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REVIEW ARTICLE

# Next-Generation Nutraceutical Delivery in Functional Foods: Bioavailability, Nanoencapsulation, and Sustainable Biotechnological Strategies - A Review

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## Abstract

The emerging existence of chronic metabolic diseases, cardiovascular diseases, neurodegenerative disorders, and lifestyle-related diseases led to the popularity of nutraceutical-based food systems around the globe. The plant, microbial, and marine-derived nutraceuticals have a wide range of biological effects, such as antioxidant, anti-inflammatory, immunomodulatory, cardioprotective, neuroprotective, and antidiabetic effects. Their incorporation into food processing makes the traditional nutrition shift from the nutrition-based approach into the preventive-health-based alternative. However, the development of any nutraceutical-containing foodstuff is difficult because of the instability of the nutraceutical in terms of physicochemical properties; insufficient solubility in water; weak bioavailability in gastrointestinal tract; oxidation; and changes in taste characteristics in food during processing as well as storage. Recently developed food biotechnologies and nanotechnologies, as well as new methods of encapsulation and extraction, can help to overcome these issues. The use of nanoemulsions, liposomes, nanostructured lipid carriers, edible films, and intelligent packaging systems has considerably enhanced the durability, precision, and controllability of nutraceuticals. In addition, innovations, such as high-pressure processing, pulsed electric fields, cold plasma, and ultrasound-assisted extraction have contributed to the preservation of bioactivity without overheating the food products. The use of omics, synthetic biology, and artificial intelligence for developing nutraceuticals is going to give rise to an all-new generation of food products. However, although a lot of advances have been made in this area, various matters, including the issues of regulation, nano-safety, commercial usability, standardization, and clinical validation, make it impossible to produce these products on an industrial scale. This paper deals with the classification, processing, stabilization, and delivery of nutraceuticals in the context of technological development, where special attention is drawn to the processes of molecular mechanisms, sustainability, and future prospects.

**Key words:** Bioavailability, food biotechnology, marine bioactives, nanoencapsulation, non-thermal processing, nutraceuticals, precision nutrition, probiotics

## INTRODUCTION

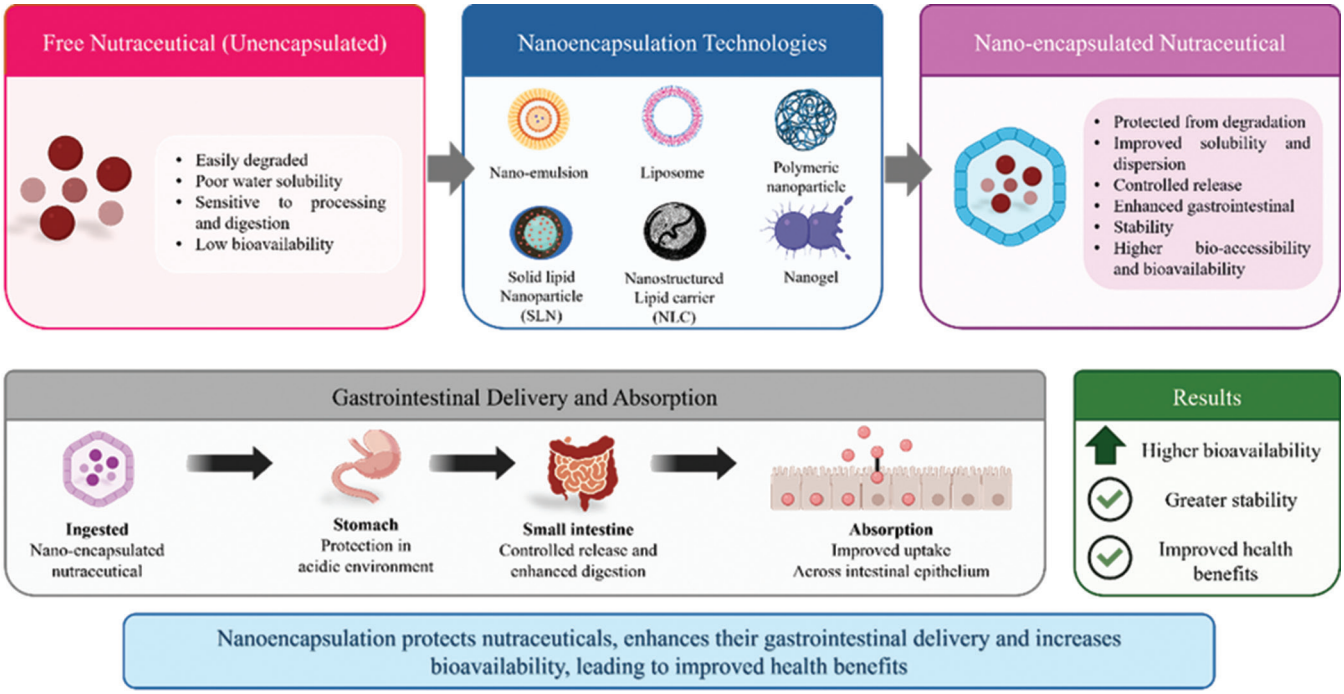
The movement from conventional dietary patterns to diets that optimize one's health has significantly increased interest among scientists and players in the food industry in nutraceuticals and functional foods. Urbanization and a lifestyle characterized by inactivity, environmental stress, and unhealthy eating lead to dramatic increases in the number of people suffering from chronic diseases,

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## GRAPHICALABSTRACT




including diabetes, heart diseases, obesity, cancer, and brain disorders. Thus, health problems have resulted in the rising demand for food products that produce health effects that go beyond ordinary nutrition. Today, the sector of nutraceuticals is one of the most rapidly growing sections of the field of food biotechnology and pharmaceutical nutrition.[1]

"Nutraceutical" is the term that is used for food products or bioactive substances known for different physiological benefits, disease prevention, or health promotion. Unlike traditional dietary supplements, modern nutraceuticals have not only been incorporated into the food matrix, but have also led to the production of functional foods that modify oxidative stress, metabolic pathways, immune response, and the composition of gut microbiota. Some examples of nutraceutical compounds widely studied include flavonoids, alkaloids, polyenes, probiotics, omega-3 fatty acids, and marine polysaccharides. Although there is progress in nutraceuticals, the process of incorporating nutraceuticals into food remains very difficult from the scientific point of view. Numerous bioactive compounds show low solubility in water, poor absorption capacity in the gastrointestinal tract (GIT), fast metabolism, and instability during thermal, oxidative, and acidic processing. For example, polyphenols get oxidized during processing, carotenoids are extremely sensitive to light, and the survival rate of probiotics is low during storage and digestion.[2]

Nanoencapsulation and other related technologies, such as microencapsulation, liposomal delivery, nanostructured lipid carriers (NLCs), and biopolymer nanogels bring many benefits for the application of such processes in nutraceuticals. In addition to this, novel green methods, such as supercritical fluid extraction (SFE), enzyme-assisted extraction (EAE), microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE) allow one to make extraction of pure bioactive compounds.[3] It is also worth noting that new non-thermal processes of nutraceutical preservation are possible due to modern technologies, such as high-pressure processing, cold plasma, pulsed electric fields, and pulsed light being used instead of the traditional application of heat in keeping food free from micro-organisms. However, despite all the benefits of applied technologies, some problems are still available. There are issues concerning lack of unified regulation, absence of clinical proof of the technology, issues with nano-toxicology, inconsistency of raw materials, issues with scale-up, and consumer doubts about efficiency.[4]

The present review gives an objective overview of the development of nutraceuticals in food systems, including such topics as classification, processing techniques, nanoencapsulation methods, mechanistic aspects, sustainability issues, regulatory hurdles, and perspectives for development. More attention is directed to the intersection of nanotechnology, biotechnology in food processing, synthetic biology, and precision nutrition in creating innovative food products based on nutraceuticals to support disease prevention.

## CLASSIFICATION AND BIOLOGICAL FUNCTIONS OF NUTRACEUTICALS

Nutraceuticals can typically be grouped based on their origin, chemical makeup, or how they function in the body. The main

types of nutraceuticals are from plants, microbes, or marine organisms. They differ in terms of their chemistry, activity, and processing attributes (figure 1).

## Plant-derived nutraceuticals

Plant-based nutraceuticals are the most commonly used among the various functional bioactives that can be applied in food processing. The predominant category of these active compounds is represented by the secondary metabolites secreted by various plants to protect them against the stressors that may exist in the environment. The most popular nutraceuticals include polyphenols, which possess beneficial antioxidant and anti-inflammatory effects. Polyphenols contain aromatic structures possessing hydroxyl groups, with the help of which it can absorb radical species of oxygen, capture metal ions, and interact with the redox-sensitive pathways.[5]

The main polyphenol subclasses are flavonoids, phenolic acids, stilbenes, lingo-tannins and tannins. Flavonoids (quercetin, catechin, kaempferol, and epigallocatechin gallate [EGCG]) are able to produce a variety of effects due to their impact on nuclear factor erythroid 2 (Nrf2)-associated pathways and the decrease of the impact of inflammatory mediators, such as nuclear factor-kappa B (NF-kB) and tumor necrosis factor (TNF)-alpha. Resveratrol, a stilbene found in grapes and berries, engages sirtuin pathways which are responsible for the functioning of mitochondria and the anti-aging process. However, the efficacy of polyphenols in food processing is diminished due to low stability during processing, low resistance to oxidative processes, and low bioavailability in the GIT.[6]

Carotenoids are a class of pigments responsible for giving color to fruits, vegetables, as well as some marine organisms. They can be found in yellow, orange, and red colorings of some algae and other processes. There are some important types of carotenoids, such as beta-carotene, zeaxanthin, astaxanthin, and others. The carotenoids have different biological functions, including antioxidant action, immunological modulation, and visual support. Beta-carotene is well known for being the precursor substance of vitamin A. Moreover, lycopene is considered to play an essential role in protection from diseases, such as prostate disease and cardiovascular diseases. Unlike carotenoids derived from land plants, marine carotenoids, for example, astaxanthin, have higher antioxidant properties because of their structure. Despite all the benefits that have been made possible to carotenoids, the disadvantages of their use should also be mentioned. These substances are not dissolved well in the water, being at the same time exposed to oxidation, photo-isomerization and thermal decomposition. Hence, methods of encapsulation and the use of lipid delivery systems are required.[7]

Peptides obtained from plants, such as soy, amaranth, rice, and pea proteins have hypertension-lowering, antioxidant, and anti-diabetic properties. Numerous peptides operate as angiotensin-converting enzyme (ACE) inhibitors and hence modulate blood pressure and cardiovascular functions. The bioactive peptides are manufactured by using fermentation or enzymatic hydrolysis. The stability of peptides and consumer acceptance continue to be major barriers in product development.

## Microbial-derived nutraceuticals

Microbial bioactives have gained considerable popularity among professionals due to being scalable, sustainable, and multifunctional. Probiotics are microorganisms that are considered beneficial for health when consumed in adequate amounts. In general, *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* species are used in food and drink production, and they play key roles in regulating the microbiota, functioning of the intestinal barrier, efficiency of the immune system, and reducing inflammation. Present research shows the link between probiotics and the gut-brain axis.[8] Post-biotics refer to inactive microbial products that consist of various metabolites, including short-chain fatty acids (SCFAs), as well as bacteriocins, and they are acclaimed for their stability, preserving the functionality of the live probiotics at the same time. They also include exopolysaccharides, which are produced as a result of lactic acid fermentation and help enhance the food properties, including consistency, water absorption, and mouthfeel, while providing prebiotic and immunomodulatory effects. The process of microbial fermentation results in the creation of bioactive peptides that have great potential in terms of their standards of antioxidant and anti-hypertension effectiveness. Advancements in synthetic biology open opportunities for the production of genetically modified microbial species showing terrific productivity rates of nutraceuticals, such as carotenoids, polyphenols, and coenzyme Q10.[9]

## Marine-derived nutraceuticals

The marine environment offers biologically active substances with unique structures and exceptional properties. Omega-3 marine polyunsaturated acids, such as eicosapentaenoic acid and docosahexaenoic acid (DHA), have cardioprotective effects and take part in functions, such as the regulation of membrane fluidity and inflammatory processes. It is important to consider that marine oils are too sensitive to lipid oxidation, which occurs during processing and storage. However, marine polysaccharides, such as chitosan, fucoidan, alginate, and laminarin possess antioxidant, anticoagulant, antimicrobial, and immunomodulatory properties.[10] Marine protein hydrolysates sourced from fish industry waste yield peptides for antihypertensive and anti-obesity purposes. Naturally occurring antioxidants include astaxanthin and fucoxanthin. Studies confirm that fucoxanthin demonstrates positive results in anti-obesity and antidiabetic use, as it has the ability to influence the processes of adipogenesis and glucose metabolism. To utilize marine bioactive substances in

food production systems, it is important to employ advanced methods of stabilization of these substances, so as to prevent the process of oxidative degradation and sensory changes.[11]

## FOOD PROCESSING AND NUTRACEUTICAL STABILITY

The functional foods containing nutraceuticals have certain limitations – stability of nutraceuticals during production, storage, transportation, and digestion. Nutraceuticals are often sensitive and unable to cope with certain processing techniques used by the industry. The main factors affecting this include temperature, exposure to oxygen, environment, humidity, light exposure, and food composition. In light of this, it is clear that it is necessary to study the issue of food processing influence on nutraceuticals stability to develop functional foods (Figure 2).[12]

### Thermal processing and bioactive degradation

Thermal processing (Heat treatment) is possibly the most widely used method applied to preserve food. Many procedures, including pasteurization, sterilization, blanching, extrusion, drying, roasting, frying, and baking, have been used successfully in the food industry to maintain food safety during the storage of products. Yet, these procedures can also reduce the effectiveness of heat-sensitive nutraceutical substances. Heat helps initiate the mechanism of degradation of the nutraceuticals, such as oxidation, hydrolysis, isomerization, decarboxylation, and polymerization. Polyphenols represent one of the important antioxidants among phytochemicals that can undergo thermal degradation. Polyphenol oxidase and peroxidase enzymes cause enzymatic oxidation and contribute to the reduction of the antioxidant properties of the polyphenols.[13] Research has indicated that the carotenoid compounds, such as β-carotene, lycopene, lutein, and astaxanthin, are extremely sensitive to heat. The rotor of this has brought many metabolic changes, with oxidation of carotenoids that leads to a loss of color and less antioxidant potential. However, other processes have created much more problems while processing the product, which is one of them the deterioration of vitamins. One of example is Vitamin C, which is extremely sensitive to heat and starts oxidizing right away.

### Oxidative and environmental instability

Environmental instability resulting in oxidation, light, moisture, ionic metals, and variation in pH adversely affects nutraceuticals in addition to thermal degradation. Oxidative degradation is one of the primary causes of the loss of bioactives during the time of food processing and storage. Lipid-based nutraceuticals, such as omega-3 fatty acids, are more vulnerable to oxidative rancidity. Polyunsaturated fatty acids are subject to lipid peroxidation through free radicals, producing hydroperoxides, aldehydes, ketones, and volatile compounds, leading to off-smell and reduced nutritive value. Furthermore, the oxidation products can exhibit pro-inflammatory and cytotoxic properties. Polyphenolic compounds undergo oxidation in alkaline solutions and also in the presence of transition metals, such as copper and iron. Oxidative polymerization leads to discoloration, precipitation, and loss of antioxidant capabilities of phenolics. Anthocyanins have very high sensitivity to light and are unstable in neutral or alkaline situations.[14]

### Food matrix interactions

The food structure has a crucial function in determining how nutraceutical substances are released, dissolve, digested, absorbed, and made available to our bodies. Interactions between nutraceutical compounds and macronutrients can significantly change their physiological efficacy, and protein-polyphenol interactions are some of the best-studied matrix effects out there. Polyphenols can attach to proteins through hydrogen bonding, hydrophobic forces, and covalent bonds. The effect of this interaction can be that it might diminish bitterness and enhance sensory properties, but its downside is that it might limit intestinal absorption and antioxidant effectiveness.[15] On the other hand, lipids play an important role in increasing the availability of nutraceuticals that are lipophilic in nature, such as coenzyme Q10, carotenoid, curcumin, as well as fat-soluble vitamins. Dietary fats trigger the secretion of bile and micelle formation that allow one to absorb non-polar compounds through the intestine. Hence, one can conclude that introducing bioactives into lipid-rich compounds greatly enhances their uptake through GIT.

### Nanoencapsulation and advanced delivery systems

Lower water solubility, chemical instability, oxidation susceptibility, and poor absorption in the GIT are issues facing the use of nutraceuticals in food products. The processing, storage, and digestion of food can lead to these complications. Nanoencapsulation seems to be a good way to shield vulnerable nutraceuticals when moving them into the food matrix. The implementation of bioactive substances into nanoparticles enables the distribution of bioactive substances; protects them from the impacts of the environment and food processing; and regulates their release (Figure 4).

Tiny droplets present in nanoemulsions hold the hydrophobic chemicals immobile. As a result, they have been used widely to enhance the bioavailability of nutraceuticals. Another mode of delivery of nutraceuticals is liposomes, which can have either an aqueous core or a liposome bilayer depending on the type of active ingredients used. Furthermore, the structure of the liposomes can be modified according to the specific characteristics of the substance that is to be delivered. Thus, with liposomes, delivery of nutraceuticals can be achieved

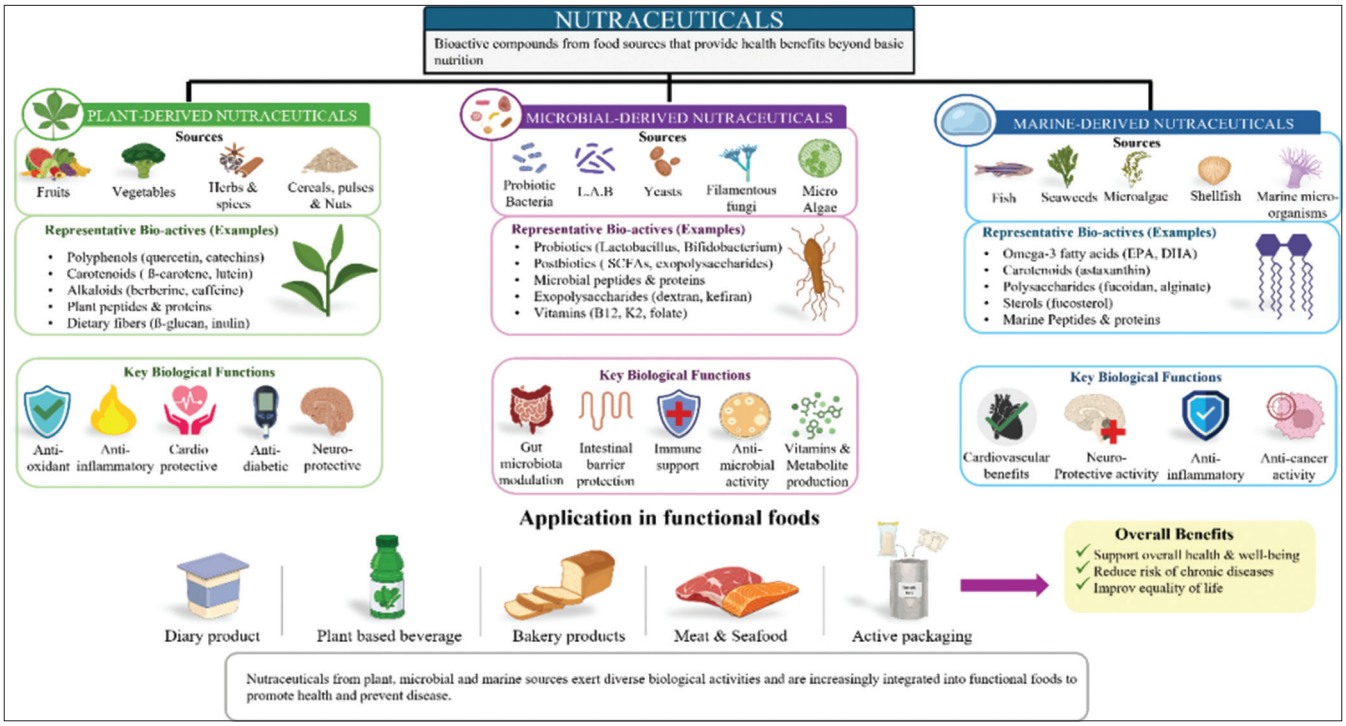



**Figure 1:** Classification, representative sources, bioactives, and biological functions of plant-, microbial, and marine-derived nutraceuticals in functional foods

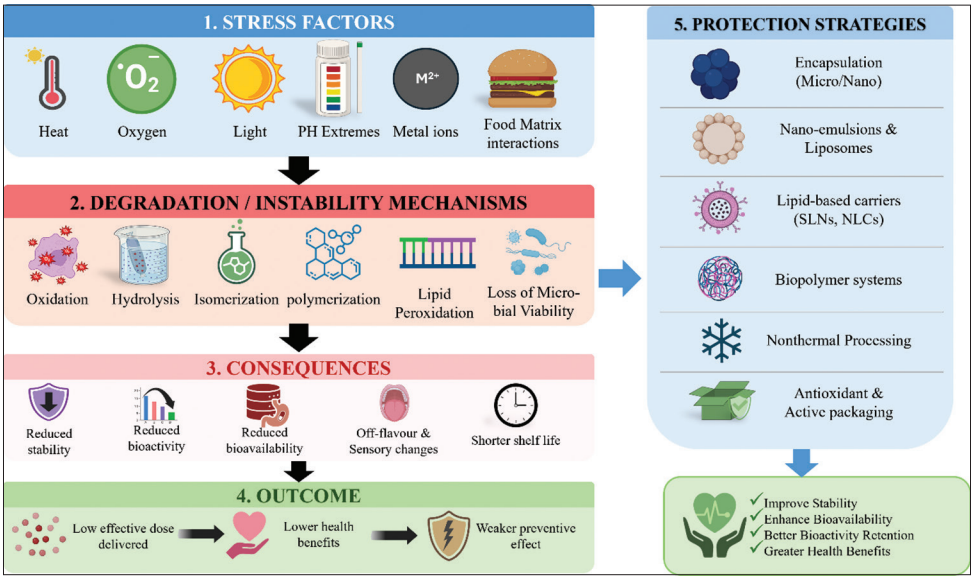



**Figure 2:** Factors affecting nutraceutical stability and bioavailability during food processing and storage, and strategies for their protection

without causing any chemical or oxidative changes of the substances. In addition, solid lipid nanoparticles and NLCs can be used to develop a lipid system for the delivery of lipophobic nutraceuticals.[16]

One alternative method of nutraceuticals compatible with food is the use of nanoparticle-based biopolymers. Within this method, the polysaccharides and proteins can protect the bioactive substances by enclosing them in a barrier and further securing them against oxygen, light, pH, and other factors leading to destabilization of the bioactive compounds. The use of biodegradable and natural materials makes this method especially applicable in the food industry. The protection is not only available during processing and storage but also applied during digestion and absorption of the food in the GIT, which is an important advantage of nanoencapsulation. When entering the body, the encapsulated substance gains an opportunity to cope with the challenged conditions in the stomach and is released in the intestines during the digestion process.

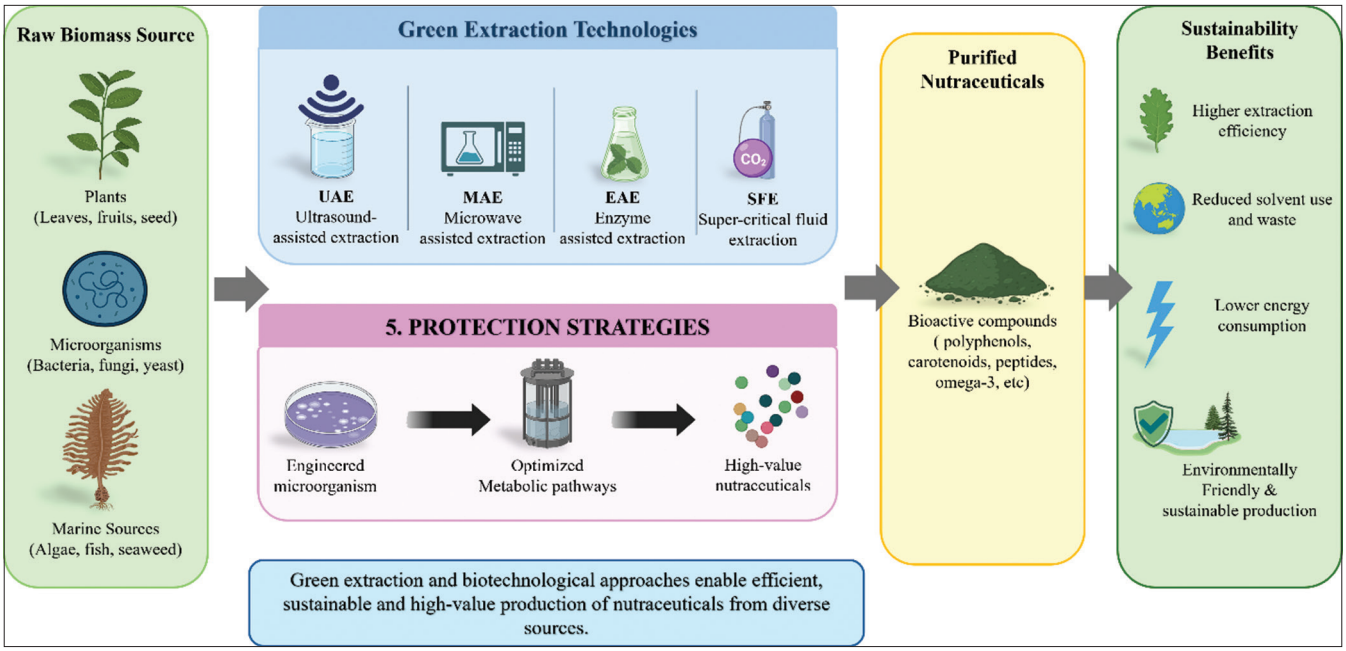



**Figure 3:** Green extraction and biotechnological approaches for sustainable nutraceutical production

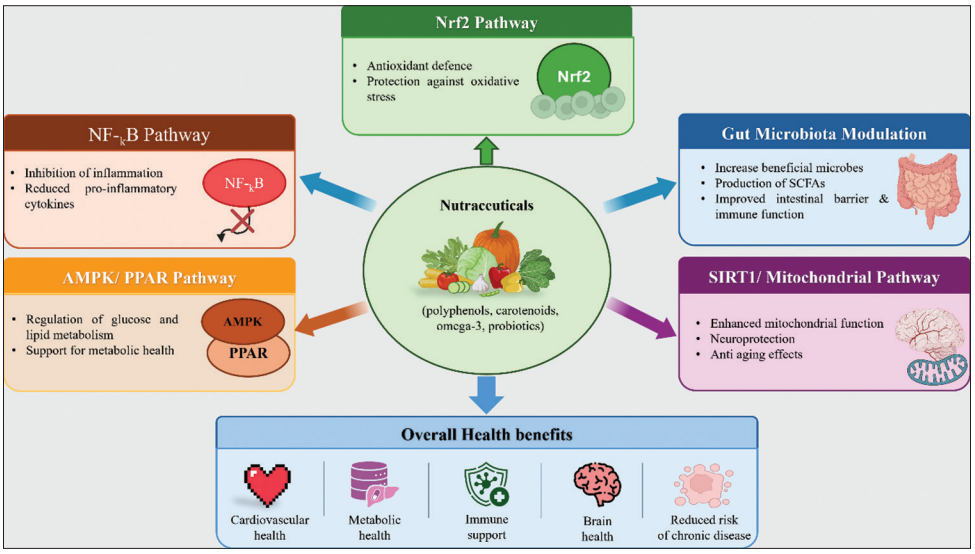



**Figure 4:** Nanoencapsulation strategies for enhancing nutraceutical stability, gastrointestinal delivery, and bioavailability

It is known that both the composition of a carrier and its interaction with the food matrix influence digestion, micelle formation, intestinal permeability, and the absorption process. Thus, it is important to note that the improvement in bioavailability is not simply the result of size reduction of particles or the mere fact of having the particles covered with a shell.[17] The system of delivery should be capable of achieving great performance. This level of performance is influenced by many factors, including particle characteristics, efficiency of encapsulation, structure of carriers, processing method, interactions with food in the digestive tract, stability of the delivery system, and behavior of the delivery system in the digestive tract. In addition to the above-mentioned factors, sensory characteristics, manufacturing costs, scalability, and regulatory issues are also factors that must be taken into account with respect to the usage of nano-encapsulated nutraceuticals. These issues remain major obstacles to the commercialization of delivery systems from the lab to food applications.

## GREEN EXTRACTION AND SUSTAINABLE PROCESSING TECHNOLOGIES

The use of environmentally friendly products by Green extraction technology has resulted in an increase in the usage of regular extraction processes. Green extraction technologies have emerged to ensure the efficiency of the extraction processes without the need for using a lot of solvents and

**Table 1:** Comparative classification of plant, microbial, and marine-derived nutraceuticals used in functional food processing

| Nutraceutical source | Representative bioactives | Major food sources | Primary molecular mechanisms | Functional food applications | Processing challenges | References |
|---|---|---|---|---|---|---|
| Plant-derived nutraceuticals | Polyphenols, flavonoids, carotenoids, alkaloids, bioactive peptides | Fruits, vegetables, cereals, medicinal plants | ROS scavenging, Nrf2 activation, NF-Kb suppression, AMPK modulation | Functional beverages, bakery products, dairy fortification | Thermal degradation, oxidation, poor bioavailability | [10] |
| Microbial-derived nutraceuticals | Probiotics, post-biotics, exopolysaccharides, microbial peptides | Fermented dairy products, probiotic beverages, fermented cereals | Gut microbiota modulation, immune regulation, ACE inhibition | Yogurt, kefir, synbiotic drinks, fermented foods | Loss of viability during processing and storage | [11] |
| Marine-derived nutraceuticals | Omega-3 fatty acids, fucoidan, chitosan, astaxanthin, marine peptides | Fish oil, algae, crustaceans, seaweed | Anti-inflammatory signaling, lipid regulation, mitochondrial protection | Encapsulated oils, seafood products, nutraceutical beverages | Oxidative instability, odor development, purification difficulty | [12] |

ROS: Reactive oxygen species, AMPK: AMP-activated protein kinase, ACE: Angiotensin-converting enzyme, Nrf2: Nuclear factor erythroid 2

**Table 2:** Comparative evaluation of extraction technologies for nutraceutical recovery

| Extraction technology | Working principle | Major nutraceuticals extracted | Advantages | Limitations | Industrial relevance | References |
|---|---|---|---|---|---|---|
| Conventional solvent extraction | Diffusion using organic solvents | Polyphenols, alkaloids, terpenoids | Simple and cost-effective | Solvent toxicity and low selectivity | Widely used but environmentally unfavorable | [22] |
| Supercritical fluid extraction | Supercritical CO2-mediated extraction | Carotenoids, essential oils, omega-3 lipids | Solvent-free and highly selective | High equipment cost | High-value nutraceutical production | [23] |
| Ultrasound-assisted extraction | Acoustic cavitation and cell disruption | Flavonoids, phenolics, pigments | Reduced extraction time and solvent use | Possible free radical generation | Suitable for heat-sensitive compounds | [24] |
| Microwave-assisted extraction | Rapid dielectric heating | Polyphenols, carotenoids | High extraction efficiency | Localized overheating | Industrially scalable | [25] |
| Enzyme-assisted extraction | Enzymatic degradation of cell walls | Polyphenols, peptides, polysaccharides | Eco-friendly and selective | High enzyme cost | Sustainable nutraceutical processing | [26] |

energy (Figure 3). The main classes of plant-, microbial-, and marine-derived nutraceuticals, their representative bioactives, food sources, mechanisms, applications, and processing challenges are compared in Table 1. The principles, advantages, limitations, and industrial relevance of conventional and advanced extraction technologies are summarized in Table 2.

## SFE

SFE is a modern green extraction technology that uses fluids in their supercritical state for extraction of bioactive materials. The most widely employed supercritical fluid for this purpose is $CO_2$ as it is non-toxic, non-flammable, inexpensive, and friendly to the environment. When used in supercritical form, $CO_2$ has both liquid-type solvability and gas-type diffusivity, which enables it to penetrate the biological matrices easily. The process of extraction, utilizing supercritical $CO_2$, is extremely effective in extracting lipophilic compounds, such as carotenoids, sterols, tocopherols, essential oils, fatty acids, and terpenoids. The method has several benefits that considerably surpass the advantages provided by the conventional extraction techniques, as it is conducted in low temperatures so that there is no thermal degradation

of the products. There are practically no residues of the solvent being used, as $CO_2$ vaporizes after depressurization. Following that, the extraction selectivity can be controlled effectively. This technique is efficient and reduces the time in extraction as well as the oxidation level, improving the purity of the materials. SFE can deal with the extraction of semi-polar compounds in combination with some co-solvents, such as ethanol. Although effective, the method has some drawbacks. The technology is complex, and the apparatus can be very expensive and demanding in pressure. All these problems limit the field of SFE use significantly.[18]

### UAE

The extraction of bioactive compounds from living tissues can be greatly enhanced with the help of UAE. The phenomenon responsible for the destruction of living biological tissues in UAE is the process of acoustic cavitation that is caused by ultrasonic waves. The bubbles created during this process eventually collapse and generate significant pressure and temperature fluctuations. These mechanical processes lead to the breakdown of cell walls, thus allowing the solvent to penetrate easier into tissues, as a result of which bioactive compounds can be extracted quickly. As a consequence, UAE improves processes of extraction by shortening the period of time necessary for extraction and reducing the quantity of the solvent needed for extraction. The process is effective in the extraction of polyphenols, flavonoids, alkaloids, anthocyanins, carotenoids, and essential oils. The essence of UAE is that it allows for extraction of sensitive substances at low temperatures. There are several factors affecting UAE efficiency, including ultrasound frequency and power, time of extraction, kind of the solvent applied, and solid-to-liquid ration.[19]

### MAE

Microwave assisted/aided extraction is a technique that utilizes electromagnetic waves for the rapid heating of solids and liquids. The energy of the waves makes it possible for the polar molecules to get rotated and the ions to move, which results in the development of sufficient energy necessary for heating and creating pressure inside the plant cells. Due to the sparking process of heating, cellular walls are destructed and the solvent can penetrate. Compared with traditional methods, MAE allows to shorten the time of extraction, use less solvent and using MAE instead of traditional extraction methods allows faster extraction procedure, using less solvent and having better results. This technique can be used for isolating phenolic acids, flavonoids, polysaccharides, alkaloids, and essential oils from plant and food materials. The method is especially efficient if polar solvents, such as water and ethanol, are used during the extraction process. In addition, this method can make the extraction process more reproducible and prevent oxidation process due to the short duration of exposure. However, the disadvantages of using microwaves are that they can destroy heat-sensitive compounds and produce uneven heating effects. Today, an effective method for MAE is the application of vacuum microwaves, solvent-free microwaves, and integrated microwave and ultrasound technology.[20]

### EAE

The application of enzymes for EAE has become a possibility for breaking down the cell wall structures of both plant and microbial cells, as well as leading to the liberation of bioactive compounds, which would otherwise be trapped inside and not available for extraction. The enzymes of the type of cellulase, pectinase, hemicellulase, amylase, protease and xylanase that are hydrolytic enzymes are used to facilitate hydrolysis of polysaccharides as well as proteins available in the biological material. Such enzymatic activity allows to increase the efficacy of extraction. EAE can be used for extracting polyphenols, flavonoids, carotenoids, bioactive peptides, and polysaccharides, among others. This extraction technique is advantageous due to being more gentle than conventional extraction procedures. This fact reduces the possibility of degradation and enables to preserve the efficiency of the extracted compounds.[21]

## PRECISION FERMENTATION AND SYNTHETIC BIOLOGY

One of the best examples of a new approach to sustainable production in the field of nutraceuticals is represented by precision fermentation. This technology makes use of microorganisms that have been genetically modified, which include bacteria, yeast, fungi, and microalgae, to produce high-value nutraceuticals utilizing controlled fermentation conditions. The combination of new metabolic techniques, systems biology, and synthetic biology has meant that microorganisms can now create very complicated bioactives, such as carotenoids, polyphenols, astaxanthin, coenzyme Q10, omega-3 fatty acids, and vitamins on an industrial scale within the fermentation process. The incorporation of CRISPR-Cas technology has increased the pace of strain optimization significantly, permitting precise modifications.

## MOLECULAR MECHANISMS OF NUTRACEUTICAL BIOACTIVITY

The biological action of nutraceuticals is mainly achieved by altering of oxidative stress, inflammatory signals, gut microbiota composition, metabolic pathways, and neuroprotection. These substances affect different molecular targets, which facilitate in the prevention and treatment of chronic pathologies, such as diabetes, heart diseases, cancer, and neurodegenerative disorders.

### Oxidative stress modulation and anti-inflammatory pathways

Oxidative stress is due to an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense systems. The accumulation of ROS leads to lipid peroxidation, protein modification, DNA damage, and cell damage. Nutraceuticals, among which are polyphenols, flavonoids, carotenoids, vitamins, and marine antioxidants, have the capacity to scavenge free radicals through mechanisms including hydrogen donation, electron transfer, and chelation of metals. Most of the bioactive molecules induce the activation of the Nrf2 signaling pathway, causing the upregulation of antioxidant enzyme genes, including superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase-1. Among the natural compounds promoting the activity of the Nrf2 pathway are curcumin, resveratrol, quercetin, and EGCG.[27] Chronic inflammation plays a major role in the development of metabolic syndrome, cardiovascular disorders, arthritis, and the progression of cancer. Nutraceuticals are responsible for the suppression of the inflammatory response by interaction with the signaling pathways. The major mechanism is the inhibition of NF-κB, which is responsible for the production of pro-inflammatory cytokines and enzymes. Substances, such as curcumin, resveratrol, omega-3 fatty acids, and EGCG lower the levels of TNF-α, Interleukin-1 beta (IL-1β), IL-6, prostaglandins, and nitric oxide by inhibiting cyclooxygenase and lipoxygenase. Omega-3 fatty acids also allow for the production of anti-inflammatory agents, such as resolvins and protectins, which help resolve inflammation.[28]

### Gut microbiota modulation and metabolic regulation and neuroprotective mechanisms

The importance of the gut microbiota in the regulation of immune defense, metabolism of nutrients, integrity of the intestine, and functioning of the nervous system cannot be overstated. Nutraceuticals can influence the composition of the microbiota in such a way that they stimulate the growth of good bacteria while inhibiting the development of harmful microorganisms. Prebiotics, for example, are substances, such as inulin and resistant starch that encourage Lactobacilli and *Bifidobacterium*. Probiotics are capable of enhancing the intestinal barrier and immunity. Polyphenols go through the metabolic process of the microbiota that makes them more bioavailable and effective. Fermentation by the microbiota also leads to the formation of SCFAs, such as butyrate and propionate, which demonstrate anti-inflammatory action and engage in glucose metabolism and the maintenance of the integrity of the gut. Certain nutraceuticals are believed to be involved in metabolic processes, such as glucose and fat metabolism through the modulation of AMP-activated protein kinase (AMPK), PI3K/Akt, and peroxisome proliferator-activated receptors (PPAR) signaling pathways. Activation of AMPK leads to an increase in the uptake of glucose and fatty acid oxidation and energy metabolism in mitochondria and inhibition of lipogenesis.

The active properties of berberine, curcumin, and resveratrol are similar to each other since they promote the enhancement of sensitivity to insulin and control the glucose process. Generally, omega-3 fatty acids play a role, too, since they are engaged in fat metabolism control as well as in the decrease of fat deposition due to the work of the PPARs. What is more, they contribute to fat and fatty acid absorption and metabolism.

Nutraceuticals are known to be important to protect the nervous system, mainly due to their antioxidant effects and anti-inflammatory ones, because they help stabilize mitochondria, which produce energy that is necessary for thought transfer. For instance, some supplements, such as DHA, astaxanthin, phytochemicals, curcumin, and resveratrol are known to reduce the oxidative and lipoperoxidation processes occurring in neurons thanks to the improvement of mitochondrial performance. While polyphenols reduce the activation of microglia and the release of pro-inflammatory cytokines, omega-3 fatty acids enhance the fluidity of synaptic membranes and neurotransmission. Both of these processes help protect the nervous system from neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases.[29]

## FUNCTIONAL FOODS AND NUTRACEUTICAL APPLICATIONS

### Dairy products

Dairy products rank among the most investigated functional food systems due to their rich nutritional content, suitable pH level, unique sensory characteristics, and ability to incorporate bioactive components. Milk proteins, such as casein and whey, have the ability to serve as natural emulsifiers and encapsulators that make the dairy matrices perfect for the carrier of probiotic bacteria, omega-3 fatty acids, vitamins, carotenoids, polyphenols, bioactive peptides, and phytochemicals. Fermented dairy products, such as yogurt, kefir, cheese, and probiotic fermented milk, have come into great prominence as they assist with the survival and delivery of beneficial microorganisms into the gastrointestinal system. Probiotics, among which *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus* are included, are used in the production of yogurts with the aim to enhance the balance of gut flora, providing immune modulation, and lowering the incidence of gastrointestinal disorders. It is believed that combining probiotics and prebiotics with plant polyphenols has synergistic effects that enhance antioxidant and anti-inflammatory capabilities.[30]

Recently, there have been advances in the application of nanotechnology and microtechnology for the preservation of sensitive nutritional compounds by nutraceuticals, which

include fish oil, curcumin, carotenoids, and vitamins, etc. When fish oil is added to yogurt, it does not undergo oxidation of oils and do not develop any unpleasant smells or bad taste, thus preserving its ability to provide certain cardiovascular effects. The same applies to dairy products with curcumin emulsions – not only are they used to make emulsions but also to enhance the efficacy. The results from the studies show that milk peptides produced from fermentation of milk have a lot of advantages of nutraceuticals, since bioactive peptides possess antihypertensive, antimicrobial, immunomodulatory and antioxidant properties. In particular, peptides that inhibit ACE as a result of milk fermentation are very beneficial for the cardiovascular system. Despite the advantages of dairy nutraceuticals, there are still some questions related to the use of these products.

### Plant-based beverages

Plant-based beverages are one of the most rapidly expanding areas of functional food because of the growing popularity of healthful, vegan, lactose-free, and other sustainable products. Various ingredients have been used in plant-based beverages, such as soy, oat, almond, coconut, rice, pea, or fruit drinks, along with supplements of nutraceutical components, such as probiotics, phytosterols, omega-3 fatty acids, vitamins, minerals, and antioxidant compounds from plants. Plant-based beverages are especially effective due to their natural content of phytochemicals, such as flavonoids, anthocyanins, isoflavones, dietary fiber, tannins, and others. For example, soy beverages are high in isoflavones with estrogenic and cardioprotective properties, and oat beverages contain β-glucans with cholesterol-lowering effects. Nanoemulsion technology has emerged as one of the most powerful methods of introducing hydrophobic bioactive ingredients, such as curcumin, carotenoids, essential oils, or coenzyme Q10, into the composition of water-based plant beverages. Nanoemulsified solutions improve the solubility, stability, gastrointestinal absorption, and bioavailability of the components. Encapsulated probiotics work the same way by improving microbial survival in the course of processing and during storage, enabling selective delivery to the intestines.[31]

### Bakery products

Bakery items including loaves, cookies, cakes, and croissants are consumed all over the world around the clock, and therefore can be considered reliable carriers of nutraceuticals. Bakery products enriched with fibers, resistant starch, plant proteins, probiotics, omega-3 fatty acids, phenolic substances, minerals, vitamins, and antioxidant powders are emerging and galloping in popularity. Fortification of bakery foods with functional components offers them better nutritional value as well as favorable effects, such as cardiovascular protection, glycemic regulation, improvement of digestive function, and antioxidant capabilities. Whole grains, flaxseed, chia seeds, oat bran, soy flour, and certain fruit pomace obtained during juice production can be incorporated to augment the fiber content. For instance, curcumin, catechins, anthocyanins, and extracts from grape seeds are also utilized. With similar benefits, protein would possess pea protein, soy protein isolate, and whey protein.[32]

### Meat and seafood products

Lipid oxidation, microbial spoilage, and quality degradation pose significant dangers to meat and fish products. As a result, nutraceutical compounds are increasingly added to these products for extensive shelf-life improvement, safety, and nutritional properties. Marine bioactives, such as omega-3s, bioactive peptides, astaxanthin, chitosan, and seaweed extracts, are widely exploited in functional meat and fish applications. Omega-3 supplementation of meat yields cardiovascular advantages, and natural antioxidants contribute to the prevention of rancidity and oxidative changes. Chitosan obtained from crustacean shells has gained much attention due to its antimicrobial, biodegradable, film-forming, and antioxidant properties. Chitosan coatings prevent microbial growth and reduce moisture loss from seafood and processed meat. Chitosan films combined with essential oils or plant extracts show higher preservative efficiency than individual compounds.[33]

### Active packaging systems

Active packaging systems are a new, innovative section in the area of food preservation and nutraceutical delivery. They are not like traditional passive packaging. The difference is that active packaging interacts dynamically with the food environment and thus helps to improve shelf life, preserve quality, reduce microbial contamination, and enhance food safety. In active packaging, bioactive substances (antioxidants, antimicrobials, enzymes, moisture absorbers, oxygen scavengers, probiotics, and controlled-release nutraceuticals) are included in the packaging materials. Sustainable biodegradable polymers (chitosan, gelatin, cellulose, starch, polylactic acid, and alginates) are widely used as active packaging matrices. Natural antioxidants (curcumin, catechins, quercetin, tocopherols, and essential oils) are utilized in films and coatings to prevent oxidative spoilage of food products. Films containing curcumin possess excellent antimicrobial and antioxidant properties. Furthermore, they are used as smart packaging materials due to their ability to change color depending on pH. Various essential oils (thyme oil, oregano oil, cinnamon oil, clove oil, and lemongrass oil) are widely used in active packaging due to their antimicrobial properties against food spoilage microorganisms.[34] Controlled release systems facilitate the antimicrobial activity over time without changing food composition. Nanotechnology has opened new avenues for active packaging. Nanocomposite films with silver, zinc oxide, titanium dioxide, and nanoencapsulated phytochemicals have better mechanical properties, barrier properties, ultraviolet protection, and antimicrobial properties.

## REGULATORY CHALLENGES AND QUALITY CONTROL

The global nutraceutical sector has many regulatory and standardization issues. Each country has its own way of defining nutraceuticals using laws that govern different products, such as dietary supplements, functional foods, and medical foods. Failure to have internationally recognized laws complicates product approval, labeling, and marketing. Safety assessments are also a key in protecting consumers. Some of the issues can be related to potential allergens, contamination, solvents, heavy metals, and nano-toxicity. Changes in the composition of raw materials and the methods of extraction affect the quality of nutraceutical products. Advanced methods of analysis, such as liquid chromatography-mass spectrometry, Fourier transform infrared spectroscopy, nuclear magnetic resonance, and metabolomics, help to confirm nutraceutical products.[35]

## EMERGING TRENDS AND FUTURE PERSPECTIVES

State-of-the-art technologies in microbiome science, nutrigenomics, and nutraceuticals provide the impetus for progress in the field of personalized nutrition. Because of artificial intelligence (AI), it is now possible to design diets according to each person's DNA and metabolism. Using the latest developments in AI, it is also possible to predict interactions of bioactive substances. Thanks to machine learning experts, a model of any substance can be created using AI technology, including its physical properties and bioavailability. The research focused on the delivery systems providing nutraceuticals in the specific physiological states is still being conducted. One should mention that processed food, portable biosensors, and smart packaging, as well as highly advanced systems, will take part in the food manufacturing process. Moreover, synthetic biology will help to create a unique bacterium that will be able to produce drugs.

Future studies should put an emphasis on producing more environmentally friendly and biodegradable nanocarriers for food applications. In addition, long-term studies on the effect of nano-nutraceuticals in terms of toxicity and pharmacokinetics should also be conducted. Conducting clinical trials to confirm the effectiveness of the nutraceuticals used in food is of great importance. The use of machine learning and AI for predicting the effectiveness of nutraceuticals should be included in the optimization process. Almost all of the latest technologies for engineering probiotics and precision fermentation will need to follow close study. The different countries' standards for nutraceuticals should be aligned too. The advancement of green extraction technologies will be necessary as well.[36]

## CONCLUSION

Nutraceuticals play an important role in the formation of advanced functional foods which combine nutrition with biotechnology and preventive medicine. Among the many nutraceuticals available on the market are plant polysaccharides, carotenoids, peptides, microorganisms, marine omega-3, and polysaccharides that allow to manage oxidative stress, inflammation, metabolic disorders, and chronic diseases. Nevertheless, the efficacy of incorporation of these compounds into food preparations is limited due to high physicochemical instability and poor bioavailability, vulnerability to oxidative breakage, and losses due to technological processing. However, the development of physical and chemical methods, such as nanoencapsulation, liposomal systems, biodegradable films, and non-thermal technologies has greatly facilitated the preservation of nutraceutical compounds and their delivery into food products, whereas sustainable techniques of extraction, precision fermentation, application of synthetic biology, and circular economy practices transform the technology of production of nutraceuticals.

The new generation of techniques, such as omics technology, AI, and nutrition technology permits the creation of many new food systems designed and developed according to personal requirements and features of human metabolism and genetic heredity. However, despite the impressive results of scientific progress, the use of technologies in practice is limited by many factors, such as lack of regulations, absence of clinical evidence, concerns related to nanotechnology safety, and absence of standardization. Future studies in this field should be directed at creating regulations in the field, long-term toxicity studies, improved clinical trials, and ecological production methods. The final result of such intersection of various disciplines, such as food science, nanotechnology, biotechnology, systems biology, and precision medicine is new nutraceuticals-based functional foods.

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