Original Article

Nanotechnology: A Novel Tool To Enhance The Bioavailability Of Micronutrients

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Abstract

Nutraceuticals, diagnostics, therapeutics, pharmaceuticals, and food systems have all been transformed by nanotechnology. The solution to increasing the bioavailability of oral delivery of bioactive compounds is largely dependent on nanoparticles. This review showed that nanoparticles can make micronutrients like vitamin B12, vitamin A, folic acid, and iron more bioavailable. After taking nano-based supplements, the toxicity of nanoparticle-based delivery systems remains a major concern. A major gap in the field of nanoceuticals is the mode of the mechanism of nanomaterials and bioactive components in various physiological conditions of the human body. In order to confirm the precise approach to physiological changes in the human body, further clinical investigations based on evidence are required in the future.

Keywords: Pharmacokinetics, Microelement, Nanoscience, Innovative Tool

INTRODUCTION

The entire food chain from production through processing, storage, and consumption is being modernized by nanotechnology. The thermal stability, water solubility, and oral bioavailability of nutrients may all be enhanced by nanotechnology, according to scientific reports [1].

For the delivery of edibles, nanoparticles (NPs) are tiny, biologically consistent materials that can be produced in a variety of ways and range in size from 1 to 100 nm. They possess significant chemical and physical properties like solubility, color, strength, infusibility, and a high surface-to-volume ratio[2]. Tissue engineering, cell therapy, drug delivery, diagnostic tools, biomaterials, and signaling molecules are just a few of the fields where these NPs' properties can be useful [3, 4].

The human body's barriers may be broken through with the help of nanobiotechnology, allowing for the targeted delivery of drugs to specific organs. For instance, getting to the brain by bridging the blood-brain barrier.

Nanomaterials have found applications in food safety and quality as well as human well-being. Numerous industries, researchers, and organizations have recently adopted novel approaches with significant food technology applications for NPs[5, 6]. Nanotechnology is being looked at as a way to treat the COVID-19 outbreak that is still going on.

Nanomedicine research into a potential COVID-19 treatment may benefit from chloroquine, an approved malaria drug[7]. For optimal human health and disease prevention, functional food components like vitamins, phytochemicals, minerals, and antioxidants are necessary. The terms "nutriceuticals" and "pharmaceuticals" are a fusion of the terms "nutrition" and "pharmaceuticals". Nutraceuticals are substances derived from food or any part of food that has physiological, preventative, or therapeutic significance beyond the basic nutritional needs [8, 9].

A significant demand for dietary supplements has emerged as a result of rising rates of chronic disease morbidity and nutrition awareness worldwide. By 2022, the global demand for nutraceuticals is expected to reach $302.307 million, based on an annual growth rate of 7.04% from 2016 to 2020[10]. Additionally, these nutraceuticals have been difficult to incorporate into food due to their chemical instability, undesirable flavor, and low solubility [11]. Although a number of formulation strategies have been proposed to overcome the low solubility, the potential interactions between the preparation excipients limit their benefits.

In contrast, nanoparticle technology has gained widespread acceptance due to its use of minimal excipients to increase micronutrient solubility [12]. Nanoparticle-based delivery systems can also be used to deliver the solution to these issues[13]. However, depending on the properties and nature of the micronutrient, precise and appropriate nanoscale delivery systems are required for the encapsulation of various micronutrients [14,15].This review aims to emphasize the role of nanotechnology in enhancing the bioavailability of micronutrients via targeted delivery systems.

REVOLUTION OF NANOTECHNOLOGY IN THE FIELD OF NUTRITION

Pharmacology, food processing, agriculture, and nutrition are just a few of the fields in which nanotechnology has made a significant impact [16, 17]. Research in nutrition that incorporates nanoscience has developed rapidly over the past few decades, inspiring a strong desire for the targeted delivery of micronutrients [18]. Drugs and micronutrients (vitamins and minerals) are being delivered to the body more effectively through nanocapsules[19].

Nano-composite, nano-structuration, and nano-emulsification are all used to encase the materials in miniature forms in order to deliver bioactive compounds more effectively in a variety of ways. Polymeric nanomaterials can be used to form encapsulated bioactive constituents, such as vitamins and flavonoids, for the protected delivery of nutrients [20, 21].

Some commercial supplements go by the names nanoceuticals, nutrition-be-nanotech, and nanotechnology. Improved absorption of nutrients like iron, curcumin, and folic acid is being considered for vitamin spray-dispersed nanodroplets. As a nano-cochleate, nano-sized powders are also used to improve nutrient absorption.

It has been demonstrated that these are an efficient method for delivering nutrients to cells without affecting the flavor or color of the food. Encapsulation methods, in which Zn and Fe nano-structured capsules direct the beneficial probiotics and other products into the human body, make up the majority of the supplement manufacturing process.

Because of their unique size, the NPs found in food supplements interact more effectively with human cells than those found in commonly used supplements [22].

Coenzyme Q10, antioxidants, essential oils, flavors, vitamins, phytochemicals, and minerals are carried in nano-capsules to increase their bioavailability in the human body [23]. The encapsulation of polyphenols with NPs may preserve their flavor and prevent any oxidative reactions[24]. Liposomal nano-vesicles have been used in the food industry to provide nutrients, enzymes, and antimicrobial compounds by encapsulating them [25].

It is also assumed that nanotechnology plays a role in enhancing the bioavailability, water solubility, and antioxidant properties of bioactive particles found in spices and herbs, allowing the active ingredients to dissolve uniformly [26].It is thought that the nanomaterials make important phytochemicals like genistein and curcumin more bioavailable [27].In addition, nano-nutraceuticals are available in nano-formulations as dietary supplements, herbal products, and bioactive particles [28].

MICRONUTRIENT BIOAVAILABILITY

A nutrient's bioavailability is the proportion of the bioactive ingredient ingested that is absorbed and used for the body's essential physiological functions[29]. Oral intake decreases the bioavailability of bioactive compounds like vitamins A, D, and E, carotenoids, curcumin, conjugated linoleic acids, omega-3 fatty acids, and coenzyme Q10[30]. It occurs as a result of bioavailability, absorption, and transformation, among other physiological and physiochemical factors (Figure 1).

Bioactive molecules' low bioavailability, stability, and solubility can be improved with of nanotechnology, particularly nano-formulations in particular.

The hydrophobic nature of many biologically active particles used to treat diseases limits their bioavailability. To make it easier to deliver these nutrients precisely, nanotechnology-based delivery systems are being developed.

Natural food-grade macro-ingredients like proteins, polysaccharides, lipids, and phospholipids are also used to make NPs, so there are no harmful side effects. A variety of food-grade ingredients, including a lipid core and a protein shell, are known as nano-emulsions[31].

Due to their encapsulating property, food-grade NPs can help improve the efficacy, stability, and utilization of micronutrients [32]. Nutraceuticals can be effectively delivered in a variety of ways. Several carriers, including liposomes, solid lipid NPs (SLNs), cubosomes, monolayers biopolymeric NPs, microemulsions, nanosensors, microemulsions, and fibers, are used to disperse nanofibers, nanosheets, fullerenes, nanowhiskers, and nanotubes.

A successful colloidal delivery system must be precisely designed for a specific application based on the functional particle's and product's nature[33]. However, in order to increase the bioaccessibility, absorption, and transformation of bioactive substances in the gastrointestinal tract (GIT), precisely designed excipient foods are utilized.

As shown in Figure 2, numerous NPs-based delivery systems are utilized to improve bioavailability through the hydrophilic and hydrophobic encapsulation of micronutrients.

STABILITY OF MICRONUTRIENTS IN THE PRODUCT

A food product's physicochemical and molecular properties, as well as the food's composition and storage conditions, significantly influence the breakdown of a micronutrient. In a food product, micronutrients may be susceptible to enzymatic, physical, and chemical instability. Chemical variability includes alterations in the molecular arrangement, which may result in significant variations in the bioactive component's nutritional attributes and physicochemical properties. Chemical breakdown of micronutrients typically takes place through oxidation, hydrolysis, isomerization, and reduction, all of which can be carried out by enzymes found in food[34].

An alteration in the locality of micronutrients, such as phase variations (such as melting, polymorphic transitions, or crystallization), gravitational separation, or aggregation, is regarded as physical instability.

For a particular micronutrient, principal degradation mechanisms and key factors (such as pH, temperature, and water activity) must be identified.

Materials that prevent the diffusion of one or more reactants into NPs can be layered on top of them. Embedding lipid molecules within a microgel surrounded by protein molecules can reduce the degree of lipid oxidation in oil-in-water suspensions[34].
The rate of lipid oxidation in fish oil droplets captured within casein pectin microgels is lower than in their free form. Antioxidant activity, chelating transition metals, and inhibiting the dissemination of reactant are some of the ways these microgels may limit oxidation[35].

NUTRIENT ENHANCER AND INHIBITORS AFFECTING BIOAVAILABILITY

Bioactive components may alter bioavailability through interactions with one another or the medium in which they are surrounded. Vitamin D for calcium and vitamin C for iron are examples of nutrient enhancers that can either prevent or enhance nutrient absorption.
Vitamin C, for instance, can increase iron absorption by two to threefold[36]. In contrast, inhibitors prevent nutrients from being absorbed by either binding to other substances or

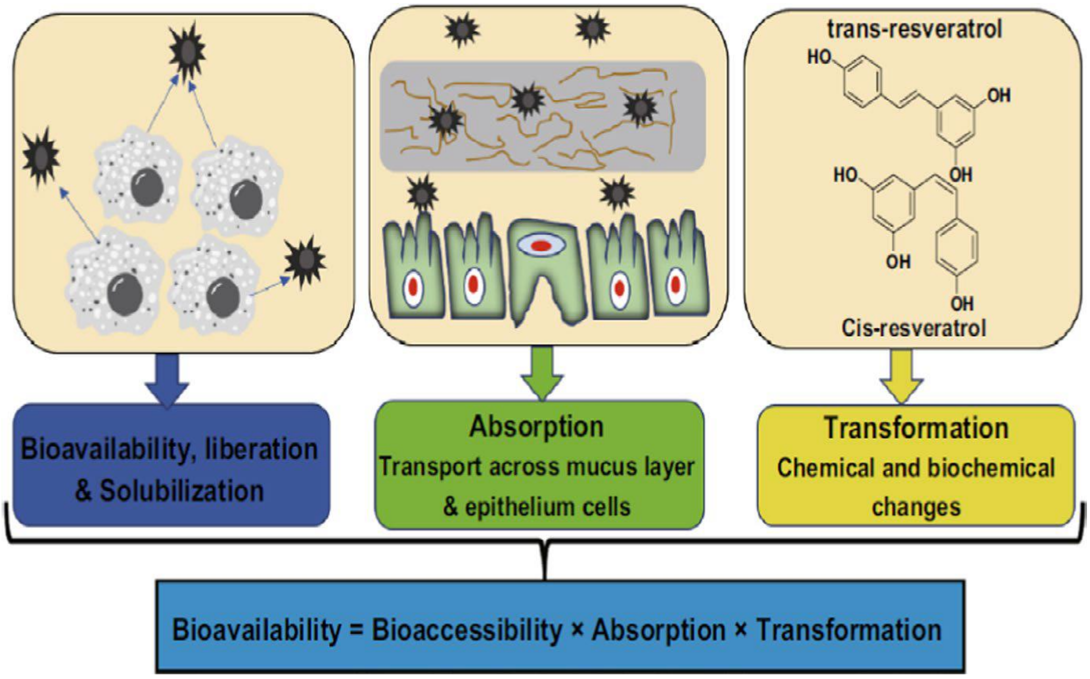

Figure 1: Mechanism of Micronutrient Bioavailability in the Human Body.

making nutrients more difficult to absorb by making them insoluble. Phytic acid is a mineral inhibitor that can be found in a lot of plant foods. It has a strong ability to bind calcium, zinc, and iron, making it harder for micronutrients to be absorbed [37].Nanotechnology has the potential to be a promising means of reducing the chemical inhibitors of bioactive particles in this setting.
Curcumin dispersed with colloidal NPs was found to be more effective than natural curcumin powder at absorbing nutrients. In the presence of a chemical inhibitor, a study found that beta-carotene's attraction to chelate transition elements (like Fe^{2+}), which typically favor oxidation, slowed the color degradation rate of beta-carotene dissolved in nano-emulsions. Additionally, when taken with an (piperine) absorption enhancer, curcumin's oral bioavailability can be nine times greater [38].

BIOAVAILABILITY AFTER INGESTION

In order to guarantee the bio-efficacy of drugs taken orally or bioactive food components, bioavailability is a crucial factor. It is influenced by manifestations in the gastrointestinal tract (GIT) and the chemical breakdown of bioactive elements during processing, manufacturing, storage, and transportation. The primary phases that are involved in the bioavailability of bioactive components are the liberation, absorption, distribution, metabolism, and elimination phases. The following equation can be used to express the bioavailability (F).

$$\mathbf{F} = \mathbf{F}c \times \mathbf{F}b \times \mathbf{F}a \times \mathbf{F}m$$

where Fc is a component of a micronutrient that, when ingested orally, functions as an active ingredient in a food product. Facebook is regarded as bioaccessible.
A micronutrient that is released from food and dissolved in GIT liquids. The portion of a micronutrient that is transported through the intestinal cavity is referred to as FA or absorption. Fm is referred to as metabolism, and it is a component of a micronutrient that functions as a bioactive form in response to alterations in the gastrointestinal (GIT), such as metabolic changes caused by enzymatic activity, liver metabolism, or systemic circulation[39].

As a result, developing a targeted delivery system can improve bioactive component bioavailability (F). By altering the structure and composition of nano-based delivery systems, this goal can be accomplished. Encapsulated triglycerides in microgels, such as calcium alginate beads, that prevent breakdown in the upper GIT, have been shown to be effective by some findings.
The bioactive fatty acid must be released when these beads reach the intestinal colon through an enzymatic breakdown.

Microgels and biopolymer nanoparticles made from dietary fibers may be able to carry several lipophilic bioactive components into the lumen while remaining intact within the GIT. However, developing a biopolymer nanoparticle (NP) that safeguards the food product's micronutrient may be essential. Using in vitro virtual GIT models, practical in vivo animal studies, and human trials are necessary when designing biopolymer NPs for controlled release systems.

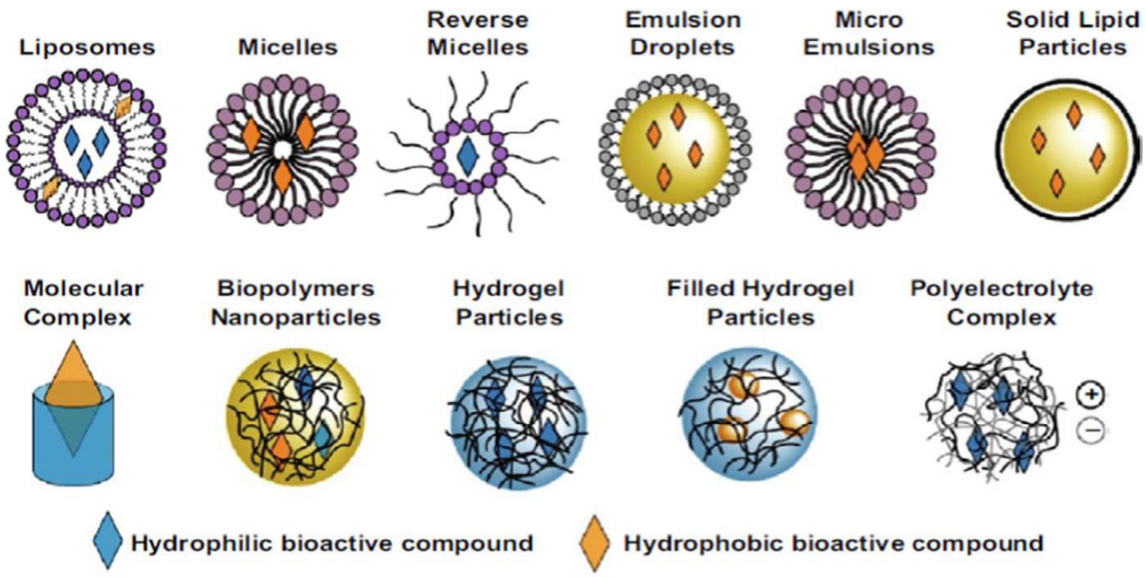

Figure 2: Different Nano-Based Delivery System To Improve The Bioavailability of Encapsulated Micronutrients.

Vitamin A

This hypothesis was validated when researchers observed enhanced bioavailability of carotenoids when consumed with nano-materials than the natural form of carotenoids [40]. Understanding the bioavailability and biological processes that regulate the absorption of vitamin A can be used to design the nano-materials for vitamin A. The encapsulation of vitamin A with nano-materials may have more bioavailability than that of free vitamin A.
Nanomaterials that aid in vitamin A paracellular transport can also increase vitamin A bioavailability. Altering the integrity of NPs' close junctions. Additionally, when lipophilic composites carried paracellularly are inaccessible to the metabolic actions of intracellular enzymes, oral bioavailability can be enhanced. The following equation can therefore be used to define encapsulated vitamin A with NPs' oral bioavailability (F):

$$\mathbf{F} = \mathbf{F}\mathrm{b} \times \mathbf{F}\mathrm{a} \times \mathbf{F}\mathrm{m}$$

Here, Fb is the proportion of vitamin A consumed that is protected in the upper GIT and discharges into the colon through the nanomaterials, becoming bioavailable for enterocyte absorption.
The percentage of vitamin that is bioavailable and enters the portal blood circulation is called Fa. After the first-pass metabolism of the liver and GIT, the FM is the vitamin A that remains in its active form.
By preventing physiochemical changes like temperature, moisture, oxidation, and pH, nanotechnology has successfully improved vitamin A's oral bioavailability [41].

Vitamin B12

As a transport system for hydrophilic bioactive elements, protein lipid composite NPs with a three-layer assembly (phospholipid, protein, and tocopherol layer) and an inner hydrophilic portion have recently been developed. Over 20 times more vitamin B12 was absorbed by these improved NPs.
An intrinsic factor that is produced by stomach parietal cells aids in the absorption of vitamin B12 in the terminal ileum. Additionally, absorbed vitamin B12 serves as a cofactor for enzymes involved in the synthesis of DNA, myelin, and fatty acids [42].Despite the fact that the altered NPs were found to be more effective than a free vitamin supplement in enhancing vitamin B12 deficiency in a rat model. To increase the bioavailability of vitamin B12 through nanotechnology, however, more research is required.

Folic Acid

NPs possess sufficient properties for targeted oral nutrition delivery. When taken orally, these NPs protect the jejunum's mucus layer and remain contained within the GIT. When compared to an aqueous suspension of vitamin B9, the encapsulation of folic acid with zein NPs increased its relatively oral bioavailability by approximately two fold. This may be due to these NPs' ability to interact with the intestinal mucosa and establish mucoadhesive associations [43].However, clinical trial data and information regarding the effects of nanotechnology on folic acid bioavailability are sparse.

Iron

When compared to commercial tablets, the preparation of iron with solid lipid NPs can increase bioavailability by more than fourfold. The significant findings as a targeted system for oral iron consumption and the production of ferrous (Fe2+) loaded with alginate NPs. Additionally, Fourier transform infrared spectroscopy and thermogravimetric analysis were used to confirm that alginate NPs effectively loaded ferrous (Fe2+) [44].However, in order to confirm the bioavailability of nano-based delivery systems for iron and other micronutrients, additional in vivo studies and clinical trials are required.

TOXICITY OF NANOPARTICLES

Nanoparticles (NPs) are linked to a number of toxicities, in addition to numerous important applications. Small size, high capacity, and high reactivity are some of the advantages of NPs, which can also be fatal by causing cellular lethal effects. Due to their early acceptance in biotechnology and prolonged exposure in GIT, NPs may have the potential to have negative effects on humans. The ability of NPs to gather near protein concentrations, which can be affected by particle size, shape, and surface, is one of the most common toxicities. Some nanomaterials cause adverse biotic effects through protein fibrillation, unfolding, loss of enzymatic activity, and thiol crosslinking as a result of this unique binding capability [45].

NPs are also bioavailable, but their larger surface areas can cause a variety of toxicities. Another premise when the thermodynamic properties of substances may favor NP discharge in a biological system is the discharge of lethal ions [46].In addition, the research into the long-term negative effects on human health of nanostructures developed for curative properties is still in its very early stages. Although a few studies are being conducted to reduce the toxicity of synthesized nanostructures, significant concerns remain regarding their potential. Nanostructures' manufacturing, handling, and storage may result in decreased efficacy and an increased risk of toxicities, both of which require in-depth investigation.

FUTURE PERSPECTIVE AND TREND

The fields of medicine, biological treatment, nutrition, food science, and biochemistry can all benefit from new insights provided by nanotechnology applications. However, claims and applications of nano-fortificants still have a long way to go [47].There is a significant lack of knowledge regarding the toxicities of nanoparticles, which necessitates addressing the safety concerns associated with these materials. However, studying the requires an hour interactions between food and nanomaterials, as well as the consequences of eating them.

It is also necessary to take into consideration the key issues associated with "nano-labeling" food supplements. [48]

Also, nanoparticles (NPs) are being made all over the world, but only a few countries have approved guidelines for using nanotechnology in the food industry. Although NPs play a significant role in the potential expansion of curative and preventive applications for the targeted delivery of micronutrients, insufficient scientific evidence on nanotechnology has made it difficult to draw definitive conclusions regarding the effective delivery of micronutrients [49, 50].

CONLUSION

Through targeted delivery systems, nanotechnology enhances the bioavailability of micronutrients. Oral delivery of bioactive compounds can be improved thanks to NPs' significant thermodynamic properties. However, the increased bioavailability of micronutrients is supported by various research findings. The questionable toxicity of NPs can be a problem after taking nano-based supplements. In addition, there are still no human-based studies or clinical findings in the literature to support the improved bioavailability of each essential micronutrient.

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