaminants and their hindrance, via using new properties related to nanomaterials (Baruah and Dutta, 2009). Biosensors for detection of the nitrate concentration in plants as well as detection for markers to identify infected plants are reported for methyl salicylate and azelaic acid (Griesche and Baeumner, 2020). The use of biosensors for monitoring of Penicillium digitatum infection in citrus fruit was reported (Chalupowicz*et al*., 2020). Smart delivery systems and nanosensors are applied to help in efficient natural agricultural means like nutrients, water, and chemicals using precision farming for example satellite monitoring, geographic systems, and distant detecting tools that remotely can detect pests on crops or indication of strain like drought (Sekhon, 2014). The application of independent sensors connected to GPS monitoring in real-time is thought to play a key role in nanotechnology-assisted tools (Davari *et al*., 2017). Arrangement of nanosensors can be carried out throughout the field for monitoring crop growth and soil parameters. Nanosensors are getting attention and playing a big role in the development of the food industry for its efficient responding tools to detect gases, microbes, or toxic substances in packed foods. Nanobiosensors have been testified for detecting pathogens in processing plants or alerting clients, protocols, and providers on the safety position of food (Cheng *et al*., 2006). It has been also employed for the existence of impurities, mycotoxins, and microbes in food (Bratovcic*et al*., 2015). Allergens have also been detected via biosensors tools with the assistance of nanoparticles and the report is about to commercialize (Warriner *et al*., 2014). These tools can also detect the history of time, expiration date, and temperature.

1). Applications of nanotechnology in Agriculture

Agriculture is practiced for food production via the cultivation of varied crops and raising of livestock. It is considered the backbone economy for most developing countries as a vital role in progress and development. The rising population in the world results in high demand for more food supply, and scientists and engineers are now practicing new methods to increase agricultural production (Baruah and Dutta, 2009). For the last several years, agriculture nanotechnology has focused on research and application to resolve agriculture and environmental issues sustainability, crop improvement, and enhanced productivity. Agricultural nanotechnology seems to be highly interesting for developing countries, regarding the decrease in hunger, underfeeding, and mortality rate in children. As a potential device, nanotechnology can be applied to renovate agricultural divisions; it helps in learning the biochemical pathways of crops via modifying the conservative methods for evaluating environmental issues and its sapplication to production improvements (Prasad *et al.*, 2017). Comparisons of nanotechnology with environmentally friendly technologies and agricultural biotechnology show an opportunity for enhanced and quicker influence upon all constituents of the agricultural-value linkage for synchronized public benefits, legal, moral, and environmental effects (Sastry *et al.*, 2011). The prospective use of nanoscale agrochemicals such as nanofertilizers, nanopesticides, nanosensors, and nanoformulations in agriculture has transformed traditional agro-practices, making them more sustainable and efficient. Multiple applications of nanotechnology exist in agriculture including wastewater treatment, reducing the quality of polluted soil, enhance the productivity of crops via security in terms of sensors to detect pathogens (Singh *et al.*, 202). For instance, nanobiosensors is the wide ranging nanotools, scaffold the growth of high-tech agricultural farms and also stand proof for the practical and proposed applications of the nanotools in terms of agricultural inputs control and their management precision. The application of nanopore bearing zeolite for slow discharge and improved efficacy of enrichers, nanosensors for measuring soil quality and smooth supply mechanisms for herbicides are among positive impact of nanotechnology in agriculture (Chinnamuthu and Boopathi, 2009). Several nanoparticles used for monitoring plant diseases are nano-forms of carbon, silica, silver, and alumino-silicates. The use of nanomaterials for agriculture is proposed to reduce spraying chemicals via the smooth supply of energetic compounds. It can minimize nutrient wastage during applying fertilizer and promote the harvests by enhancing the water and ingredient management (Gogos *et al.*, 2012).

2) Applications of nanotechnology in phyto-nutraceutical

Nutritional therapy and phyto-therapy have emerged as new concepts of health aid in recent years. Strong recommendations for consumption of nutraceuticals from plant origin have become progressively popular to improve health, and to prevent and treat diseases. Nutraceuticals are "naturally derived bioactive compounds that are found in foods, dietary supplements and herbal products, and have health promoting, disease preventing and medicinal properties." Plant derived Nutraceuticals/functional foods have received considerable attention because of their presumed safety and potential nutritional and therapeutic effects. Some popular phyto-nutraceuticals include glucosamine from ginseng, Omega-3 fatty acids from linseed, Epigallocatechin gallate from green tea, lycopene form tomato etc. Some important phytonutraceuticals with their properties are Allicin from Allium sativum: It is a powerful antifungal antibacterial. It has been shown to be an antioxidant and has been used to treat arteriosclerosis and serum cholesterol. Betaine (Trimethyl Glycine) from green leafy vegetables and germinated grain it reduces toxic buildup of homocysteine (Pulliainen *et al.*, 2010.) Bromelain from Ananas sp. it is pineapple protease enzyme used to prevent heart disease, reduce the effects of aging, improve the immune system, and to reduce arthritis and inflammation. Camphor from Cinnamomum camphora used as an inhalant to treat cold and flu. (Chen *et al.*,2002). Capsaicin or trans-8-methylN-vanillyl-5 nonenamide from Capsicum annum used for pain relief topically and as a digestive aid when taken internally. It is also seen as a possible antioxidant for the body. It can pose a risk of allergic reactions and the severe damage to the eyes or skin if used in higher doses. Ellagic Acid from strawberries and raspberries this phytochemical fights cancer in humans Vattem and Shetty, 2005. Ricinoleic acid from Castor oil or Ricinus communis. contains ricinoleic acid the active ingredient. Castor oil is used both externally (multiple skin problems) and internally for constipation, upper respiratory problems, and liver Okui, 1963. paday Curcumin from Curcuma longa the colorant in turmeric a fraction of which has been shown by studies done at the University of California in Los Angeles to clear brain plaque caused by Alzheimer's disease mishra Ram *et al.*, 2000. Isoquercitin from mangoes and from Rheum nobile (Enzyme Modified) increases blood flow for varicose veins, and possible use for arterial flow as well. Recent studies have shown possibilities in increased brain functions and it might be useful in the treatment of progressive Alzheimer's disease. Lutein and Lutein Esters from marigold extracted from marigold seeds, and also found in spinach, rosemary and kale, it is a carotenoid which shows healthful eye benefits. Resveratrol especially high in grape skin anti-inflammatory, inhibits COX-1 enzyme, blocks adhesion of blood cells to vessel walls shown to reduce skin and breast cancer Gehm *et al.*, (1997). Zeaxanthin a carotenoid used as an antioxidant. It is the coloring agent in marigolds and is extracted from them. It is used for eye health and some claim will retard the effect of 'aging eyesight' or Age-Related Macular Degeneration (AMD). But, the main challenge still in fully realizing the potential of nutra-ceuticals has been their poor bioavailability after consumption. These substances are generally having low solubility, leading to their poor absorption and bioavailability in the human body. In this regard, one of the most important applications of nanotechnology in food sector has been the formulation of novel nutraceutical compounds with improved properties viz. enhanced solubility, stability, bioavailability and efficacy. This is achieved by encapsulation of nutraceuticals by nanoparticles, which modifies their pharmacokinetics (PK) and biodistribution (BD). The choice of the correct vehicle of delivery for the active nutraceutical or pharmaceutical ingredients into the human body is very crucial for facilitating the direct contact of the ingredients with the target site of action in the body. As most of these are either poorly soluble or lipophilic compounds their delivery is significantly enhanced by altering the physicochemical properties like water solubility, partition coefficient, lipophilicity, crystallinity, etc. The poor solubility of the active ingredients poses multiple challenges to their full utilization: route of administration, transport in the physiological system and reaching the site of action. All these in turn ultimately lead to the poor bioavailability of the same in the organisms. Bioavailability is one of the most crucial and indispensable property of any dietary or pharmaceutical ingredient, which decides what proportion of the therapeutically active component reaches the systemic circulation in the host and is available at the target site for action. Many types of nutraceuticals are available today in the market with various proclaimed health benefits. One such prominent example among nutraceuticals are the phytochemicals including plant polyphenols (curcumin, resveratrol) carotenoids, (lycopene, βcarotene, lutein) etc. These are widely favoured by the researchers, food manufacturers and consumers alike, because of their multiple health benefits viz. blood pressure regulation, reducing the probability of having malignant diseases like cancer, promoting digestion, immunity and growth, regulating glucose and cholesterol levels and also reducing stress by acting as antioxidants. Nanotechnology is a latest and advanced field, wherein the unique physicochemical characteristics of nanoparticles are used to significantly alter the structure, texture and quality of phytoutaceuticals. Applications of nanotechnology in this sector has been the formulation of novel phyto nutraceutical compounds with improved properties viz. enhanced solubility, stability, bioavailability and efficacy. This is achieved by encapsulation of nutraceuticals by nanoparticles, which modifies their pharmacokinetics (PK) and bio-distribution (BD).

Types of Nanotechnology in Phytonutraceuticals

There are mainly four types of nanoparticles in nutraceuticals *viz;* nanoliposomes, nanoemulsions, nanoparticles. The nano-emulsion formulations of active ingredients can be used for developing biodegradable coating and packaging films to enhance the quality, functional properties. Nanoencapsulation technique provides the possibility to protect the chemical structure ofphyto nutraceuticals from environmental agents such as pH, light, temperature, radicals, or oxygen Cristianno*et al*., 2021 increases their bioavailability; allows specific delivery to target sites and allows a controlled release of the encapsulated compound Assadpur*et al.*, 2019. Concerning the ability of nanosystems to control the release of the delivered active compounds, it consists of a specific concentration/time release profile at the desirable site of action and it is the main challenge for nutraceuticals encapsulation. Therefore, an ideal delivery system should be able to release its content following specific stimuli such as pH, moisture, enzymes, and temperature, and, at the same time, to protect the nutraceutical from the same stimuli Mclementis*et al.*, 2010 Moreover, the encapsulation of nutraceutical compounds leads to an enhancement in their solubility, as, once the nutraceutical is loaded into the carrier, features are dependent on the physico-chemical characteristics of the vesicle rather than to the entrapped compound. Nanosystems also provide the possibility to co-deliver water- and lipid-soluble molecules, thus supporting their synergistic effect. They are also able to guarantee the physico-chemical stability and avoid undesirable changes in smell and taste that might result from the addition of nutraceuticals to food products. The materials used for the realization of the drug delivery system can be of various nature (lipid, polymeric, protein) as long as it has the Generally Recognized as Safe (GRAS) status Fox *et al*., 2014.

Nanoparticles: Nanoparticles (NPs; 1–100 nm in size) have a special place in nanoscience and nanotechnology, not only because of their particular properties resulting from their reduced dimensions, but also because they are promising building blocks for more complex nano structures tritional value, and shelf life of foods. Nanoparticles are widely used drug delivery systems and can be made of different material, for example, polymers (poly-D,L-lactide-co-glycolide, polylactic acid, poly-ε-caprolactone), proteins , and lipids Desfrancois*et al*., 2018. In particular, in order to be applied in food and nutraceutical fields, food-grade material for the fabrication of nanoparticles must be used . Among the food grade material zein, a maize protein , chitosan , and gelatin are widely used Feng *et al*., 2020. Due to their biodegradability, bioavailability, and the possibility of encapsulating hydrophobic compounds, soy proteins have attracted the researchers' attention to be used in the design of nanocarriers for the delivery of bioactives, nutraceuticals included Verma *et al*., 2018. Soy β-conglycinin (a storage globulin) was employed for the development of nanoparticles for the encapsulation of hydrophobic curcumin, a polyphenol with anti-oxidant and anti-inflammatory activities . A new method, based on disassembly and reassembly of β-conglycinin, which is the vicilin storage protein of soybeans, was performed using urea and without adding any organic solvent; the obtained nanoparticles, produced with this new technology, turn out to be more natural and are characterized by a good solubility and encapsulation efficiency (around 80%) greater than that obtained in previous works. The bioaccessibility of curcumin was found to be around 40% (while that of free curcumin was found to be around 20%). β-conglycinin nanostructures represent promising biocompatible delivery systems for hydrophobic compounds Liu *et al.*, 2019. Another field of application of nanoparticles for the delivery of nutraceuticals is the field of cancer, to improve the activity of drug therapies and to decrease their side effects. Recently, Cosco and collaborators proposed hyaluronan-coated PLGA (Poly Lactic-co-Glycolic Acid) nanoparticles in which sclareol, a diterpene obtained from Clary sage (Salvia sclarea Linn.) Dimas *et al*., 1999, was encapsulated to favor its administration in physiological media, thus improving its anticancer efficacy. Characterization studies showed that the realized nanoparticles had mean sizes of 100–150 nm showing a reduction in their diameter due to the addition of sclareol. The coating of nanosystems was performed to improve the anticancer efficacy of the delivered phytochemical, due to the interaction and internalization of the realized structures with HA+ cancer cells. In fact, it was concluded that the anticancer efficacy was properly related to the coating of nanoparticles, using hyaluronic acid (1.5 MDa), which promoted the interaction with the hyaluronan receptors expressed on breast cancer cell lines, MCF-7 and MDA-MB468. The amount of hyaluronic acid adsorbed on the surface of the nanosystems was detected through the carbazole assay showing that the coating efficiency did not increase over 1 mg of hyaluronic acid added to the formulation. Another nanosystem, comprising beta carotene-loaded zein nanoparticles, was developed by Jain and collaborators to study its potential use in breast cancer. The obtained system showed a greater anticancer activity, with respect to free beta-carotene both in vitro (MCF-7 cells) and in vivo (induced breast cancer in rats): this is probably due to the increased cellular intake of zein nanoparticles. It also is worth mentioning that the association between beta-carotene-loaded nanoparticles with free methotrexate, the most widely used anticancer drug, showed a double positive effect: a synergistic effect, obtaining a strong in vitro anticancer activity on MCF-7 (breast cancer cell line) cells and a reduction in methotrexate side effects on the liver and kidneys [59].Resveratrol is another nutraceutical, which showed greater anticancer efficacy against MCF-7 when encapsulated into nanoparticles. This polyphenolic compound shows different anti-oxidant, anti-inflammatory, and anticancer activities. Unfortunately, it is practically insoluble in water (~0.03 mg/mL at 25 °C), and to overcome this difficulty, the encapsulation into cyclodextrins was recently proposed in particular, it was evidenced that complexation produced a consistent improvement in the solubility of resveratrol in water and consequently a significant improvement in the anticancer activity of resveratrol on several cell lines Chen *et al*., 2019.

Liposomes

Nanoliposome technology presents exciting opportunities for food technologists in areas such as encapsulation and controlled release of food materials, as well as the enhanced bioavailability, stability, and shelf-life of sensitive ingredients. Liposomes are lipid-based vesicles and represent a versatile and biocompatible drug delivery system used for the encapsulation of both hydrophilic and hydrophobic drugs . Liposomes are employed for the delivery of actives with different pharmaceutical activities nutraceuticals included Subramani *et al*., 2020.The all trans-retinoic acid (ATRA) is a metabolite of vitamin A. It is a nutraceutical compound widely studied for its anticancer property It was encapsulated in liposomes, obtaining an entrapment efficiency of around 82% in order to protect it from degradation. In particular, Cristiano et al. demonstrated that the encapsulation of ATRA within liposomes allows it to protect the drug from photo-degradation phenomena that would compromise its pharmacological activity.

Nanoemulsions

Nanoemulsions have small droplet size and are kinetically stable colloidal systems. They have enhanced functional properties in comparison to conventional emulsions. The composition and structure of the nanoemulsions can be controlled for the encapsulation and effective delivery of bioactive lipophilic compounds. Nanoemulsions have potential application in the food industry for the delivery of phytonutraceuticals, coloring and flavoring agents, and antimicrobials. Nanoemulsions are formulations made of a water phase, an oily phase, and an emulsifier, and are characterized by a droplet size of around 100 nm Gupta *et al*., 2016. Oil-in-water and water-in-oil nanomulsions are used for the encapsulation and protection of active ingredients and represent a suitable delivery system for the encapsulation of nutraceuticals, improving the efficacy of hydrophobic and hydrophilic active molecules and food components Zhang *et al*., 2020. Nanoemulsions were shown to be promising drug delivery systems for nutraceuticals, tomato extract rich in lycopene and curcumin, two antioxidant agents, was encapsulated into this system. Chang and collaborators nanoemulsion formulation was prepared by using the ultra-high-pressure homogenization method for the encapsulation of the oil extracted from the pulp of sea buck-thorn. Liu and collaborators were able to improve the oral bioavailability of the nutraceutical astaxanthin, a carotenoid which possesses numerous health benefits Ambati *et al*., 2014. Three types of long chain triglycerides, varying according to the fatty acid composition, were used for the nanoemulsions preparation: corn oil, olive oil, and flaxseed oil.

3) Characterization of nano-materials used for phyto-nutraceutical purposes

Data about certain other physical parameters are needed for that e.g., the physical form, morphology, particle size distribution etc, which can be obtained through imaging techniques like scanning and transmission electron microscopy (SEM and TEM). Light scattering techniques e.g., Dynamic light scattering (DLS) can provide additional information about particle size distribution of NMs in liquid samples, like average size and even size distribution of NMs, both during the synthesis and in physiological processes like digestion. Stability, which is another very basic and important property of any of the active ingredients inside the body, like the various nutraceutical components, can be measured by laser Doppler micro-electrophoresis method over a period of time, as zeta potential.

4) Product development: Phytoutraceuticals

Nanocurcumin: Turmeric or Curcuma is a natural creation, whose therapeutic properties have been widely studied and an extensive variety of therapeutic effects on several diseases. Nano curcumin particles were prepared by Vibra-Cell Ultrasonic Liquid Processors device. The particles are characterized by scanning probe microscope (SPM) and Ultraviolet-visible spectroscopy (UVVis spectrophotometer). The results confirm that the prepared Nano curcumin has mean diameter 82 nm. The prepared Nano curcumin is exposed to plasma to enhance the properties of their Nano particle the result is improve the enhanced characterization.Sabah *et al.*, 2020

Allicin nanocapsules

They were prepared via ionotropic pre-gelation. The wall materials were alginate-chitosan biopolymers. Nanocapsules were characterized using Fourier transform infrared spectroscopy (FT-IR) and field emission scanning electron microscopy (FESEM). Ghadir *et al.*, 2016

Other products are

Table 1 : Alginate-chitosan biopolymers

Nanonutraceutical	Synthesis method	Characterization technique	References
Nano paramagnetic oleuropein	four stage co-precipitation	ft-ir, eds, sem	Barzegar *et al* ., 2019
Beta carotene loaded nanoparticles of zein	modified phase separation technique	xrd, uv-vis spectroscopy	Jain *et al.*, 2018
Nano formulation of trans retionic acid		sem, tem, uv-vis spectroscopy	Kasper *et al.*, 2021
Ellagic acid encapsulated chitosan NPs	Ion gelation method	SEM, UV-Vis Spectroscopy, Zeta sizer and zeta potential analysis, FT-IR analysis, EDX analysis, TGA Analysis	Hasheminejad*et al* ., 2019

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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