



Nanotechnology-based Delivery Systems for Enhanced Bioavailability of Antioxidant Compounds in Fruits and Vegetables

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Abstract

Recent increase in the onset of diseases is evidenced because of poor quality of foods and lifestyle. Food-borne natural bioactive compounds including polyphenols, sterols, short chain or polyunsaturated fatty acids, numerous minerals, terpenes, short active peptides, and numerous phytochemicals are known to effectively cure chronic, or metabolism-associated diseases like cancers, diabetes, and cardiovascular issues. Many of the nutrients showed lower bioavailability i.e., molecules are not easily absorbed to take part in certain physiological activities in the cell, may have chemically unstable structures under oxidoreductase cellular environments and unwanted flavors make a serious challenge for these bioactive compounds. Enhancing the bioavailability of natural antioxidants may improve the nutritional levels to increase the standard of life. Enhancing the bioavailability of natural bioactive compounds or antioxidants at targeted sites is made possible by utilizing nano-based delivery systems called nanotechnology. Furthermore, the addition of pharmacologically active nutrients may help reduce metabolic disorders. The current review article aimed to highlight the importance and classify the ever-increasing application of nanotechnology for enhancing the bioavailability of natural antioxidants by amalgamating them into food science and miniaturizing them for targeted delivery systems. Prominent features of various techniques for natural antioxidants bioavailability enhancement, stabilizing their structural organization and application in functional foods shall also be discussed. The discussion led us to conclude that food-grade



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nano formulations involving different fabrication methods, lipid-based preparations, naturally occurring nanoparticles (NPs) and biopolymers showed higher efficacy with no toxicity after incorporating into nano-delivery systems. The enhancement in nutrient bioavailability will improve overall health and could be a potential zone of future research.

Introduction

Nutraceuticals are the bioactive molecules or antioxidants abundantly present in all fruits and vegetables, that positively affect human health and wellbeing.¹ To enhance the nutritional value of foods that may help improve quality of life and possibly slow the aging process. Nanotechnology dominates in strengthening the quality of health by incorporating and enhancing the bioavailability of certain antioxidants or phytochemicals in fruits and vegetables.¹ However, problems such as poor solubility, chemical reactivity, and issues with taste and flavor profile remain challenging given the importance of antioxidants in human body. A considerable number of bioactive molecules showed lower bioavailability i.e., molecules have restricted absorption to take part in certain physiological activities in the cell,² may have chemically unstable structures under oxidoreductase cellular environments and unwanted flavors make a serious challenge for these bioactive compounds.^{3,4} Bioavailability is the capacity of any bioactive molecule readily available for proper assimilation and metabolized inside the body.^{3,5} Moreover, processing of foods significantly influences bioactivity of these phytochemicals, and hence requires certain biochemical alterations in order to enhance the bioactivity primarily by nanotechnological tools like encapsulation or complexing with nanoparticles (NPs).^{3,6,7} However, the application of nanotechnology to encapsulate nutraceuticals in nanoscale for delivery within the body has revealed the high potential and seems to be a favorable concept regarding these issues.⁶ These nanotechnology-based methods enhance the polyphenols bioavailability which later modulates the stimulation Nrf2 and different phase-II detoxification enzyme activities.⁸ Antioxidants along with the diverse class of natural phytochemicals have exceptional capability to reduce the risk of the onset of diseases like osteoporosis, tumors,

cardiovascular issues, diabetes and obesity, and joints issues.^{5,9} As metabolic-associated disease cases pile up in different communities across the world, there is an ever-increasing demand for superior quality foods with better bioavailability of natural bioactive antioxidants to cure these disorders.⁶ Herein, we highlighted and emphasized the role of a nanotechnology-based delivery system for antioxidants to enhance their bioavailability.

Bioavailability can be considered as the ability to characterize a compound that is required to give the minimum concentration in the blood. Some of these natural antioxidant compounds can either be only partially or poorly absorbed in the gastrointestinal tract meaning that most of the drugs are chucked out of the body and made ineffective at the cellular level.^{10,11} Thus, nanotechnology-based delivery systems can be considered a novel approach to improve the ability of these antioxidants to be delivered to cells as depicted in Figure 1. Nevertheless, the safety or toxicity aspect of in vivo applications of nanotechnology presents some of the great challenges that need to be overcome.¹² Some of the key side effects held with this technology include Overloading or unwanted loading and retention of NPs in the body and slow decomposition and clearance that may cause toxic effects.¹³ Hence, the utilization of food-grade biodegradable materials has the potential to be highly productive in dealing with these challenges. Nevertheless, the use of nanotechnology to enhance the bioavailability of antioxidants has been picked up in the recent past due to encouraging outcomes. In this discussion, consideration is made to fundamental nanotechnological instruments used in the improvement of antioxidants bioavailability. Bioavailability is essential as it defines which extent antioxidants can be available in the biological systems and contribute to their health for decreasing various pathologies.

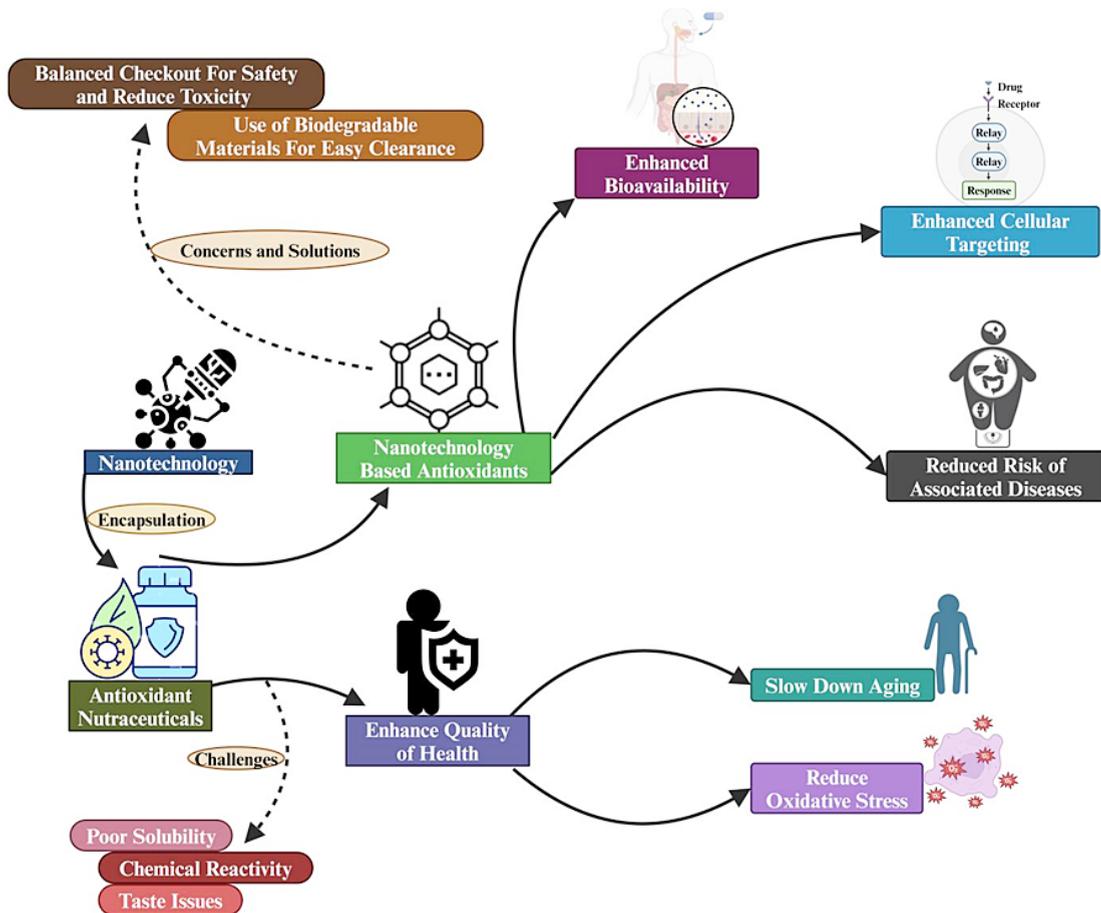


Fig. 1: Nanotechnology enhances the bioavailability and stability of nutraceuticals, improving health outcomes and addressing challenges like solubility and toxicity. This approach promotes disease prevention and better antioxidant delivery

Nanotechnological Advances in Bioavailability

Extracting materials down to the nanometer scale improves the surface area to volume ratio whereby the nano-carriers of antioxidants exhibit peculiar physicochemical properties. The technique of nano-encapsulation of antioxidants increases fold absorption by the GI and therefore bioavailability of small natural molecules. Nanotechnology is currently transforming almost every link in the food chain from production to processing, storage, and consumption.¹⁴ According to scientific literature, stabilizing antioxidant ingredient holders through nanotechnology can potentiate the gaining of heat stability, water solubility, and superb bioavailability of natural antioxidant absorption in the gut.¹⁵ The Bioavailability of natural antioxidants is really a serious issue that always needs enhancement to

target specific therapeutic interventions.¹⁶ Herein, we will be highlighting the basic types and the mode of action of the few most acceptable nano formulation technologies that may enhance the bioavailability of natural antioxidants (Figure 2).

Nanoencapsulation

The new exceptional use of functional foods has been due to the need to attend to consumer's health issues and the need for more natural, nutritive, and healthy foods.¹⁷ The compositions can be considered as other natural polymers, chitosan, peptide-chitosan, and β -lactoglobulin NPs and emulsion biopolymer complexes have been defined for functional foods. The techniques used are somewhat more complex and include the incorporation of BACs into liquid, solid or gaseous

structures, which maintain the enclosed properties of substances.^{18,19} In addition, nanoencapsulation is more advantageous and superior to many other nanotechnological strategies, primarily in terms of improved structural stability and release mechanism of BACs. Polysaccharides, peptides and lipids are the frequently used biomaterials in cases of food preparation and nutraceutical purposes.²⁰ The functional BACs commonly used in functional foods, food coatings, and pharmaceuticals include antioxidants, antimicrobials, vitamins, probiotics, prebiotics, and some other nutrients including minerals, enzymes, and Flavors.²¹ In addition, new nanotechnology methods for preparing organic foods are also used to create products that are organized based on a specific need of global interest for better-quality food with improved nutritional value.

Fabrication Technologies for NPs

Proteins, polysaccharides lipids surfactants, and minerals of food grade are used to synthesize NPs by using various methods. Though most of these NPs fabrication techniques have been proven to be effective at the laboratory scale, it may not be possible to apply them at an industrial scale, but at the same time, some of them have very high potential for scale-up.²² Several factors should be taken into consideration when choosing a nano-encapsulation technology: selection of the antioxidants, the particle size, any physiochemical coating of the core, physiochemical properties of the core, safety features, modes of break down and release, cost of processing, methods of delivering the drug, activity, stability suitable for commercial purposes and identification of the product.²³ Hence, among all the methods that establish appropriate relations between these parameters, the production method that optimizes them is most suitable because it minimizes a few issues pertaining to fabrication.

Lipid-based NPs

Lipid NPs have the ability to dissolve natural antioxidants or BACs bearing variable physicochemical properties for instance lipophilic molecules in order to enhance bioavailability and activity for controlled release at target sites while no any side effects have been seen.²⁴ Lipid formulation can be prepared through microfluidization and homogenization methods in a relatively easiest way. Some hydrophobic food BACs and preservatives require lipid-based encapsulations.²⁵ This is due to

the increased concentration of micelles that lipid NPs can provide to help transport BACs into the small gut, whereas, ongoing research suggests they will be absorbed efficiently due to their higher drug release activity.²⁶ Moreover, these lipid NPs can be classified into different categories such as nanoliposomes, and nanoemulsions (water in oil & oil in water emulsions) are noteworthy.²⁷

Nanoemulsions

Nanoemulsions are a heterogeneous mixture of oils and water, where one gets mingled into the other as tiny droplets and normally classified into two major forms i.e., H₂O in oil or oil in H₂O.¹⁹ Majority of the natural antioxidants or BACs have structural complexities that have less solubility, and hence reduced absorption in the GI tract suffers low bioavailability. Nanoemulsions work in a way to alter the absorption, biological accessibility, and stability of the complex structural frameworks in order to promote higher bioavailability.²⁸ For the lipophilic BACs, oil in H₂O nanoemulsions has tiny oil droplets (>200 nm) scattered in H₂O and gets stabilized by a hydrophilic emulsifier coat. For hydrophilic antioxidants such as polyphenols, H₂O in oil nanoemulsions full of H₂O droplets scattered in the oil and H₂O droplets wrapped by a hydrophobic emulsifier.²⁹ H₂O to oil ratio helps define the size and stability of droplets in the emulsion in addition to the type and composition of oil used, and what solute or solvent has been mixed in it.^{29,30} Based on requirements and targeted release demand, nanoemulsions can be liquids or either powdered forms prepared through freeze or spray drying methods are a superior choices.³¹ Certain related studies have also proven the enhanced bioavailability of antioxidants such as astaxanthin (α keto-carotenoid) due to increased mixed micelle formation that improves its solubilization,³² and pterostilbene in oils shown increased bioavailability.³³ On the other hand, addition of multiple surfactants may improve the stabilization of nanoemulsions but prolonged use may cause toxicity to the tissues.³⁰

Solid-lipid NPs

Recently, a novel nanotechnological tool nano-bubbles is in extensive utilization with greater achievements in targeted drug delivery systems. Nano-bubbles formation laden with natural antioxidants could be a prioritizing choice in order to avoid any added carbohydrates or proteins in

the diet to aid chemotherapy or functional foods. Satisfactory *in vivo* results showed betterment in neurodegenerative diseases and diabetes also achieved due to enhanced bioavailability of the natural antioxidants.⁸ Polyphenols including green tea-derived EGCG, apigenin, curcumin, resveratrol, and alkaloid berberine showed *in vitro* activity that is much higher than FDA and EU approved drugs.^{8,34} Nano-bubbles seem a superior drug delivery system due to their small size and prolonged circulation time compared to micro-bubbles,³⁵ and have no toxicity and higher biocompatibility.³⁶

receiving much attention recently. The research work of NLCs is useful in discovering safe and crucial drug delivery structures due to their superior physicochemical behaviors and higher biocompatibility. NLCs consisted of a binary system consisting of solid and liquid lipids with a view of producing a less ordered lipidic core. These inclusions of the NLCs have the potential to alter the physicochemical properties and the efficiency of the final product optimally. NLCs can be developed with immense ease using various approaches and methods. More use of NLCs is desirable because of the simplicity of preparation methods, versatility of uses, and a better understanding of the mechanism of transport through different routes of administration: oral, dermal, ocular, and inhalation.³⁷

Nano-Lipid Carriers (NLCs)

The improvement of the uptake and efficacy of natural antioxidants in the form of NLCs is now

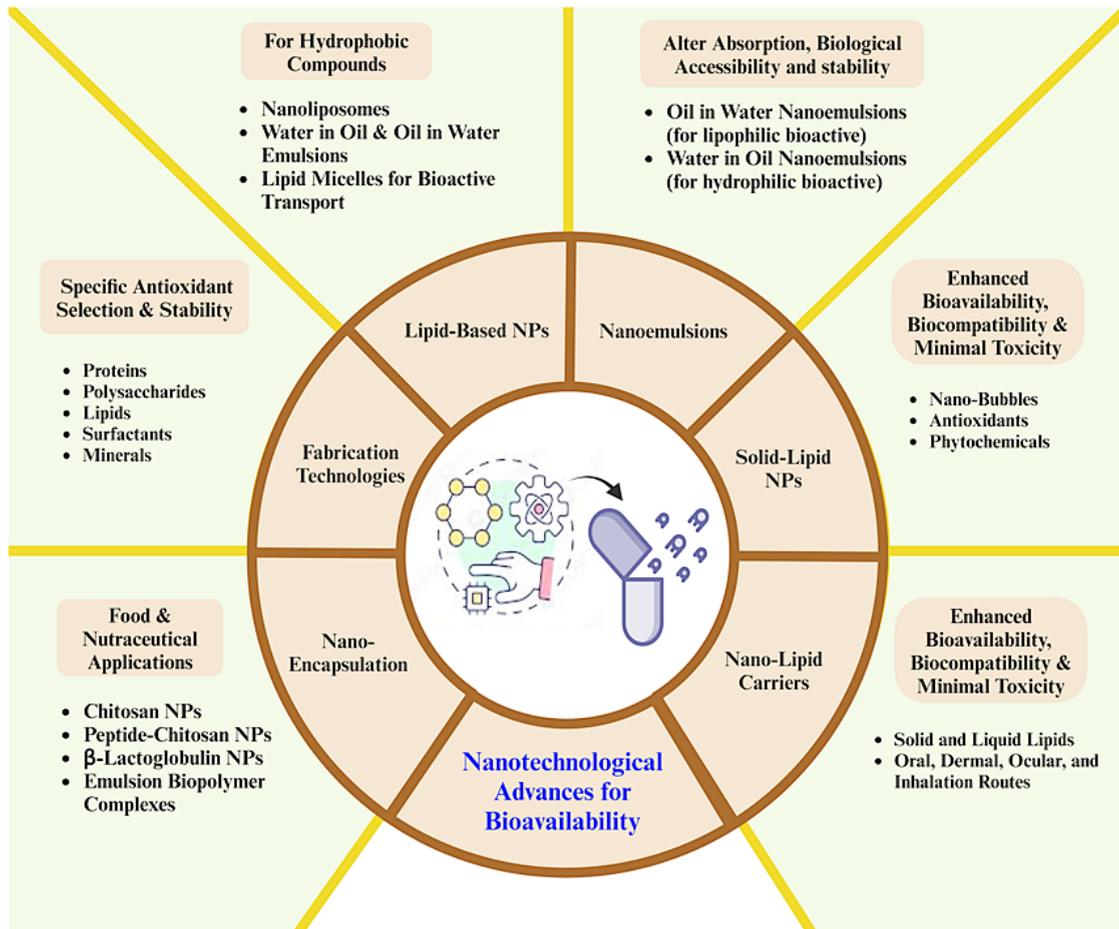


Fig. 2: Overview of nanotechnological advances in antioxidant bioavailability through nanoencapsulation using different delivery systems containing different carriers for enhanced bioavailability and specific targeting

Nature-Inspired NPs Delivery Systems

The concept of NPs actually came from nature since many NP assemblies already exist, and their application can be used to promote the bioavailability

of different natural antioxidants.³⁸ A few of the naturally occurring NPs are discussed below and also illustrated in Figure 3.

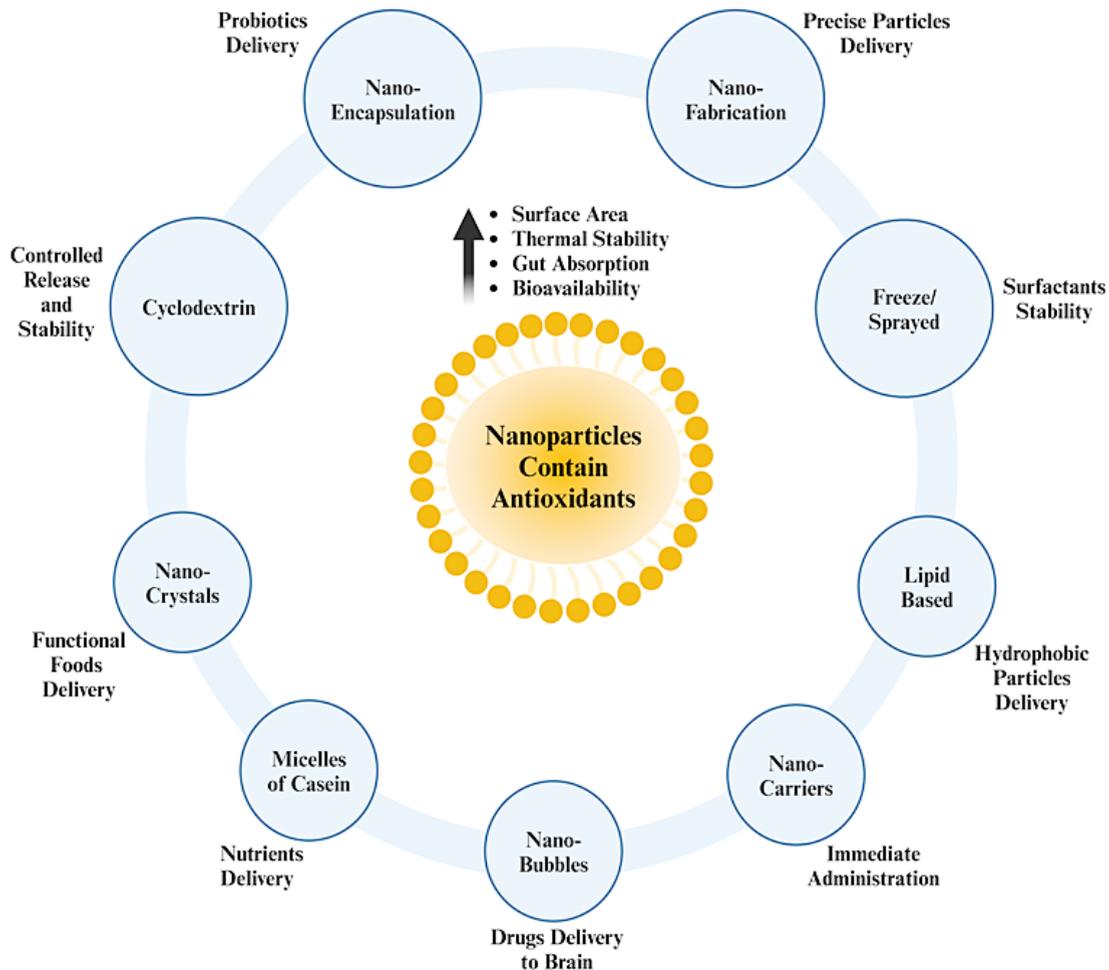


Fig. 3: Illustration of NPs delivery systems for enhancing bioavailability and stability of natural antioxidants through unique structural properties

Micelles of Casein

Encapsulation systems of milk nutrients are often evident in casein nano-assemblies native to milk.³⁹ Usually, casein protein (CP) is crystalline and in an amorphous form called micelles with a radius from 50 to 500 nm. These micelles are made up of inner core of α s1, α s2 and β casein and an outer 'hairy' layer of κ -casein. The hydrophilic glycosylated part of κ -casein, glycomacropeptide, prevents aggregation by explicitly engaging with water molecules.⁴⁰ Casein

micelles have no toxicity and are regarded as highly biocompatible, bioresorbable, and biodegradable.^{39, 41} Also, due to their lipophilic character and their ability to be transported actively through the plasma membrane, they are well absorbable if taken orally.⁴² Other natural systems include starch granules and cyclodextrin inclusion complexes with food nutraceuticals, and amylose chains of bread with added amount of flavor compounds that leach out as bread bakes.^{43,44}

Nanocrystals

Nanocrystals (NCs) are the solids that mix nanoscience along with crystalline BACs to get higher solubility, dissolution, and physicochemical properties.⁴⁵ Natural NCs are made up of nano-sized crystalline forms of polysaccharides (cellulosic nanocrystals or CNCs)⁴⁶ and lipids.⁴⁷ Polysaccharides (cellulose, starch, & chitin), are present in both crystalline and amorphous forms.⁴⁸ The regions of NCs that are not crystalline get hydrolyzed preferentially while the nanosized crystalline regions remain biocompatible, biodegradable, and have high bioavailability. This ranges from the provision of new surface area, strength, processability, affordability, and distinct nanoscale characteristics make these NCs suitable for biological uses.⁴⁹ Moreover, their functional groups, high rigidity, large aspect ratio, crystalline structure, and inherent chirality allow them to interact highly with several bioactive compounds and form complexes with them;⁵⁰ because food grade NCs lack toxicity they are increasingly being used in functional foods to enhance the solubility and bioavailability of natural antioxidants. NCs can directly or indirectly interact with physic-chemically unstable bioactive chemical compounds (BACs).⁵¹ By protecting these compounds through encapsulation in liposomes or by layering with biopolymers and surfactants.⁵² For instance, the cellulose NC system was prepared to deliver curcumin with enhanced bioavailability while acetylation of starch NCs improves its biocompatibility and bioavailability for encapsulation of BACs with low availability.^{53,54}

Cyclodextrins

The use of natural cyclodextrins is greatly preferred since the nanocarrier does not necessitate much processing and is biocompatible. Comprised of cyclic non-reducing glucopyranose units cyclodextrin is formed naturally through the catalysis of enzymes and starch.⁵⁵ They are categorized into three types with 6, 7, and 8 glucopyranose units in their structure, correspondingly.⁵⁶ Cyclodextrins have a lipophilic cavity and a hydrophilic exterior thus they can encapsulate lipophilic molecules, and they are used commonly in controlled drug delivery mechanisms.⁵⁷ Cyclodextrins can be further functionalized to develop a broad spectrum of nano structures with higher host guest complexing ability for various BACs or antioxidants. These adaptations enhance their physical characteristic, especially the rich hydrophilic faces which enhance

their solubility and bio pharmacokinetic profile.⁵⁷ Cyclodextrin molecules can self-organize into numerous nanostructures via self-assembly, covalent bond formation, chemical derivatization, or by combining with other biocompatible polymers.⁵⁸ The two widely investigated types of cyclodextrin-based nano formulations are nano sponges and nanospheres that increase the permeability and solubility of BACs but also create the controlled-release associated with improved effectiveness.⁵⁹

Nps Synthesis using Specialized types of Equipment

A few techniques are in use to fabricate a multitude of NPs. Few of these fabrication techniques demand the involvement of specific equipment to prepare desired sizes and types of NPs. Frequently used fabrication procedures require specific equipment such as electro-spinning, electro-spraying, and nanospray drying.^{60,61} Variety of NPs can be formed using procedures highlighted in the coming heads and depicted in figure 4.

Nanofibers Formed by Electro-spinning

Nanoscale fabrication techniques still maintain one of the biggest advantages which is cost effectiveness, especially with techniques like electro-spinning making it convenient to be used in different industries. Nanofibers are developed by electro-spinning equipments where the bio-active compound (BAC) incorporated with the polymer solution is forced through a spinner which is connected to a high-voltage supply.⁶² This result into the creation of a certain condition within the solution where there is a kind of repulsion force that form nanofiber. Due to specific properties, the nanofibers are well suited for use in nanocarriers for BACs as in nutrient delivery systems.⁶³

NPs formed by Electro-spraying

Another successful technique of fabrication is electro-spraying, which applies an electrical charge to transform a polymeric solution into desired NPs. The same to electro-spinning process it employs mechanisms of surface tension where the emerging liquid forms a cone under a stimulated electric field for NP formation. These NPs have various uses including delivery of BAC, controlled drug release, diagnostics, and therapeutic applications. Significantly, the researchers have only observed some changes in the biological polymers during

NP formation but there were no alterations in their activity and properties. Some of the few benefits of electro-spraying include; it is easier to reproduce the

process with high levels of accuracy, it has a higher NP loading density, and is also easier to scale up production.⁶⁴

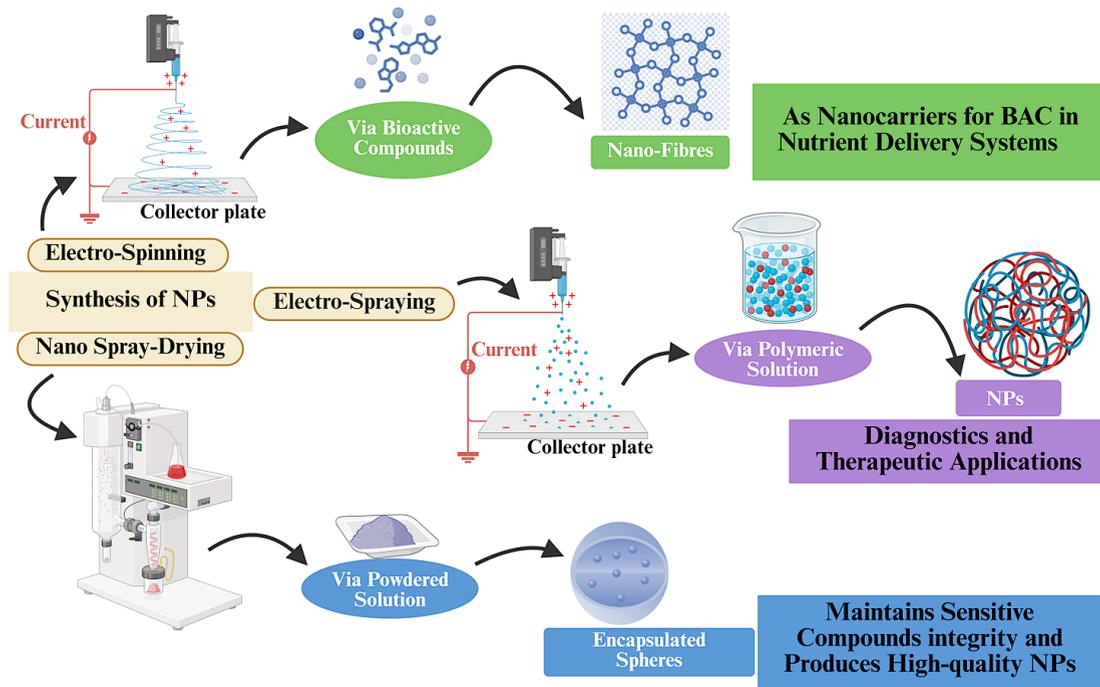


Fig. 4: Synthesis of multiple types of nanofibers or NPs using various techniques for specific applications

Nano Spray-Dried NPs

In this method, the typical spray dryers are used for the conversion of liquid solutions into powder effectively and quickly by using a drying technique. This technique is especially useful given that the high speed and relatively short time of the transformation process do not harm temperature-sensitive products. Further, this method has been used to prepare encapsulating matrices with the sphericity of hollow spheres depending of materials used and drying conditions.⁶⁵

Biopolymer NPs

Many of the investigated materials for functional food application are GRAS due to low or negligible toxicity and outstanding biocompatibility. Proteins and polysaccharides are GRAS materials and have often been used as encapsulation materials to prepare food-charged NPs for enhancing the bioavailability of related BACs per se, especially antioxidants with relatively poor bioavailability. These NP formulations

are useful in creating a release-controlled shell to encapsulate and protect nutraceutical or other BACs both hydrophobic and hydrophilic to improve their bioavailability and effectiveness in general.⁶⁶

Protein, polysaccharides, and Polysaccharide-Protein NPs

The development of mucoadhesive and optimally designed biopolymer conjugated natural compounds and probiotics containing NPs is vital for catering to the increased consumer demands. Every type of protein NPs is quite flexible and can be altered to cover several purposes. Native proteins may be employed in the formulation of NPs or subject to physical, chemical or enzymatic changes to modify the functional characteristics.⁶⁷ These NPs can be tailored for their intended applications and the significant benefits they have over other delivery systems including high biodegradability, biocompatibility, non-toxicity to the host, no size restriction, non-accumulation in the body, and

slow elimination. Affordable, biocompatible, easily available and biodegradable with low or no toxicity biopolymers includes polysaccharides that can be potent candidates for developing food-grade NPs with improved nutrition bioavailability.⁶⁸⁻⁷⁰ As in the case of proteins, polysaccharides can be chemically, enzymatically or physically altered to introduce several functional characteristics.^{71,72} Polysaccharide gelation can provoke the formation of NPs through cold-set, heat-set, as well as by ionotropic processes. Some of the nine biopolymers used in the preparation of food-grade NPs are agar, alginate, carrageenan, cellulose, chitosan, dextran, gelling gum, inulin, pectin, pullulan and starch.⁷³⁻⁷⁵ Considering this, protein-polysaccharide complexes can be utilized to prepare NPs from both biopolymers having higher bonding strengths could be of interest.⁷⁶ The formation of the complex NPs requires templating, injection, the process of electrostatic complex formation, anti-solvent precipitation, and principle of thermodynamic incompatibility.⁷⁷ It can be confirmed that their shape, size, composition, and charge can easily be controlled by different regimes of the fabrication process.⁷⁷ The synthesis of Protein-polysaccharide biopolymer complex NPs often involves electrostatic complexation.⁷⁶

Comparative Analysis of the usage of Nanotechnology in Enhancing Bioavailability

Regarding the advantages and disadvantages, the emergence of nanotechnology also has pros and cons that should be considered prior to use in terms of their production methods and applications. Green synthesis of NPs using different natural plant based BACs may have exceptional functional surfaces by exposing certain organic ligands, peptides, oligo- or poly-saccharides, and alcohols, which are not found on NPs prepared through chemical or physical methods.⁷⁸ The preparation of NPs through chemical or physical methods may pose certain level of toxicity in the environment and human body along with higher costs incurred.⁷⁹ Green synthesis of NPs is quite advantageous over the physical or chemical methods that involve the use of natural BACs that are potent in binding and reducing metal ions into NPs.⁸⁰⁻⁸³ Moreover, green synthesis of NPs is cheaper, quick, no toxicity to human body, and requires little energies.⁸⁴ Additionally, encapsulation of BACs onto NPs may enhance bioavailability, surface area, and targeted release.^{19,85} This technique of NPs-based BACs target release is highly viable under

hydrophobic and hydrophilic environments. BACs delivered via oral routes may encounter numerous physiological barriers such as gut variable pH conditions, mucus, and epithelium layers, and hence in this regard smart delivery systems such as NPs are a promising strategy to protect BACs from degradation having improved bioavailability.⁸⁵

Safety and Toxicity of Nanostructures Applied in Food Systems

Nanotechnology has numerous opportunities to intervene in the food industry.^{86,87} Some nanomaterials are employed to design NPs carriers for BACs of nutritional importance that show low accessibility, and hence, effectiveness.^{19,88} On the same note, enhancement of rheological, optical, and flow characteristics of food.⁸⁹ Most food commodities are intrinsically associated with nanomaterials present naturally in itself such as casein micelles in milk, or nanostructures.^{90,91} In addition, food processing techniques such as grinding, homogenization, or cooking also give rise to a wide range of NPs. While nano-sized solids are often used in foods but their safety and toxic effects still remain questionable.²⁸ Presumably, because these NPs have a large surface area, such NPs might affect the GI tract functions by binding and inactivating digestive enzymes causing a decline in enzymatic activity and digestion.⁹² Additionally, large quantities of indigestible organic nanoparticles reduce the ability of the GI tract to digest lipids, proteins or starch.^{92,93} In certain situations, with NPs intrusions, pathways to exert OS and inflammation in the GI tract could be activated by immune responses.⁹³ Based on the above discussion, it became clearer that any reported toxicities linked with the NPs, may also be the result of diets habits and diet plans, food types, and passage through the gut are mostly disregard. These important factors also contribute about the biochemical characteristics and any toxicities of the NPs, and deemed indepth studies.

Future Perspectives

Majority of antioxidants are less bioavailable in biological system and hence their beneficial properties are not often upto the mark or expectations. Utilizing functional foods that improve the absorption of such antioxidants or BACs using nano-modalities presents one of the best solutions. Such systems can effectively encapsulate, target and release nutraceuticals of poor bioavailability to meet the

highest possible therapeutic value. Besides, they aid in minimizing nutrient and flavor deterioration, or changes in food texture that are occasionally induced during processing. Specifically, BACs such as those occurring in nature or either derived from biomolecules through functionalization are always desirable. Several methods have improved the accuracy and specificity in fabrication of these NPs systems with minimal toxicity to the tissues. Mounting literature has revealed the utilization of NPs in the field of nanofoods, but successful application of these nanotechnological approaches at industrial scale application still demands further validation with specific health and safety concerns.

Conclusion

Nanotechnology in the food industry focusing on the enhancement of antioxidant bioavailability is one of the most prospective strategies for a better future and public health. Hence, more in depth in vivo studies are needed to enhance the bioavailability using NPs encapsulation strategies to elucidate the potential for food and nutraceutical industry.

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Conflict of Interest

The authors do not have any conflict of interest.

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Even though adequate data has been given in the form of tables and figures, however, all authors declare that if more data is required then the data will be provided on a request basis.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to Reproduce Material from other Sources

Not Applicable

Author Contributions

- **Muhammad Farrukh Nisar:** Data Collection, Methodology, Writing – Original Draft.
- **Chunpeng Wan:** Conceptualization, Analysis, Writing – Review & Editing, Visualization, Supervision, Project Administration, Funding Acquisition.

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