Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-822-9_5

Chapter 5: Fundamentals of Nanotechnology in Targeted Nutraceuticals Delivery

Prashant Kumar Gupta[1*], Priya Tiwari[1], Rajat Srivastava[2], Mandvi Tiwari[3], Jatin Agarwal[4], Priya Singh[5]

[1*]*Department of Pharmaceutics, Om Sai Vindhya College of Pharmacy, Tisuhi, Marihan, Mirzpur, Uttar Pradesh 231210, India.*

[1,4]*Department of Pharmaceutics, Moradabad Educational Trust, Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, 244001, India.*

[2]*Department of Pharmaceutics, BBS College of Pharmacy & Polytechnic, Phaphamau, Prayagraj, Uttar Pradesh, 211013, India.*

[3]*Department of Pharmacology, Shambhunath Institute of Pharmacy, Prayagraj, Uttar Pradesh, 211016, India.*

[5]*Department of Pharmacy, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur, Rajasthan, India.*

Corresponding author*

Mr. Prashant Kumar Gupta

Email: prashant.guptaph@gmail.com

Abstract

The nutraceutical or 'bioceutical' functions as a medical treatment which contains active components that meet established nutritional standards and deliver health benefits and performance advantages and body functions improvements to human users. Nutraceuticals exist between bioactive substances and pharmaceutical products because they provide medical benefits while their harmful effects remain non-existent. The clinic usage of these materials becomes limited because their physical and chemical properties create multiple problems which include their low bioavailability and their environmental instability and their poor water solubility and their instability and their structural breakdown which occurs after they enter the body. The solution to all these issues requires nanotechnology which serves as an effective method to enhance both therapeutic performance and the absorption of nutraceuticals. Nano-scale carriers like liposomes nanoparticles nano-emulsions and nanogels improve the process of encapsulating nutraceuticals while also maintaining product stability and increasing product bioavailability and enabling better cellular absorption and creating specific delivery systems for nutraceuticals. The nanocarriers provide nutraceutical protection from severe processing conditions while they enhance product solubility and extended product circulation time and they deliver nutraceuticals to specific tissue or cell targets. The functionalization of nanocarriers through antibodies peptides aptamers and polysaccharides enables targeted delivery to specific cells or tissues while the stimulus-responsive nanocarriers offer controlled release through pH changes and enzyme activity and thermal effects. The stability and bioavailability of nutraceuticals receive improvements through the application of nanotechnologies. The full potential of nanotechnology for functional food and health applications remains unachievable because scientists need to address safety issues and obtain regulatory approvals while building public trust in the technology and developing methods for producing it at large scales. The use of nanotechnology-based delivery systems has shown that various nutraceuticals can achieve better therapeutic results. Curcumin nanoparticles exhibited superior anti-inflammatory and anticancer properties when compared to free curcumin while resveratrol nanoemulsions showed improved oxidative stability and antioxidant properties. Omega-3 fatty acids present as nanoliposomes exhibit reduced oxidation rates while delivering higher levels of bioactive substances. Probiotic bacteria achieve targeted delivery to the colon through alginate-chitosan nanogel encapsulation which also improves their survival rate. The development of large-scale processing technologies requires optimization to achieve cost-effective results which must maintain their reproducibility while being acceptable to consumers. Interdisciplinary collaboration between food technologists and pharmacologists and nanotechnologists and regulatory authorities needs to resolve all these issues.

Keywords: *Nanotechnology, Nutraceuticals, Targeted delivery, Nanoencapsulation, Bioavailability; Liposomes, Solid lipid nanoparticles, Nanoemulsions, Polymeric nanoparticles, Nanogels, Probiotics, Functional foods, Chronic disease prevention.*

1. INTRODUCTION

The combination of nanotechnology and nutraceuticals has become a cutting-edge field with revolutionary promise in the rapidly changing fields of healthcare and well-being. The health-promoting qualities of nutraceuticals, which are made up of bioactive compounds derived from natural components, have long been acknowledged. However, obstacles including poor transport efficiency, stability problems, and low bioavailability have prevented them from having their full therapeutic potential. The field of nanotechnology, which works with matter at the nanoscale, offers exact answers to these enduring problems. This investigation will explore the complexities of nanoencapsulation, nanoemulsions, and nanoparticle-based delivery systems three important tactics advancing innovation in the field of nutraceutical nanotechnology as we go deeper into this area. We will also explore how personalized nutrition solutions could be made possible by nanotechnology, which could allow interventions to be customized to each person's physiological demands and preferences[1].

1.1 Nutraceuticals

"Nutraceuticals" and "functional foods" serve as two distinct terms that media outlets and academic research papers use to describe the same concept. The term "nutraceutical" is the result of Stephen DeFelice M.D. establishing this word through his work at the Foundation for Innovation in Medicine which he founded in Cranford New Jersey. The product range includes functional foods and isolated nutrients and medicinal foods and fortified foods and dietary supplements. The more accurate description of nutraceuticals includes dietary ingredients and whole foods which provide health benefits through their ability to prevent and treat illnesses. Nutraceuticals include natural substances which consist of vitamins and minerals and fatty acids and phytochemicals which include polyphenols and carotenoids and probiotics and herbal extracts and biotechnological products which encompass both fortified and recombinant foods. The classification system divides items into three categories which include food source and chemical properties and methods of operation. Nutraceuticals serve an essential purpose because they enable people to fulfill their nutritional requirements while providing protective effects against multiple chronic diseases which include heart disease and cancer and diabetes and neurodegenerative diseases and inflammatory disorders. Nutraceuticals exist outside the same strict drug regulations that govern pharmaceuticals yet they provide substantial advantages for both health maintenance and disease prevention. People commonly use the terms dietary supplements and functional foods yet these two categories of products exist as separate types of products. Dietary supplements provide concentrated nutrient sources that people use to enhance their dietary intake while functional foods deliver health benefits beyond standard nutritional value. Scientific evidence establishes nutraceuticals as health-improving substances that offer medical solutions for human health issues.

Nutraceuticals market throughout the world experiences rapid expansion because consumers now choose natural health products which deliver health benefits without showing pharmaceutical side effects. The legal definition of nutraceuticals differs between countries because no single definition exists across all nations. Safety and efficacy together with quality control work as essential components which protect consumers and establish credibility for businesses in the industry. Researchers use nanotechnology to develop drug delivery systems which include liposomes nanoparticles nanosuspensions and polymeric micelles that enhance drug solubility and therapeutic effects and permeability and stability and oral bioavailability. Nutraceuticals particles encounter multiple barriers which prevent them from reaching their designated target site because active medicinal substances face gastrointestinal tract (GIT) absorption issues that stem from their poor solubility. The therapeutic effects of nutraceuticals can be affected by their interactions with chemicals and medications and other nutraceutical products. Nanotechnology provides a solution for addressing both solubility and absorption challenges. The intended biological process becomes more effective through size reduction because smaller molecules present greater surface area. The first step to defeat the barriers involves transforming a nutraceutical molecule into a nanocarrier[2].

1.2 Importance of Nutraceuticals

Nutraceuticals have gained significant importance due to their dual role in providing nutrition along with therapeutic benefits, serving as a preventive and supportive therapy for many chronic and lifestyle-related diseases. Their importance includes:

- **Disease Prevention and Support:** Nutraceuticals show advantages for multiple therapeutic fields which include cardiovascular health through omega-3 fatty acids and diabetes treatment and cancer prevention and digestive system health and immune system support and mental well-being.
- **Safety Profile:** Compared to conventional drugs, nutraceuticals often have fewer side effects, making them a preferable option for long-term health maintenance.
- **Complementary Medicine:** They have become integral to Complementary and Alternative Medicine (CAM), offering natural alternatives or adjuncts to pharmaceutical treatments.
- **Growing Global Demand:** Increasing health awareness worldwide, especially after the COVID-19 pandemic, has surged interest and demand for nutraceuticals as an immune booster and health promoter, despite supply chain challenges.
- **Wide Range of Sources:** Nutraceuticals include macronutrients like omega-3 fatty acids, micronutrients such as vitamins and minerals, and phytochemicals including carotenoids and polyphenols. Functional foods enriched with these compounds can be consumed directly or as supplements.
- **Research and Development Focus:** Nutraceutical research focuses on standardization, clinical validation of efficacy, formulation innovation (including nano-formulations), and safe delivery systems to optimize their health effects[3].

1.3 Challenges in Conventional Nutraceutical Delivery

Challenges in conventional nutraceutical delivery systems are primarily related to the inherent physicochemical properties of nutraceutical compounds and biological barriers in the gastrointestinal tract. These challenges significantly affect their stability, bioavailability, therapeutic efficacy, and commercial viability.

Major Challenges in Conventional Nutraceutical Delivery

1. **Poor Solubility and Low Bioavailability:** Nutraceutical components experience water solubility issues because most bioactive phytochemicals face this problem. The body fails to absorb these compounds because they dissolve poorly in gastrointestinal fluids. The therapeutic concentration that reaches target tissues decreases because of both solubility and permeability restrictions.
2. **Chemical Instability and Degradation:** Nutraceutical compounds show high sensitivity to environmental factors which include light and heat and oxygen and changes in pH. The substances experience oxidation and hydrolysis together with various degradative reactions throughout the stages of processing and storage and digestion. The acidic environment of the stomach together with digestive enzymes breaks down active molecules which results in reduced efficacy and decreased bioavailability.
3. **Low Permeability and Biological Barriers:** The gastrointestinal system creates major biological challenges because it contains three different obstacles which include enzymatic breakdown and mucus defensive layers and restricted absorption through the intestinal lining. The barriers obstruct proper nutra-ceutical delivery which should reach the bloodstream because they interfere with dosage effectiveness.
4. **Poor Flowability and Compressibility in Formulations:** The manufacturing process of nutraceutical powders faces difficulties because their physical characteristics include flowability and compressibility which make it hard to create products. Manufacturing problems occur because poor flow results in irregular product dosing while poor compressibility produces weak tablets which disrupt product quality and customer satisfaction.
5. **High Doses and Swallowability Issues:** Nutraceutical products require major active ingredient doses which force manufacturers to create oversized tablets and capsules that consumers find hard to swallow and unappealing. The established active load requirement presents difficulties which arise when trying to maintain product stability throughout the entire formulation process.

6. **Regulatory and Marketing Hurdles:** The global market faces challenges because standardized regulations do not exist and product labeling shows variations while scientific evidence remains unproven. The issues undermine consumer trust while creating difficulties for businesses who operate across borders because they affect both international trading and marketing operations.
7. **Cost and Complexity of Advanced Delivery Systems:** The nutraceutical industry cannot use new delivery systems because nanoparticles liposomes and nanoemulsions solve standard delivery issues but their expensive price and difficult technical requirements and unclear regulatory status
8. **Chemical and Physical Instability:** Nutraceutical components lose their effectiveness when they are exposed to environmental factors which include heat and light and oxygen and moisture. The storage and usage of antioxidants and vitamins lead to their oxidation which results in the loss of their active strength. The traditional methods of storage do not have protective features. which results in decreased product effectiveness and shorter product lifespan.
9. **Short Biological Half-Life:** Many bioactive nutraceutical compounds have short half-lives in the body due to rapid metabolism and elimination, requiring frequent dosing. Conventional delivery systems do not provide controlled or sustained release, leading to fluctuations in blood levels and suboptimal therapeutic effects[5].

1.4 Role of Nanotechnology in Nutraceutical Sciences

Nanotechnology transforms nutraceutical sciences because it solves multiple problems that traditional nutraceutical delivery methods face while it boosts the healing power of bioactive substances. Nanomaterials exhibit distinct characteristics at the nanoscale which improve the solubility, bioavailability, stability, targeted delivery, and controlled release of nutraceutical ingredients. The Role of Nanotechnology in Nutraceutical Sciences are followings-

1. **Enhanced Solubility and Bioavailability:** The water solubility of many nutraceuticals which include hydrophobic bioactives such as curcumin and omega-3 fatty acids and fat-soluble vitamins prevents their effective absorption. The use of nanotechnology-based delivery systems which include nanoparticles and nanoemulsions and nanoliposomes allows these compounds to achieve higher aqueous solubility which leads to better bioavailability. The body can absorb it more effectively through the gastrointestinal tract which leads to greater treatment effectiveness.
2. **Protection Against Degradation:** Nutraceuticals are prone to degradation due to exposure to oxygen, light, heat, and the acidic environment of the stomach. Nanoencapsulation techniques protect sensitive bioactives from chemical and enzymatic degradation by encapsulating them in protective nanocarriers like liposomes and solid lipid nanoparticles, thereby improving stability and shelf-life[6].
3. **Targeted Delivery and Controlled Release:** Researchers can develop nanocarriers which deliver targeted medicines to particular body tissues and cell types in order to improve the therapeutic effects of nutraceuticals. The stimuli-responsive nanocarriers enable controlled release and extended release of their active ingredients which helps to determine proper dosage while minimizing adverse effects. Traditional nutraceutical formulations lack this advantage because they cannot deliver precise active ingredient doses.
4. **Improved Bio-interactions and Cellular Uptake:** Nanoparticles have a high surface area to volume ratio, facilitating stronger interactions with biological membranes, thereby promoting efficient cellular uptake of encapsulated nutraceuticals. Enhanced transport across biological barriers increases the bioefficacy of nutraceutical compounds[7].
5. **Novel Nanoformulations:** Several nanoformulation platforms are employed, including:
    - Nanoliposomes and liposomes: For encapsulation of vitamins, enzymes, and peptides.
    - Nanoemulsions: For improving solubility and stability of oils and lipophilic compounds.
    - Nanosuspensions: Enhancing dissolution rate of poorly soluble nutraceuticals.
    - Polymeric nanoparticles, dendrimers, and nanohydrogels: Providing controlled release and protection.

6. **Applications Beyond Delivery:** Nanotechnology also enables immobilization of enzymes and bioactives in food and feed processing, biosensor development, and novel packaging solutions that improve food quality and safety, thereby expanding the scope of nutraceutical sciences[8].
7. **Versatile Formulation Flexibility:** Nanotechnology enables the incorporation of nutraceuticals into diverse food matrices, beverages, and supplements without altering sensory attributes, texture, or stability.
8. **Multifunctional Delivery Systems:** Nanoformulations can co-deliver multiple nutraceutical compounds or combine nutraceuticals with conventional drugs for synergistic effects.
9. **Enhanced Stability in Formulation:** Nano-based delivery systems improve the physicochemical stability of formulations, reducing batch-to-batch variability and enhancing shelf life.
10. **Reduced Dosage and Side Effects:** Improved bioavailability and targeted delivery reduce the required dosage of nutraceuticals, lowering the risk of adverse effects and enhancing safety profiles.
11. **Nano-biosensors for Quality Control:** Nanotechnology-based biosensors enable real-time monitoring of nutraceutical quality and detect contamination or degradation.
12. **Improved Manufacturing Efficiency:** Nanoparticles allow precise control of ingredient distribution, reducing wastage and enabling efficient large-scale production[9].
13. **Potential for Personalization:** Nanocarriers can be functionalized for responsive or personalized delivery in nutraceuticals, adapting release based on physiological conditions like pH or enzyme presence.
14. **Enhancing Nutraceutical Functionality in Food:** Nanotechnology enhances textural, flavor, and sensory properties of functional foods fortified with nutraceutical ingredients without compromising food quality[10].

2. FUNDAMENTALS OF NANOTECHNOLOGY IN NUTRACEUTICAL DELIVERY

Nanotechnology in nutraceutical delivery uses nanosized carriers which range from 1 to 1000 nanometers for improving bioactive compound stability and solubility and absorption. Many nutraceuticals such as curcumin and resveratrol and omega-3 fatty acids have poor bioavailability because their gastrointestinal tract stability prevents their absorption through gastrointestinal tract walls[11]. The conversion of these compounds into nanoparticles and liposomes and nanoemulsions and nanocapsules increases their surface area which leads to better dissolution and absorption. The use of nanotechnology enables the protection of sensitive ingredients from degradation which results from exposure to light and oxygen and digestive enzymes. The body receives nutrients through controlled and sustained release systems which maintain a continuous supply of nutrients over an extended time period[12]. The process of surface modification enables nanocarriers to deliver their contents to designated body areas which enhances their delivery results while decreasing their negative effects. Nanotechnology serves as the foundation for nutraceutical delivery systems which use nanoscale formulations to improve solubility and provide protective measures and enable controlled release and targeted absorption. The approach enhances nutraceutical bioavailability which increases their therapeutic effects thus resulting in greater health benefits[13].

2.1 Principles of Nanoencapsulation

Nanoencapsulation serves as a contemporary method which enables the protection of active substances through the application of protective nanometer-sized coatings that enclose materials such as drugs and vitamins and enzymes and nutraceuticals. The process of nanoencapsulation creates particles that exist within the nanometer range (1–1000 nm) because it produces a core material which contains the active ingredient that is enclosed by a protective shell made of polymers and lipids and other appropriate materials. The process enables protection of the active substance because it prevents degradation while maintaining stability and controlling release and improving absorption and bioavailability of the substance[14]. Nanoencapsulation utilizes a core–shell structure as its fundamental architecture. The core contains the bioactive substance, while the shell acts as a barrier against environmental factors such as

heat, light, oxygen, or pH changes. The method of coating material selection together with the applied method determines two essential properties of the process which include encapsulation efficiency and release properties. Researchers typically use natural and synthetic polymers which include chitosan and alginate and PLGA together with lipid-based materials that contain phospholipids and waxes as coating materials[15] The second fundamental principle of the system requires a process which reduces particles to their smallest size while maintaining their structural integrity. The process of reducing particles into nanoscale dimensions leads to an increased surface area which enhances their capacity to interact with biological membranes. Formulators frequently use stabilizers or surfactants during the formulation process because these substances help to stop aggregation while sustaining nanoparticles distribution across various sizes. The system establishes standard performance levels which enhance how well the encapsulated compounds work in their bioavailability to the body[16].

Nanoencapsulation works through its method of effective drug delivery which enables the timed release of its active ingredient through its protective coating that controls its dispensing. The coating properties determine three different release methods which include diffusion and erosion and swelling. The system maintains bioactive compound delivery at constant levels which decreases the need for medication and enhances treatment results. Protection and targeted delivery stand as essential elements of the system. Through its encapsulating layer the system protects delicate bioactive molecules from losing potency during storage and their journey through the gastrointestinal system. The process of surface modification allows nanocarriers to obtain specific ligands or functional groups which they use to reach designated cells or tissues while decreasing side effects and boosting treatment efficiency.

The active ingredient that scientists want to contain within the nanocarrier system will decide the scientists actual material preparation method through which they create the active compound which they will use to build wall material for their system. The system achieves high encapsulation efficiency because it protects valuable components from loss while delivering enhanced product performance.

2.2 Mechanisms of Improved Bioavailability

Nanotechnology serves as a powerful method which increases the bioavailability of nutraceuticals that face challenges with poor solubility and unstable nature and restricted absorption capacity. Bioactive compounds such as curcumin and resveratrol and coenzyme Q10 and omega-3 fatty acids show low bioavailability when taken in their standard forms. The formulation of these compounds into nanoscale systems results in improved absorption and stability and therapeutic effectiveness through multiple mechanisms. One of the primary mechanisms is the increase in solubility and dissolution rate[19]. Reducing the particle size of bioactive compounds to the nanometer scale greatly increases their surface area, which results in accelerated dissolution rates that occur during gastrointestinal fluid contact. The improved dissolution process enables enhanced absorption through biological membranes. Nanocarriers function as intestinal wall permeability enhancers because they establish direct contact with cell membranes. They use transcellular pathways or paracellular pathways or endocytosis through intestinal epithelial cells and M-cells to enter the body, which leads to enhanced entry into the bloodstream system[20]. The protection of nutraceuticals from gastrointestinal tract degradation constitutes an additional vital mechanism. Acidic pH and enzymes and light and oxygen exposure make many compounds lose their activity before people can absorb them. The process of nanoencapsulation creates a protective shield which prevents the molecules from damaging effects to their original state until they reach body absorption points. The development of nanocarriers enables scientists to create systems which deliver bioactive compounds at controlled rates, achieving optimal blood concentration levels for extended periods. The application of nanotechnology improves the ability of substances to be absorbed by the body through their distribution via the lymphatic system[21]. Lipid-based nanocarriers, which include liposomes and nanoemulsions, assist the body in absorbing substances through the intestinal lymphatic system, which allows these substances to avoid first-pass hepatic metabolism. The mechanism increases systemic circulation because it delivers a greater quantity of active compound into the bloodstream. The intestinal mucosa can be targeted by mucoadhesive nanoparticles which use chitosan as their main material, which extends their presence on the intestinal surface and boosts absorption能力

[22]. The combination of targeted delivery systems with cellular uptake capabilities results in better bioavailability. The process of surface modification enables nanoparticles to use specific ligands for binding to intestinal or tissue cell receptors, which directs their absorption to specific absorption sites. Their tiny size at the nanoscale level combined with their specific surface characteristics enables cells to perform endocytosis, which accomplishes successful delivery of nutrients and bioactive substances to the inside of cells[23].

2.3 Targeted and Controlled Release Strategies

The delivery systems which use nanotechnology in their modern form require both targeted release methods and controlled release methods as their main operating systems for delivering pharmaceutical and nutraceutical products. The purpose of these methods is to deliver the active compound exactly when and where it needs to be delivered in the necessary amount because this approach helps maximize therapeutic effectiveness while reducing side effects and waste materials. Controlled release refers to the ability of a delivery system to release the encapsulated bioactive compound gradually over a specific period. The system accomplishes this function through the implementation of polymers and lipids together with other coating materials which control the speed at which the encapsulated compound moves through the system or breaks down. Controlled release systems maintain a steady concentration of the active ingredient in the bloodstream, reducing the need for frequent dosing and enhancing patient compliance. The release mechanisms may include diffusion-controlled, erosion-controlled, or stimuli-responsive release, which uses external factors such as pH or temperature or enzymes to start active substance release. Targeted release method delivers active substances to designated body locations which include specific tissues. The active ingredient targets specific locations in the body which helps to reduce its impact on surrounding non-targeted regions. The process of targeting involves two methods which include passive targeting that occurs when nanoparticles build up in specific tissues because of their two fundamental characteristics and active targeting which requires ligands to bind with their respective cell receptors through antibodies and peptides and sugars that scientists attach to nanocarriers. The delivery of nutraceuticals becomes more effective through these methods which improve how bioactive compounds like curcumin and coenzyme Q10 and omega-3 fatty acids are retained and absorbed and used in the body. The digestion process of polymeric nanoparticles and liposomes allows them to distribute nutrients through their ability to release nutrients both gradually over a period and at designated points in the body such as the intestine and liver for maximum effectiveness24.

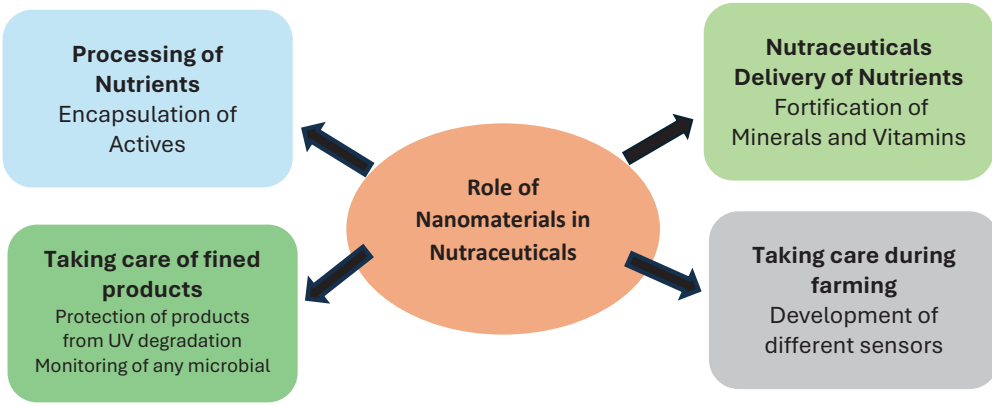

Fig 1: Fundamentals of Nanotechnology in Nutraceutical Delivery

3. TYPES OF NANOCARRIERS FOR NUTRACEUTICAL

Nanocarrier systems represent advanced delivery mechanisms which improve the stability and bioactive availability of nutraceuticals while providing controlled release. The tiny carriers establish protection for delicate bioactive materials which boosts their body absorption. The following document presents various nanocarrier types which researchers use to deliver nutraceuticals according to source [25].

3.1 Polymeric Nanoparticles (PNPs)

The biocompatibility and adjustable structure and sustained release capability and protective function for delicate bioactive substances make polymeric nanoparticles (PNPs) the most common option for transporting nutraceuticals. The particles with a size range of 10 to 1000 nanometers are designed to trap three different types of nutraceuticals which include hydrophilic and hydrophobic and amphiphilic substances. Polymeric nanoparticles are colloidal carriers made from natural or synthetic polymers. The systems can exist as two different types which include matrix type nanospheres and reservoir type nanocapsules.

- **Nanospheres** consist of a matrix structure in which the active ingredient is uniformly dispersed.
- **Nanocapsules** have a core–shell structure where the core contains the active, surrounded by a polymeric shell.

Advantages

- Enhanced protection of sensitive nutraceuticals from degradation and premature metabolism, extending bioactivity.
- Controlled and sustained release profiles reduce dosing frequency and improve therapeutic efficacy.
- High encapsulation efficiency for both hydrophilic and hydrophobic nutraceuticals due to polymer versatility.
- Surface functionalization allows targeted delivery, improving site-specific accumulation and reducing side effects.
- Biocompatibility and biodegradability of polymers make these systems safe for human consumption.
- Flexibility in formulation methods and polymer types enables tailoring to specific nutraceutical delivery requirements.

Disadvantages

- Potential cytotoxicity and immunogenicity depending on polymer type, degradation products, and residual solvents.
- Challenges in large-scale reproducible manufacturing with controlled particle size and distribution.
- Premature release or burst effect of nutraceuticals may reduce effectiveness.
- Stability issues affected by polymer degradation and environmental conditions during storage
- Complex regulatory approval paths due to novel formulation and safety concerns[26].

Applications of Polymeric Nanoparticles in Nutraceuticals

- Delivery of lipophilic vitamins (A, D, E, K), antioxidants (curcumin, resveratrol), and polyphenols with enhanced bioavailability and stability.
- Targeted delivery systems for nutraceuticals in cancer prevention and metabolic disorders, utilizing surface modifications.
- Oral, transdermal, and intravenous nutraceutical delivery benefiting from controlled release and improved absorption.
- Functional food fortification by embedding polymer nanoparticles to improve solubility and protect bioactives during food processing.
- Polymeric nanoparticles as adjuvants in dietary supplements for immune modulation and antioxidant support[27].

3.2 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are one of the most promising nanocarrier systems in food, nutraceuticals, and pharmaceuticals. They are submicron colloidal carriers with sizes typically ranging between 50–1000 nm**,** composed of biocompatible lipids that remain solid at room and body temperature**.** SLNs were introduced in the 1990s as an alternative to polymeric nanoparticles and emulsions**,** offering benefits such as high stability, controlled release, and low toxicity. Key Features of SLNs are-

- Matrix lipid particles that can encapsulate both hydrophilic and lipophilic nutraceuticals within a solid lipid matrix.
- Protect bioactive compounds from degradation due to environmental stresses like pH or enzymatic actions.
- Controlled and sustained release profiles depending on lipid matrix composition and drug location inside the matrix.
- Enhance oral bioavailability by improving solubility and absorption of poorly soluble nutraceuticals.
- Biocompatible, biodegradable, and non-toxic, suitable for large-scale production.
- The solid crystalline nature allows stability but may cause drug expulsion during storage.

Structure and Composition: SLNs consist of-

- **Core:** A solid lipid matrix that encapsulates the nutraceutical. **Common solid lipids are** Glyceryl monostearate, Stearic acid, Cetyl palmitate, Glyceryl behenate (Compritol), Glyceryl palmitostearate (Precirol)
- **Surfactants: It** used to stabilize the lipid nanoparticles and prevent aggregation. **E.g.** Tween 80 (polysorbate 80), Poloxamers, Lecithin (natural phospholipid), Sodium cholate.

Advantages

- Enhanced chemical stability and protection of sensitive nutraceutical compounds from degradation during storage and administration.
- Controlled and sustained release profiles that improve therapeutic efficacy and reduce dosing frequency.
- High biocompatibility and biodegradability owing to the use of physiological lipids, minimizing toxicity and immune reactions.
- Potentially improved oral bioavailability due to enhanced absorption and lymphatic uptake.
- Industrial scalability with relatively simple processes such as high-pressure homogenization and ultrasonication.
- Ability to incorporate both hydrophilic and lipophilic active compounds.

Disadvantages

- Low drug loading capacity caused by the highly ordered crystalline structure of solid lipids may limit therapeutic dose delivery.
- Drug expulsion during storage because of polymorphic transitions and lipid crystallization altering the structure.
- Initial burst release phenomena for some formulations affecting controlled delivery.
- Limited capacity for loading highly water-soluble nutraceuticals due to lipid solubility constraints.
- Potential issues related to nanoparticle aggregation, gelation during storage, and changes in particle size[28].

Applications of Solid Lipid Nanoparticles in Nutraceuticals

- Oral delivery of antioxidant nutraceuticals such as curcumin, resveratrol, and vitamins to improve solubility, stability, and bioavailability.
- Formulations for lipid-based dietary supplements and functional foods with enhanced nutrient uptake.
- Topical and transdermal delivery of nutraceutical agents providing controlled release and improved skin penetration.
- Vehicle for combination nutraceutical therapies targeting inflammation, cancer prevention, and metabolic health.
- Encapsulation of natural oils and bioactive plant extracts in SLNs to improve antioxidant and anti-inflammatory properties[29].

3.3 Nanostructured Lipid Carriers (NLCs)

The development of Nanostructured Lipid Carriers (NLCs) as the second generation of lipid-based nanocarriers emerged from the need to solve Solid Lipid Nanoparticles (SLNs) problems which occur because they can only deliver a small amount of medication while they also lose their active ingredients during

storage. NLCs consist of a mixture of solid and liquid lipids which create an imperfect crystalline matrix that provides both increased loading capacity and enhanced stability. The main applications of this technology involve using it to deliver lipophilic nutraceuticals which include carotenoids and polyphenols and vitamins and essential oils. NLCs function as submicron colloidal carriers that maintain particle sizes between 40 and 1000 nanometers.

Types of Nanostructured Lipid Carriers: While NLCs are primarily classified by their lipid composition, their structure and formulation techniques can vary:

- **Imperfect Type:** It contains a mixture of solid and liquid lipids creating imperfections in the lipid matrix to enhance drug loading.
- **Amorphous Type:** It formulated to avoid crystallization entirely, maintaining an amorphous lipid matrix.
- **Multiple Type:** It contains small oil nanocompartments within the solid lipid, further enhancing solubility and stability.

Components of NLCs

- **Solid Lipids:** It remain solid at room and body temperature. Examples: Glyceryl monostearate, Compritol® 888 ATO (glyceryl behenate), Precirol® ATO 5 (glyceryl palmitostearate), Stearic acid, Cetyl palmitate
- **Liquid Lipids (Oils): It** provide structural imperfections in the lipid matrix. Examples: Medium-chain triglycerides (MCT), Oleic acid, Miglyol®, Vegetable oils (olive, sunflower, coconut oil)
- **Surfactants: It** stabilize nanoparticles. Examples: Poloxamers, Tween 20/80, Lecithin, Sodium cholate.

Advantages

- **High Drug Loading Capacity:** Imperfect lipid matrix provides more space for encapsulation compared to SLNs.
- **Improved Stability:** Reduced drug expulsion during storage due to less ordered lipid crystallinity.
- **Controlled and Sustained Release:** Enables prolonged action and better bioavailability of nutraceuticals.
- **Biocompatibility and Biodegradability:** Uses physiological lipids minimizing toxicity and immune responses.
- **Enhanced Oral Bioavailability:** Protects sensitive nutraceuticals from gastrointestinal degradation and improves absorption.
- **Scalable Production:** Simple preparation methods suitable for commercial scale-up.

Disadvantages

- **Potential Surfactant Toxicity:** Some surfactants may cause irritation or cytotoxicity in sensitive applications.
- **Physical Stability Issues:** Though improved over SLNs, lipid nanoparticle systems can still face aggregation or change in size distribution over time.
- **Limited Encapsulation to Lipophilic Compounds:** Primarily suitable for hydrophobic nutraceuticals; hydrophilic compound encapsulation may require additional modification.

Applications

- Delivery of antioxidants, vitamins, polyphenols, and carotenoids with poor water solubility to improve bioavailability.
- Protection of sensitive compounds (e.g., curcumin, resveratrol) from degradation during storage and in the gastrointestinal tract.
- Enhanced targeting and controlled release for functional food ingredients and dietary supplements.
- Use in cosmetic formulations for skin delivery of nutraceuticals with antioxidant and anti-aging properties.
- Suitable for oral, topical, and parenteral routes depending on formulation[30]

3.4 Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers encapsulating an aqueous core. They can carry both hydrophilic substances (in their aqueous interior) and lipophilic substances (within the lipid bilayer). Typically, liposomes have sizes ranging from 50 to 500 nm and are biocompatible, biodegradable, and non-toxic[31,32].

Structural Types of Liposomes

- **Small Unilamellar Vesicles (SUVs):** Size: They have a size range of 30–100 nm, consist of a single lipid bilayer, and provide high encapsulation efficiency for hydrophobic nutraceuticals.
- **Large Unilamellar Vesicles (LUVs):** They have a size range of 100–1000 nm and provide high encapsulation efficiency for hydrophilic molecules.
- **Multilamellar Vesicles (MLVs):** These structures contain multiple concentric lipid bilayers, which provide higher stability but result in lower encapsulation efficiency.
- **Multivesicular Vesicles (MVVs):** They have internal compartments containing many vesicles and are used for sustained release.

Components of Liposomes

- **Phospholipids:** Primary structural components. Examples: Phosphatidylcholine, Phosphatidylethanolamine, Sphingomyelin, Lecithin (soy or egg derived)

- **Cholesterol:** Increases membrane rigidity, Improves stability
- **Surface Modifiers:** PEGylation agents (increase circulation time), Charged lipids (e.g., DMPG, stearylamine.

Advantages

- Liposomes enhance bioavailability and absorption of poorly soluble nutrients due to their ability to encapsulate both hydrophilic and hydrophobic compounds.
- They protect encapsulated bioactives from degradation in the gastrointestinal tract and improve stability during storage.
- Liposomal delivery offers non-invasive administration, improved intracellular delivery, and reduced adverse effects.
- Surface modifications enable targeted delivery and extend systemic circulation, optimizing therapeutic outcomes.
- Flexible composition and simple preparation methods facilitate encapsulation of complex botanical extracts and single compounds[33].

Disadvantages

- High production costs and complex manufacturing processes can limit widespread use.
- Liposomes are prone to leakage, fusion, and oxidation, potentially reducing stability and encapsulation efficiency.
- Short half-life in biological systems unless specially modified (e.g., PEGylation).
- Possible immune system recognition and clearance by macrophages, leading to altered biodistribution.
- Limited shelf life and sensitivity to physical stress such as temperature fluctuations[34].

Applications of Liposomes in Nutraceuticals

- Delivery of vitamins (e.g., vitamin C, D, E), antioxidants (e.g., curcumin, CoQ10), and other bioactives with increased bioavailability and efficacy.
- Encapsulation of complex botanical extracts for enhanced stability and controlled release in functional food and supplement industries.
- Targeted delivery systems for nutraceuticals in disease prevention and health promotion.
- It uses in cosmeceuticals and topical formulations for enhanced skin penetration and efficacy of nutraceuticals.
- Development of liposomal dietary supplements improving patient compliance due to reduced dosing frequency and side effects[35].

3.5 Niosomes

The development of Nanostructured Lipid Carriers (NLCs) as the second generation of lipid-based nanocarriers emerges from the need to address Solid Lipid Nanoparticles (SLNs) challenges which include their limited ability to carry drugs and their tendency to lose nutraceuticals during storage. NLCs consist of a mixture of solid and liquid lipids which create an imperfect crystalline matrix that provides both increased loading capacity and enhanced stability. The main applications of this technology involve using it to deliver lipophilic nutraceuticals which include carotenoids and polyphenols and vitamins and essential oils. NLCs function as submicron colloidal carriers that maintain particle sizes between 40 and 1000 nanometers.

Types of Niosomes: Niosomes vary based on size, vesicle lamellarity, and preparation method.

- **Small Unilamellar Vesicles (SUVs):** SUVs are nanosized vesicles (10–100 nm) containing a single lipid bilayer. The vesicles demonstrate excellent surface area properties which enable them to effectively contain hydrophobic nutraceuticals that boost absorption.
- **Large Unilamellar Vesicles (LUVs):** LUVs show a size range of 100 to 500 nanometers which enables them to contain greater amounts of aqueous solution that hydrates with substances such as ascorbic acid and polyphenol.
- **Multilamellar Vesicles (MLVs):** MLVs consist of multiple concentric bilayers which develop both structural stability and controlled release features.
- **Proniosomes:** Proniosomes function as dry powders which flow freely until they transform into niosomes through water contact. The product provides better storage and transportation capabilities for nutraceuticals because its shelf-life requirements are critical.
- **Components of Niosomes:** Niosomes are composed of three primary components:
- **Non-Ionic Surfactants:** Non-Ionic Surfactants Non-ionic surfactants create the main structural components which build niosomal bilayers. The Span series which includes Span 20 Span 40 Span 60 Span 80 and Tween series which includes Tween 20 Tween 60 Tween 80 and Brij series are common examples. The vesicle stability increases when surfactants have higher phase transition temperatures according to their higher temperature required for transition from solid state to liquid state.
- **Cholesterol:** Cholesterol inserts itself between surfactant molecules which creates a barrier that protects membrane structure while decreasing material loss.
- **Charge Inducers:** Charge Inducers The vesicles stay stable through charge induction because charged molecules like directly phosphate which carries a negative charge and stearylamine which has a positive charge stop the particles from coming together.

Advantages

- Improved bioavailability and enhanced absorption of nutraceuticals due to protection from degradation and controlled release.

- Biodegradable, biocompatible, and non-immunogenic, which makes them safe for human consumption.
- Higher stability than liposomes during storage, allowing for longer shelf life.
- Ability to encapsulate both hydrophilic and lipophilic nutraceuticals in the aqueous core or lipid bilayer respectively.
- Site-specific delivery reducing systemic side effects and improving therapeutic efficacy.
- Niosomes allow for sustained or targeted delivery of nutraceuticals, improving the therapeutic response.

Disadvantages

- Physical instability issues such as aggregation, fusion, and leakage of the encapsulated bioactive molecules can occur over time.
- Preparation can be technically demanding, requiring specialized equipment such as sonicators or extruders, which may increase manufacturing costs.
- Relatively low drug loading capacity for certain compounds, potentially necessitating higher doses or repeated administration.
- Potential hydrolysis of encapsulated compounds limits shelf life if not properly stabilized.

Applications

- Niosomes protect nutraceuticals from degradation in the digestive system, improving oral bioavailability and efficacy of compounds like antioxidants, vitamins, and herbal extracts.
- Niosomal encapsulation enhances the stability and release of bioactive food components, enabling fortified foods and drinks with improved health benefits.
- It used for delivery of herbal bioactive compounds in skin care products, enhancing penetration and stability.
- It facilitates controlled release and stability of plant-based bioactive compounds for disease management and crop protection.
- Besides nutraceuticals, niosomes are used for delivering anticancer, anti-inflammatory, and antimicrobial agents, showcasing their versatility.
- Essential oils, known for their antioxidant and antimicrobial activity, often degrade rapidly. Encapsulating oils such as clove, cinnamon, and ginger in niosomes enhances stability and functional activity in food systems.
- Niosomes protect probiotic bacteria from gastric acid, enhancing survival and colonization in the intestine-important for gut health nutraceuticals.
- Niosome-encapsulated herbal nutraceuticals (e.g., berberine, green tea extract) show enhanced metabolic benefits due to better absorption[36].

3.6 Nanoemulsions

Nanoemulsions have become the leading nanocarrier system for nutraceutical delivery because of their ability to maintain stability and their transparent appearance and their enhanced bioavailability and their compatibility with multiple food products. The system operates effectively to transport lipophilic nutraceuticals which include polyphenols carotenoids essential oils vitamins and bioactive lipids.

The thermodynamically unstable nanoemulsion system exists as a stable colloidal dispersion that contains two immiscible liquids which are oil and water and their surfactant stabilization system creates droplets that measure 20 to 200 nanometers. The system can be developed into two different formulations which are oil-in-water O/W and water-in-oil W/O based on the ratio between its dispersed phase and continuous phase. The system operates as a nutraceutical delivery system because it uses nanoemulsions which provide high optical clarity and low viscosity and better digestibility.

Types of Nanoemulsions: Nanoemulsions can be broadly classified based on **droplet structure, composition, and method of preparation.**

- **Oil-in-Water (O/W) Nanoemulsions:** O/W nanoemulsions consist of **oil droplets dispersed in a continuous aqueous phase**, stabilized by surfactants. These are the most widely used systems for nutraceuticals due to better compatibility with beverage and aqueous food products. They are commonly used for hydrophobic nutraceuticals such as curcumin, lycopene, and vitamin E.
- **Water-in-Oil (W/O) Nanoemulsions:** W/O nanoemulsions, **water droplets are dispersed in a continuous oil phase**. These systems are suitable for delivering **water-soluble nutraceuticals** in lipid-rich food formulations. W/O nanoemulsions can protect hydrophilic bioactives from degradation in aqueous environments.
- **Bi-continuous Nanoemulsions:** Bi-continuous nanoemulsions exhibit **interconnected oil and water networks**, stabilized by high concentrations of surfactants. They occur near the phase-inversion composition and are useful for encapsulating both hydrophilic and lipophilic nutraceuticals simultaneously.
- **Spontaneous Nanoemulsions (Self-emulsifying Systems):** Spontaneous or self-emulsifying nanoemulsions (SEDDS, SNEDDS) are formed upon dilution in aqueous media without high-energy processing. These systems are widely used in oral nutraceutical formulations due to their superior bioavailability enhancement, particularly for lipophilic compounds[37].

Advantages of Nanoemulsions

- They markedly improve the solubility and oral bioavailability of poorly water-soluble nutraceutical compounds, enabling enhanced therapeutic efficacy at reduced dosages.

- Nanoemulsions provide high kinetic stability against gravitational separation, aggregation, and coalescence, which extends the shelf life and maintains the functional integrity of bioactive compounds.
- Their small droplet size leads to optical clarity and improved texture, which is beneficial in beverage and functional food formulations.
- Nanoemulsions enable controlled and targeted delivery of nutraceuticals, minimizing side effects and improving patient compliance.
- They use relatively safe and biocompatible ingredients, making them suitable for nutraceutical and food applications.

Disadvantages of Nanoemulsions

- Production often involves high energy consumption and requires specialized equipment such as high-pressure homogenizers or ultrasonicators, increasing manufacturing costs.
- The requirement for high concentrations of surfactants and cosurfactants can pose toxicity concerns and affect product acceptability.
- Nanoemulsion systems have limited solubilizing capacity for certain high-melting or large molecular weight bioactives.
- Stability can be affected by environmental factors such as temperature, pH, and ionic strength, necessitating careful formulation and storage conditions.
- A limited understanding of long-term bio-distribution and potential toxicity of nanoemulsions still restricts wider regulatory acceptance.

Applications of Nanoemulsions in Nutraceuticals

- **Oral Nutraceutical Formulations:** Nanoemulsions are used to deliver lipophilic vitamins (A, D, E, K), essential fatty acids, antioxidants, and polyphenols, enhancing their absorption in the gastrointestinal tract.
- **Functional Foods and Beverages:** They improve the stability and bioavailability of bioactive compounds in fortified drinks, dairy products, and dietary supplements.
- **Cosmetic and Topical Applications:** Nanoemulsions facilitate enhanced skin penetration and sustained release of antioxidants and herbal extracts in skincare formulations.
- **Food Packaging:** Nanoemulsions are used as edible coatings or antimicrobial agents to increase the shelf life and safety of food products.
- **Pharmaceutical Nutraceutical Hybrids:** Beyond food, nanoemulsions are applied for delivering natural drugs with improved pharmacokinetics in medical nutraceuticals [38].

3.7 Microemulsions

Microemulsions have become an important class of nanocarrier systems for improvingthe delivery and solubility and stability and bioavailability of nutraceuticals. The material exhibits distinctive physicochemical characteristics which enable it to achieve thermodynamic stability and optical transparency and maintain extremely low interfacial tension properties that permit the solution of hydrophilic and hydrophobic bioactive substances. Microemulsions offer better solubility than traditional emulsions which enables their use in different functional food products and nutraceutical products. Microemulsions exist as thermodynamically stable dispersions which maintain optical transparency and isotropic properties through their composition of oil, water, surfactant and co-surfactant that creates droplets within a 10 to 100 nanometer dimension range. Microemulsions create themselves through a natural process because their interfacial tension reaches extremely low levels which eliminates the need for energizing processing methods. Their ability to dissolve nutraceuticals with poor water solubility makes them effective delivery systems for food products and pharmaceutical products and nutraceutical products.

Types of Microemulsions: Microemulsions exhibit distinct structural types depending on their internal phase composition and surfactant characteristics[39].

- **Oil-in-Water (O/W) Microemulsions:** O/W microemulsions consist of **oil droplets dispersed in a continuous aqueous phase**. These systems are widely used for solubilizing hydrophobic nutraceuticals such as carotenoids, curcumin, and vitamin E. O/W systems are compatible with aqueous food and beverage formulations.
- **Water-in-Oil (W/O) Microemulsions:** W/O microemulsions involve **water droplets dispersed within an oil-continuous phase.** These systems are ideal for protecting water-soluble nutraceuticals from hydrolysis or degradation in aqueous environments.
- **Bicontinuous Microemulsions:** Bicontinuous microemulsions form interconnected oil and water channels stabilized by a surfactant film. These structures allow simultaneous solubilization of both hydrophilic and hydrophobic nutraceuticals, supporting multifunctional delivery applications.
- **Multiple Microemulsions:** These are complex systems such as W/O/W or O/W/O microemulsions. They are used for **controlled or sustained release applications**, though they are more difficult to stabilize.

Advantages of Microemulsions[40]

- Microemulsions improve the solubility and bioavailability of poorly water-soluble nutraceuticals, enhancing absorption and therapeutic effects.
- They form spontaneously without the need for high-energy processes, simplifying manufacturing and scale-up.
- Thermodynamically stable with long shelf life, microemulsions protect encapsulated nutraceuticals from degradation and promote sustained release.

- Their small droplet size and low surface tension facilitate enhanced penetration across biological barriers, ideal for oral, topical, and transdermal delivery.
- It can be tailored for targeted delivery, reducing systemic side effects and increasing efficacy.

3.8 Protein Based Nanocarrier [41]

Scientists have found that protein-based nanocarriers function as effective delivery systems for nutraceuticals because they possess biocompatible and biodegradable and non-toxic and highly functional properties. The proteins whey protein and casein and gelatin and soy protein and zein display natural emulsifying and gelling and binding capabilities which allow them to efficiently encapsulate and safeguard bioactive substances. The nanocarriers enhance hydrophobic nutraceuticals' solubility and stability and ability to reach specific targets and their overall bioavailability which includes curcumin and carotenoids and polyphenols and omega-3 fatty acids. The protein-based nanocarriers function as delivery systems with nano-sized dimensions between 10 and 300 nanometers which use either natural or artificial proteins to create a system that protects nutraceuticals through encapsulation and binding and controlled release. The nanocarriers use protein–ligand interactions together with hydrophobic binding pockets and charged regions and self-assembly capabilities to achieve stabilization of both hydrophilic and lipophilic bioactive substances.

Advantages

- Proteins provide excellent biocompatibility, biodegradability, and low toxicity, making them safe for oral or parenteral nutraceutical delivery.
- High binding capacity and ability to form diverse nanostructures allow stable encapsulation of various bioactive molecules, including polyphenols and vitamins.
- Ability to modify surface properties enables targeted delivery and prolonged circulation times, improving bioavailability and therapeutic efficacy.
- Protein nanocarriers facilitate protection of sensitive nutraceuticals from degradation during processing and in vivo, improving stability.
- Preparation methods are versatile, including desolvation, emulsification, coacervation, nanoprecipitation and electrospraying, enabling scalable manufacturing.

Disadvantages

- Protein nanocarriers may face batch-to-batch variability arising from natural protein sources affecting reproducibility.
- Possible immunogenicity or allergenicity, especially if not purified or modified adequately (e.g., sericin in silk fibroin).
- Slow degradation rates for some protein nanostructures may delay clearance from the body, posing safety concerns.

- Relatively complex preparation and stabilization steps are necessary to maintain nanoscale size and protein functionality.
- Protein corona formation around nanocarriers in biological fluids can alter biodistribution and cellular uptake unpredictably.

Applications of Protein Nanocarriers in Nutraceuticals

- Effective delivery of plant polyphenols, antioxidants, vitamins, and peptides to improve solubility, stability, and bioavailability in oral nutraceutical formulations.
- Targeted delivery systems for cancer-related nutraceuticals using protein nanocages like ferritin to exploit receptor-mediated endocytosis.
- Protein nanocarriers as vehicles for transdermal delivery of herbal extracts and phytochemicals improving skin penetration and efficacy.
- It uses in fortification of functional foods and beverages by protecting sensitive nutraceutical compounds during processing and digestion.
- Protein-based nanosystems for controlled and sustained release formulations tailored for personalized nutrition and therapy.

3.9 Polysaccharide Based Nanocarrier[42]

Polysaccharide-based nanocarriers have emerged as highly promising systems for delivering nutraceuticals because they possess biocompatibility and biodegradability and renewable nature and functional versatility. Researchers use polysaccharides including chitosan and alginate and pectin and starch and cellulose derivatives and dextran and gums to create nano-delivery systems which enhance bioactive compounds through improved solubility and stability and controlled release and mucoadhesion and targeted delivery. The materials create effective encapsulation solutions because they use hydrogen bonding and electrostatic forces and hydrophobic interactions to interact with phytochemicals and polyphenols and vitamins and sensitive bioactives.

Polysaccharide-based nanocarriers are nano-sized delivery systems (10–500 nm) prepared from natural polysaccharides or their derivatives to encapsulate nutraceuticals and enhance their bioavailability and stability and controlled release. The nanocarriers use polysaccharide structural diversity to create performance-enhancing nanoparticles and nanogels and nanofibers and nano-complexes which improve nutraceutical ingredient functionality.

Types of Polysaccharide Nanocarriers

Polysaccharide nanocarriers include various forms based on structural and functional characteristics:

- **Nanoparticles:** Spherical particles formed from polysaccharides like chitosan, hyaluronic acid, alginate, dextran, and cellulose.

- **Nanogels:** Crosslinked, hydrogel-like network structures capable of high loading and controlled release of hydrophilic nutraceuticals[43].
- **Nanomicelles:** Self-assembled amphiphilic polysaccharides forming core-shell structures for hydrophobic nutraceutical encapsulation.
- **Nanoemulsions and nanoliposomes:** Polysaccharides stabilize lipid-based nanosystems for delivery of lipophilic nutraceuticals.
- **Nanofibers and nanocomposites:** Electrospun polysaccharide fibers or composites for sustained delivery and functional food applications.

Advantages

- Polysaccharides are biodegradable, biocompatible, and generally non-toxic and non-immunogenic, making them safe for human consumption and minimal adverse effects.
- They offer tunable physicochemical properties, including size, charge, and hydrophilicity/hydrophobicity balance, facilitating targeted and controlled nutraceutical release.
- High loading capacity coupled with protection of sensitive nutraceuticals during processing and digestion enhances oral bioavailability and therapeutic efficacy.
- Polysaccharide nanocarriers can undergo chemical modifications for stimuli-responsive (pH, enzyme) release, improving site-specific delivery, such as targeted colon delivery using xanthan gum.
- Cost-effective and environmentally friendly production methods using abundant renewable materials offer advantages over synthetic nanocarriers.

Disadvantages

- Some polysaccharides have limited ability to encapsulate hydrophobic nutraceuticals due to inherent hydrophilicity.
- Variability in molecular weight and source-dependent heterogeneity can affect reproducibility and consistency of nanocarrier properties.
- High water solubility of certain polysaccharides may lead to premature release or reduced stability unless crosslinked or chemically modified.
- Complex synthesis processes and scale-up challenges remain for some polysaccharide nanocarriers requiring further optimization.
- Potential immunogenicity and toxicity of chemically modified polysaccharides warrant thorough evaluation[44].

Applications of Polysaccharide Nanocarriers in Nutraceuticals

- Efficient delivery systems for plant-derived antioxidants, vitamins, polyphenols, and probiotics, significantly improving bioavailability and gastrointestinal stability.

- Functional food formulations incorporating polysaccharide nanocarriers enable improved nutraceutical fortification with sustained release properties.
- Targeted delivery of nutraceuticals to specific tissues such as the colon using pH- or enzyme-sensitive polysaccharides like xanthan and alginate.
- It uses in cosmetic and topical formulations for enhanced skin penetration of bioactive natural compounds.
- Application in food packaging as nanocomposite films providing controlled release and antimicrobial functions, enhancing shelf life[45].

3.10 Nanogels

Nanogels serve as efficient carriers for nutraceuticals because their properties include high water content and tunable structure and they exhibit excellent biocompatibility and they can encapsulate both hydrophilic and hydrophobic bioactive compounds. The three-dimensional nanostructured hydrogel particles operate as environmental sensors which detect changes in pH and temperature and ionic strength to enable accurate control of nutraceutical release. The application of nanogels in functional foods and nutraceutical delivery systems has increased because of their ability to enhance solubility and stability and deliver products to specific targets.

Nanogels exist as cross-linked polymeric hydrogel nanoparticles which typically measure between 20 and 300 nanometers because their hydrophilic polymer networks can expand to their maximum size in water while preserving their original shape. The nutraceutical industry uses nanogels to encapsulate bioactive compounds which they release in a controlled manner throughout the gastrointestinal system.

Advantages

- High biocompatibility and biodegradability make nanogels safe carriers, reducing toxicity concerns.
- Nanogels have exceptional loading capacity due to their swelling properties, enabling incorporation of both hydrophilic and hydrophobic nutraceuticals.
- Their nanoscale size allows for enhanced permeability and retention effect (EPR), promoting tissue-specific accumulation.
- Nanogels protect unstable nutraceuticals from enzymatic and chemical degradation, improving stability and shelf life.
- Stimuli-responsive nanogels enable controlled and targeted release, reducing adverse effects and improving therapeutic efficacy.
- They exhibit low viscosity, facilitating ease of administration and compatibility with sterilization processes.

Disadvantages

- Residual surfactants or monomers may cause toxicity if not completely removed during formulation.

- Potential challenges with particle size uniformity and polydispersity can affect reproducibility and clinical performance.
- Premature degradation or release before reaching the target site may occur, limiting efficacy.
- Preparation methods can be complex and costly, and nanogels may face stability and storage issues, especially thermoresponsive types.
- Possible issues with scale-up production and regulatory approval remain hurdles.

Applications of Nanogels in Nutraceuticals

- Nanogels are used to encapsulate antioxidants, polyphenols, vitamins, and peptides, enhancing their bioavailability and protecting them in oral nutraceutical formulations.
- Topical and transdermal nutraceutical delivery benefits from nanogel systems with improved skin penetration and sustained release profiles.
- Stimuli-responsive nanogels provide targeted delivery applications in functional foods and therapeutic supplements.
- Nanogels facilitate co-delivery of synergistic bioactives for enhanced therapeutic outcomes.
- Their use is extending towards personalized nutrition and combined nutraceutical and pharmaceutical delivery systems[46].

3.11 Nanofibers

Nanofiber-based delivery systems have emerged as innovative platforms in the field of nutraceuticals due to their high surface area-to-volume ratio and their superior encapsulation capabilities and their controlled bioactive compound delivery system. The production of nanofibers requires different polymer materials which can be processed through electrospinning solution blow spinning and self-assembly methods to create nanofibers that contain sensitive nutraceuticals which include vitamins and polyphenols and carotenoids and probiotics and essential oils. Their structural similarity to natural extracellular matrices also enhances their compatibility with biological environments.

Nanofibers exist as ultrafine fibers which have diameters that range between 50 and 1000 nanometers and they originate from natural or synthetic polymers through electrospinning production methods. In nutraceutical applications, nanofibers serve as carriers capable of encapsulating bioactive compounds within their polymeric matrix or on their surface, protecting them from degradation and enabling controlled release during digestion[47].

Types of Nanofibers

Nanofibers can be classified based on their morphology, composition, and fabrication techniques into:

- **Nonwoven nanofibers:** Randomly oriented fibers commonly produced by electrospinning for broad applications.
- **Core-shell nanofibers:** Fibers with distinct core and shell layers enabling multi-functional delivery.

- **Aligned nanofibers:** Oriented fibers that mimic extracellular matrix structures, beneficial for tissue engineering.
- **Porous nanofibers:** Fibers with surface and internal porosity enhancing loading capacity and release kinetics.
- **Inorganic and composite nanofibers:** Incorporate inorganic materials or combine various polymers for enhanced properties

Advantages

- The high specific surface area and porosity of nanofibers provide superior loading capacity and facilitate rapid and sustained release of nutraceutical compounds.
- Nanofibers improve the solubility and bioavailability of hydrophobic nutraceuticals like resveratrol and curcumin, enhancing their therapeutic effects.
- They offer versatile administration routes including topical, transdermal, oral, and transmucosal, adapting to diverse delivery requirements.
- Nanofibrous mats mimic natural extracellular matrices, supporting cell proliferation and tissue regeneration in biomedical applications.
- Electrospinning allows for scalable, reproducible production of nanofibers with controllable fiber diameter, morphology, and drug release kinetics.
- Nanofibers facilitate multifunctional delivery by co-encapsulation of synergistic compounds and offer ease of functionalization.

Disadvantages

- Scale-up production challenges remain due to equipment costs and process optimization needs.
- Structural instability and porosity maintenance can be difficult during storage and processing.
- Residual organic solvents from electrospinning may pose toxicity risks if not properly removed.
- Mechanical strength may be insufficient for certain applications without composite strengthening.
- Uniformity in fiber diameter and orientation can be difficult to maintain in large batches, impacting consistency.

Applications of Nanofibers in Nutraceuticals

- Nanofibers are widely used to deliver antioxidants, anti-inflammatory agents, vitamins, and herbal extracts for improved bioavailability and prolonged activity.
- Topical and transdermal nanofiber formulations enhance skin penetration and controlled release of nutraceuticals in wound healing, cosmetics, and tissue regeneration.
- Nanofiber scaffolds serve as functional food matrices and biodegradable packaging materials imparting antimicrobial and antioxidant properties.

- Oral and transmucosal administration of herbal bioactives via nanofibers allows fast dissolution, improved solubility, and targeted delivery.
- Nanofiber drug delivery systems are explored for combinational nutraceutical and pharmaceutical therapies due to their multi-drug loading capability and tailored release profiles[48].

4. TARGETING APPROACHES IN NUTRACEUTICAL DELIVERY

Nutraceuticals- bioactive compounds derived from foods, plants, or natural sources-have gained increasing attention for their therapeutic roles in disease prevention and health promotion. The existing nutraceuticals experience multiple challenges because their active ingredients face difficulties with solubility and their products lose effectiveness through physiological environments and their active ingredients become less effective during systemic distribution. Researchers have created advanced delivery systems to solve existing problems through their ability to deliver materials precisely to targeted areas while increasing their effectiveness and decreasing their unintended impacts. The nutraceutical sector uses targeted delivery systems to improve how bioactive compounds reach their intended locations while increasing their therapeutic effects and bioavailability. The passive targeting method operates as a basic targeting method which uses natural body processes and disease mechanisms to deliver nutraceuticals to specific body areas while reducing unwanted effects and improving treatment results.

Targeted delivery strategies for nutraceuticals can be broadly classified into:

- **Passive targeting**, guided by physiological factors like the enhanced permeability and retention (EPR) effect.
- **Active targeting**, which relies on ligand–receptor interactions for selective accumulation.
- **Stimuli-responsive (smart) delivery**, triggered by internal or external environmental cues[51].

4.1 Concept of Passive Targeting

Passive targeting is predicated on the natural tendency of certain carriers or molecules to accumulate in specific tissues or cells without requiring specific interactions with cellular receptors. This phenomenon is largely governed by unique characteristics of the target tissue microenvironment, such as enhanced vascular permeability, retention properties, and tissue architecture[50-52].

The Enhanced Permeability and Retention (EPR) Effect

A cornerstone mechanism in passive targeting is the Enhanced Permeability and Retention (EPR) effect. This effect was initially characterized in the context of solid tumors but has broad implications in delivering macromolecules and nanoparticles, including nutraceuticals, to pathological sites exhibiting aberrant vasculature.

Mechanism of the EPR Effect

- Tumor tissues and inflamed sites typically have leaky vasculature due to defective endothelial linings, creating fenestrations that allow nanoparticles and macromolecules (usually >40 kDa) to extravasate from blood vessels into the interstitial space.
- These tissues also exhibit impaired lymphatic drainage, which leads to retention of these extravasated particles, resulting in their accumulation within the target tissues.
- The EPR effect distinctly relies on the size, shape, surface charge, and physicochemical characteristics of the carrier system to facilitate penetration and retention[53].

Importance in Nutraceutical Delivery

- Nanocarrier systems encapsulating nutraceutical compounds leverage the EPR effect for preferential localization in disease sites such as tumors or sites of inflammation.
- This passive targeting improves the therapeutic index of nutraceuticals by enhancing local concentration while reducing systemic exposure and side effects.
- For instance, lipid nanoparticles, polymeric micelles, and other nanocarriers have demonstrated the ability to exploit the EPR effect to protect sensitive nutraceuticals from degradation and enhance their bioavailability[54].

Factors Affecting the EPR Effect in Nutraceutical Delivery

- **Particle Size and Shape:** Nanoparticles sized between 10-200 nm are optimal for EPR-mediated accumulation. Particles too small may be cleared renally, while particles too large may not penetrate vascular fenestrations.
- **Surface Properties:** Hydrophilic surfaces with neutral or slightly negative charges often enhance circulation time and reduce opsonization, improving the chances of extravasation.
- **Tumor/Inflammation Microenvironment:** The heterogeneity of vascular permeability and interstitial fluid pressure in diseased tissues influences the extent of EPR effect and drug accumulation.
- **Physiological Modifiers:** Application of agents such as nitric oxide donors or radiation may enhance the EPR effect by further increasing vascular permeability, thereby improving delivery efficiency.

Advantages of Passive Targeting via EPR in Nutraceuticals

- Simplifies formulation by avoiding complex ligand attachment steps.
- Prolonged systemic circulation due to evasion from immediate immune clearance.
- Increased accumulation at diseased sites enhances efficacy.
- Reduced side effects owing to minimal off-target exposure.
- Facilitates co-delivery of multiple bioactives with synergistic therapeutic potential.

Limitations and Challenges

- EPR effect varies significantly between patients and disease types, with low or heterogeneous permeability limiting effectiveness in some cases.
- Prolonged circulation may increase accumulation in non-target tissues, posing toxicity risks.
- Nanoparticles and macromolecules may face barriers in deep tissue penetration beyond the perivascular region.
- The physiological environment's complexity demands design optimizations to maximize EPR-based delivery[55].

Strategies to Enhance Passive Targeting via EPR

- Surface modification of nanoparticles with polymers like PEG to extend half-life.
- pH-sensitive or enzyme-responsive carriers that release nutraceuticals in acidic or enzyme-rich microenvironments.
- Combination therapies using EPR enhancers such as mild hyperthermia or ultrasound.
- Designing nanocarriers with optimized size, shape, and surface chemistry to exploit the EPR effect maximally[56].

4.2 Active Targeting via Ligand Functionalization

The active drug delivery system of active targeting delivers therapeutic agents to specific cells and tissues which results in better delivery performance through their enhanced ability to reach particular targets. Active targeting uses molecular recognition mechanisms to deliver drugs to specific sites whereas passive targeting relies on physiological traits that include vascular permeability. The process of active targeting requires delivery systems to undergo surface modifications through biorecognition ligand attachment, which allows them to bind specifically with receptors and biomarkers that exist in excessive amounts on targeted cells.

Mechanism of Active Targeting

Active targeting involves functionalizing the surface of a carrier system (e.g., nanoparticles, liposomes, micelles) with ligands—molecules that specifically bind to receptors or antigens overexpressed on target cells. Upon systemic administration, these ligand-functionalized carriers recognize and bind to their corresponding receptors, often followed by receptor-mediated endocytosis that enables an efficient intracellular uptake of nutraceuticals.

Key points:

- Ligands act as homing devices targeting specific biomarkers on disease cells, enhancing cellular selectivity.

- This receptor-ligand binding mediates selective accumulation at the diseased site, minimizing off-target effects.
- Active targeting can complement passive targeting by enhancing intracellular drug delivery efficiency[58].

Types of Ligands Used in Nutraceutical Delivery

Various ligands are employed depending on the target tissue and disease pathology. Common classes include:

- **Antibodies and antibody fragments:** High specificity for cell surface antigens (e.g., HER2 in breast cancer).
- **Peptides and proteins:** Moderate size, high affinity ligands such as RGD peptides targeting integrins.
- **Carbohydrates and polysaccharides:** For example, hyaluronic acid targets CD44 expressed in several cancer cells.
- **Small molecules:** Such as folic acid targeting folate receptors overexpressed in tumor cells.
- **Aptamers:** Short oligonucleotides that bind specifically to target molecules with high affinity[59].

Ligand Functionalization Strategies

Effective ligand attachment to nanoparticles or delivery systems is crucial for the success of active targeting. Strategies include:

- Covalent conjugation through linkers that maintain ligand orientation and bioactivity.
- Non-covalent interactions such as adsorption, though these may lack stability in circulation.
- It uses of cleavable linkers that release the drug selectively within the target cell environment.

Applications in Nutraceutical Delivery

Active targeting enhances the therapeutic efficacy and bioavailability of nutraceuticals by:

- Improving site-specific delivery to target cells, such as tumor cells or inflamed tissues.
- Facilitating receptor-mediated endocytosis, ensuring intracellular delivery.
- Protecting sensitive nutraceuticals from premature degradation.
- Reducing systemic side effects by limiting off-target distribution.

Examples:

- Folic acid-functionalized nanoparticles delivering curcumin for targeted anticancer effects.
- Hyaluronic acid-coated carriers delivering resveratrol targeting CD44+ cancer stem cells.
- Peptide-ligand nanoparticles delivering antioxidants to oxidative stress sites in neurodegenerative diseases[60].

Advantages of Active Targeting

- Enhanced selectivity and accumulation in target tissues.

- Greater therapeutic efficacy due to increased intracellular drug concentration.
- Possibility to cross biological barriers via receptor-mediated pathways.
- Reduced toxicity and adverse effects compared to non-targeted delivery.

Challenges and Considerations

- Ligand-receptor interactions depend on receptor expression variability and heterogeneity.
- Stability of ligand conjugation during circulation is critical.
- Potential immunogenicity of ligands like antibodies.
- Complexity and cost of functionalization increase formulation challenges.
- The steric hindrance and spatial orientation of ligands on nanoparticles affect binding efficiency[61].

Future Directions in Ligand-Functionalized Nutraceutical Delivery

- Development of multifunctional nanoparticles with dual ligand targeting and stimuli-responsiveness.
- Exploring natural phytochemical ligands for safer, biocompatible active targeting.
- Advanced ligand engineering to optimize binding affinity and reduce off-target binding.
- Clinical translation requires rigorous evaluation of targeting efficacy, safety, and scalability[62].

4.3 Stimuli-Responsive (Smart) Delivery Systems

The research develops advanced nutraceutical delivery systems which function as smart delivery systems that react to environmental changes. The systems are designed to release nutraceutical compounds in a controlled manner at specific locations through their detection of particular internal and external cues. The research team aims to achieve three objectives by developing release patterns which match the patients' natural body processes and their medical conditions. The system activates its release mechanism when it detects particular internal or external triggers, which allows precise control over the timing and location of nutraceutical delivery.

This enables:

- Reduction of systemic side effects
- Precise, on-demand release
- Enhanced therapeutic index[63]

Mechanism of Stimuli-Responsive Systems

Stimuli-responsive systems utilize material designs that exhibit physicochemical or structural transformations upon exposure to defined stimuli. These changes may involve swelling, degradation, solubility alteration, or conformational modifications that facilitate the release of the encapsulated nutraceutical.

Stimuli can be broadly divided into:

- **Internal (endogenous) stimuli:** pH variations, redox potential, enzyme activity, temperature, glucose concentration.
- **External (exogenous) stimuli:** Light (UV/visible/near-infrared), magnetic fields, ultrasound, electrical pulses[64].

Examples of Common Stimuli and Their Responsive Mechanisms

pH-Responsive Systems

- Exploit the differential pH environments in the human body (e.g., acidic tumor microenvironment, gastric pH vs. intestinal pH).
- Carriers undergo protonation/deprotonation leading to swelling or degradation to release nutraceuticals selectively.

Redox-Responsive Systems

- Target the intracellular reductive environment characterized by elevated glutathione levels.
- Incorporation of disulfide bonds in polymers or linkers that cleave under reducing conditions, triggering drug release.

Enzyme-Responsive Systems

- Use specific enzymes overexpressed at disease sites (e.g., matrix metalloproteinases in tumors).
- Enzymatic cleavage of peptide linkers or polymer matrices releases the nutraceutical payload.

Temperature-Responsive Systems

- Utilize thermo-sensitive polymers that transition from hydrophilic to hydrophobic states or vice versa above/below certain temperatures.
- Enable controlled release in response to localized hyperthermia or fever[65].

Applications in Nutraceutical Delivery

- Protect sensitive bioactives (e.g., polyphenols, vitamins) from premature degradation and enhance stability.
- Achieve site-specific delivery and controlled release in the gastrointestinal tract or target tissues.
- Examples include pH-responsive nanocarriers for curcumin targeting acidic tumor microenvironment and redox-responsive delivery of resveratrol for antioxidant therapy.

Advantages of Stimuli-Responsive Delivery Systems

- Precise spatiotemporal control of nutraceutical release.
- Enhanced bioavailability and therapeutic efficacy through targeted delivery.
- Reduced systemic side effects by limiting off-target exposure.
- Improved patient compliance by reducing dosing frequency.

Challenges in Development

- Complexity in carrier design and manufacturing scalability.
- Variability in physiological stimuli between individuals and disease states.
- Potential instability or premature release under non-target conditions.
- Need for biocompatibility and safety validation of smart materials[66].

Emerging Trends and Future Perspectives

- Multifunctional platforms integrating multiple stimulus sensitivities for synergistic control.
- Integration with diagnostic capabilities for theranostic applications.
- Use of natural polymers and green synthesis for biocompatible and sustainable formulations.
- Application of artificial intelligence and machine learning to optimize stimuli-responsive formulations[67].

5. APPLICATIONS OF NANOTECHNOLOGY IN NUTRACEUTICALS

Nanotechnology has transformed the nutraceutical industry through its ability to improve bioactive compounds' solubility and stability and their distribution throughout the body and their specific delivery methods. (2) Many nutraceuticals face challenges with their therapeutic effectiveness because they exhibit both poor water solubility and low absorption rates and chemical instability. The use of nanotechnology allows scientists to create nano-sized carriers which help increase the clinical effectiveness of these drugs through their ability to transport active ingredients]

5.1 Curcumin Nanoparticles

The natural polyphenolic compound curcumin exists in the rhizomes of Curcuma longa which people commonly know as turmeric. The substance possesses strong anti-inflammatory and antioxidant and antimicrobial and anticancer and neuroprotective effects. Curcumin has therapeutic applications but its clinical use remains limited because of its poor water solubility and fast metabolism and low bioavailability and physiological condition instability.69.

Challenges in Curcumin Delivery

- **Poor aqueous solubility:** Curcumin's hydrophobic nature results in very low solubility in gastrointestinal fluids.
- **Rapid metabolism:** Extensive first-pass metabolism leads to rapid clearance.
- **Low systemic bioavailability:** Oral absorption is minimal, limiting its therapeutic effectiveness.
- **Chemical instability:** Curcumin degrades in alkaline and oxidative environments.

These challenges necessitate innovative delivery approaches to maximize curcumin’s therapeutic benefits[70].

Nanotechnology-Based Solutions: Curcumin Nanoparticles

Nanoparticles encapsulating or incorporating curcumin improve its physicochemical properties and biological performance by:

- Increasing aqueous solubility and dissolution.
- Protecting curcumin from degradation in the gastrointestinal tract.
- Facilitating controlled and sustained release.
- Enhancing cellular uptake and tissue targeting[71].

Physicochemical Characteristics

- **Size:** Typically ranging from 50 to 200 nm, optimal for enhanced permeability and cellular uptake.
- **Surface charge:** Adjustable zeta potential to stabilize suspensions and modulate biological interactions.
- **Encapsulation efficiency:** High loading (>70%) ensures sufficient therapeutic dose.
- **Morphology:** Spherical and uniform nanoparticles improve consistency[72].

Advantages of Curcumin Nanoparticles

- **Improved solubility and dissolution:** Nanoparticles increase surface area, enhancing dissolution rate.
- **Enhanced chemical stability:** Protective nano-encapsulation prevents degradation by pH or light.
- **Increased bioavailability:** Enhanced intestinal absorption through improved permeability and prolonged circulation.
- **Targeted delivery:** Passive targeting via enhanced permeability and retention (EPR) effect to pathological tissues; potential active targeting via surface ligand modification.
- **Controlled release:** Sustained or stimuli-responsive release profiles ensure prolonged therapeutic action[73].

Therapeutic Applications

- **Anti-inflammatory and anticancer:** Curcumin nanoparticles show enhanced inhibition of tumor growth and inflammation in preclinical models.
- **Neuroprotective effects:** Nanoparticles designed for brain delivery demonstrate improved cognitive function and neuroprotection in neurodegenerative disease models.
- **Antimicrobial activity:** Improved efficacy against drug-resistant microbial strains.
- **Cosmeceutical applications:** Enhanced skin penetration and antioxidant activity for anti-aging formulations[74].

5.2 Resveratrol Nanoformulations

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural polyphenolic compound found in grapes, berries, peanuts, and red wine. It has attracted significant attention due to its diverse pharmacological activities, including antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and anticancer effects. However, clinical application of resveratrol is hindered by poor water solubility, rapid metabolism, and low systemic bioavailability[74].

Challenges in Resveratrol Delivery

- **Low aqueous solubility:** Resveratrol is practically insoluble in water, limiting absorption.
- **Rapid metabolism and elimination:** Extensive phase II metabolism (glucuronidation and sulfation) in the liver and intestine reduces bioactive systemic levels.
- **Poor chemical stability:** Susceptible to photoisomerization and oxidation.
- **Limited bioavailability:** Oral bioavailability is estimated to be **less than 1%.**

Nanotechnology-Based Solutions: Resveratrol Nanoformulations[75]

Nanotechnology offers promising strategies to overcome the limitations of resveratrol by improving its stability, solubility, and targeted delivery.

Types of Resveratrol Nanoformulations

1. **Lipid-Based Nanoparticles**
    - **Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):**
        - Enhance solubility and control release.
        - Protect resveratrol from degradation.
        - Improve bioavailability by facilitating lymphatic uptake.
    - **Liposomes:** Phospholipid bilayer vesicles encapsulate resveratrol, improving stability and cellular uptake.
    - **Nanoemulsions:** Provide increased surface area and better absorption.
2. **Polymeric Nanoparticles**
    - Made from biodegradable polymers such as polylactic-co-glycolic acid (PLGA), chitosan, and polycaprolactone.
    - Enable sustained release and improved cellular internalization.
    - Surface modification allows targeted delivery.
3. **Inorganic Nanoparticles**
    - Silica nanoparticles, gold nanoparticles, and carbon-based nanomaterials used as carriers.
    - Facilitate controlled release and multi-functional delivery platforms.
    - Enhance stability and therapeutic efficacy.

4. **Nanocrystals**
    - Pure resveratrol crystals reduced to nanometer size.
    - Enhance dissolution rate and saturation solubility.

Physicochemical Properties

- Particle size typically ranges from 50 to 300 nm, optimizing bioavailability and tissue penetration.
- Surface charge and hydrophobicity/hydrophilicity balance tailored to enhance systemic circulation and cellular uptake.
- High encapsulation efficiency (>70%) protects against premature degradation[76].

Advantages of Resveratrol Nanoformulations

- Improved solubility and dissolution rate enhance oral absorption.
- Protection from enzymatic and chemical degradation increases systemic circulation half-life.
- Enhanced bioavailability through improved stability and permeation.
- Targeted and controlled release reduces dosing frequency and side effects.
- Versatility in administration routes: Oral, topical, intravenous, and intranasal for site-specific delivery.

Therapeutic Applications[77]

- **Cardiovascular Protection:** Improved delivery increases resveratrol's efficacy in reducing oxidative stress and inflammation.
- **Cancer Therapy:** Enhanced intracellular delivery leads to superior antiproliferative activity.
- **Neuroprotection:** Brain-targeted nanoformulations support treatment of neurodegenerative diseases through improved BBB penetration.
- **Anti-aging and Skin Health:** Topical formulations improve antioxidant effects and skin penetration.
- **Metabolic Disorders:** Enhanced pharmacokinetics facilitate therapeutic effects in diabetes and obesity models.

Brain-Targeted Resveratrol Delivery

- Intranasal delivery of resveratrol-loaded nanoparticles bypasses the blood-brain barrier for rapid and enhanced brain bioavailability.
- Ligand-functionalized nanoparticles targeting brain receptors facilitate receptor-mediated endocytosis.
- Promising outcomes in Alzheimer's disease and stroke models demonstrate neuroprotective benefits[78].

5.3 Omega-3 Fatty Acid Nanocarriers

Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential nutrients well-known for their cardiovascular, neurological, anti-inflammatory, and metabolic health benefits. Despite their therapeutic potential, direct oral administration of omega-3 fatty acids is challenged by poor aqueous solubility, susceptibility to oxidation, and inefficient absorption[79].

Challenges in Omega-3 Fatty Acid Delivery

- **Poor water solubility:** Lipophilic nature limits dispersion in aqueous gastrointestinal fluids.
- **Oxidative instability:** Omega-3 PUFAs are prone to lipid peroxidation, reducing efficacy and shelf life.
- **Low bioavailability:** Limited intestinal uptake and first-pass metabolism reduce systemic levels.
- **Unpleasant taste and odor:** Affect patient compliance[80].

Nanotechnology-Based Solutions: Omega-3 Fatty Acid Nanocarriers

Nanotechnology provides innovative delivery platforms to overcome these challenges by enhancing solubility, stability, and targeted delivery.

Types of Nanocarriers for Omega-3 Fatty Acids

Nanostructured Lipid Carriers (NLCs)

- It composed of solid and liquid lipids, NLCs encapsulate omega-3 oils in a semi-solid matrix.
- It protects omega-3s from oxidation and provide controlled release.
- The particle sizes typically range from 100 to 200 nm, optimizing absorption.

Lipid Nanoemulsions

- Oil-in-water nanoemulsions solubilize omega-3s with droplet sizes below 200 nm.
- Enhance oral bioavailability via improved dissolution and lymphatic uptake.
- Often stabilized with surfactants to improve physical stability.

Liposomes

- Phospholipid bilayer vesicles encapsulating omega-3 fatty acids.
- Promote targeted delivery to tissues and improved cellular uptake.
- Enhance protection against oxidative degradation.

Polymeric Nanoparticles

- Biodegradable polymers such as PLGA, chitosan, or alginate used to encapsulate omega-3s.
- Enable sustained release and mucoadhesive properties for better gut absorption.

Solid Lipid Nanoparticles (SLNs)

- Use solid lipids to encapsulate omega-3 fatty acids.
- Improve stability, control release, and provide enhanced bioavailability.

Physicochemical Properties

- Particle size: 50–300 nm for optimal absorption and stability.
- High encapsulation efficiency (>80%) to ensure protective loading.
- Surface charge: Modified to enhance mucoadhesion and stability[80].

Advantages of Omega-3 Nanocarriers

- **Improved solubility and dispersion:** Nano-sizing provides greater surface area for enhanced emulsification.
- **Protection from oxidation:** Nanocarriers shield omega-3s from oxidative degradation, extending shelf life.
- Enhanced bioavailability: Nanocarriers promote lymphatic transport bypassing first-pass metabolism.
- **Taste masking:** Encapsulation masks fishy odor and taste, improving palatability.
- **Controlled and targeted delivery:** Potential to deliver omega-3s to specific organs (e.g., brain, heart)[81].

Therapeutic Applications

- **Cardiovascular health:** Nanoformulated omega-3s effectively reduce triglycerides and inflammatory markers.
- **Neuroprotection:** Nanocarriers facilitate transport across the blood-brain barrier, supporting cognitive function and neurodegenerative disease management.
- **Anti-inflammatory effects:** Targeted delivery enhances efficacy in autoimmune and inflammatory disorders.
- **Metabolic syndrome and diabetes:** Improved bioavailability aids in glycemic control and lipid modulation[82].

5.4 Encapsulation of Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host by modulating the gut microbiota and enhancing immune functions. They are widely used in dietary supplements and functional foods to promote gastrointestinal health, prevent infections, and improve metabolic and immune-related disorders[83].

Challenges in Probiotic Delivery

- **Viability loss:** Exposure to harsh gastrointestinal conditions such as acidic pH of the stomach, bile salts, digestive enzymes, and oxygen can significantly reduce probiotic viability.
- **Poor stability:** Many probiotic strains are sensitive to temperature, moisture, and oxygen during storage.
- **Inefficient colonization:** Low survival rates through the digestive tract limit colonization and efficacy.
- **Handling and formulation:** Maintaining stability in food matrices and supplements without compromising viability is complex[84].

Nanotechnology Solutions: Probiotic Encapsulation

Nanotechnology-based encapsulation techniques provide a protective microenvironment to enhance probiotic viability, stability, and targeted delivery.

Types of Nanocarriers for Probiotic Encapsulation

Polymeric Nanoparticles

- Use biocompatible and biodegradable polymers (e.g., chitosan, alginate, PLGA).
- Form protective nano- or microcapsules around probiotic cells.
- Provide controlled release and enhanced mucoadhesion to intestinal mucosa.

Lipid-Based Nanocarriers

- Liposomes and solid lipid nanoparticles form lipid bilayers or matrices encapsulating probiotics.
- Protect against oxygen and gastrointestinal enzymes.

Nanoemulsions

- Fine oil/water emulsions protect probiotics and promote stability.

Electrospun Nanofibers

- Fiber mats incorporating probiotics for enhanced protection and ease of application in food matrices[85].

Mechanisms of Protection and Benefits

- **Physical barrier:** Encapsulation isolates probiotics from acidic gastric fluid and bile salts.
- **Controlled release:** Nanocarriers degrade or swell under intestinal conditions to release probiotics at the target site.
- **Improved adhesion:** Surface-modified nanoparticles enhance adhesion and colonization in the gut mucosa.

- **Enhanced shelf-life:** Protection against oxygen, moisture, and temperature extends probiotic viability during storage.

Applications in Nutraceuticals and Functional Foods

- Encapsulated probiotics are incorporated into yogurt, cheese, beverages, and dietary supplements.
- Functional foods with nanocoated probiotics offer improved stability and health benefits.
- Targeted delivery of probiotics to specific gut regions enhances therapeutic efficacy in disorders like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and antibiotic-associated diarrhea.
- Combination therapies co-encapsulating probiotics with prebiotics or nutraceuticals foster synergistic effects (synbiotics)[86].

Advantages of Nanotechnology-Based Probiotic Encapsulation

- Significantly increased survival rates of probiotics in harsh gastric environments.
- Enhanced colonization and bioactivity at the intestinal mucosa.
- Flexibility in formulation and compatibility with diverse food matrices.
- Potential for targeted and controlled delivery improving therapeutic outcomes.
- Facilitates development of novel probiotic formulations with specific release profiles[87].

5.5 Polyphenols in Nanosystems

Polyphenols are a diverse class of plant-derived bioactive compounds characterized by multiple phenol structural units. They include flavonoids (such as quercetin, catechins), phenolic acids (gallic acid), stilbenes (resveratrol), and tannins. Polyphenols exhibit potent antioxidant, anti-inflammatory, anticancer, cardiovascular protective, and neuroprotective activities. However, their clinical and nutraceutical applications are limited by poor bioavailability, low solubility, rapid metabolism, and chemical instability[88].

Challenges in Polyphenol Delivery

- **Poor water solubility:** Many polyphenols are hydrophobic or poorly soluble in aqueous environments.
- **Low stability:** Susceptible to degradation caused by pH changes, enzymatic hydrolysis, light, and oxygen.
- **Rapid metabolism:** Extensive intestinal and hepatic metabolism limits systemic availability.
- **Poor absorption:** Low intestinal permeability restricts bioefficacy[89].

Nanotechnology-Based Solutions: Polyphenols in Nanosystems

Nanotechnology provides efficient delivery platforms to enhance the solubility, stability, absorption, and bioavailability of polyphenols.

Types of Nanosystems for Polyphenol Delivery

Polymeric Nanoparticles

- Biodegradable polymers such as PLGA, chitosan, and zein are used to encapsulate polyphenols.
- Protect polyphenols from premature degradation and allow sustained release.
- Enhance cellular uptake and provide mucoadhesion.

Lipid-Based Nanocarriers

- Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) can solubilize and stabilize polyphenols.
- Improve bioavailability by increasing lymphatic transport and protecting from enzymatic degradation.

Nanocrystals and Nanosuspensions

- Pure crystalline polyphenols reduced to the nanometer scale.
- Enhanced dissolution rates and saturation solubility promote absorption.

Nanoemulsions

- Oil-in-water emulsions with droplet size <200 nm increase solubility and protect polyphenols from degradation.

Inorganic Nanoparticles

- Silica or gold nanoparticles functionalized with polyphenols enhance stability and enable targeted delivery.

Advantages of Nanoencapsulation of Polyphenols

- **Improved solubility and dissolution:** Nano-sizing increases surface area for rapid dissolution.
- **Enhanced chemical stability:** Controlled microenvironment protects against oxidative degradation and hydrolysis.
- **Increased bioavailability:** Enhanced permeability and cellular uptake improve systemic exposure.
- **Controlled release:** Sustained and stimuli-responsive release profiles optimize therapeutic effect.
- **Targeted delivery:** Surface modification of nanoparticles can add specificity to diseased tissues.

Therapeutic and Nutraceutical Applications

- **Antioxidant therapy:** Enhanced scavenging of reactive oxygen species leading to reduced oxidative stress.
- **Anti-inflammatory and anticancer:** Improved inhibition of inflammatory pathways and tumor suppression.

- **Cardiovascular health:** Improved bioefficacy in preventing atherosclerosis and improving lipid profiles.
- **Neuroprotection:** Enhanced crossing of the blood-brain barrier and neuroprotective effects in neurodegenerative diseases.
- **Skin care:** Improved topical delivery of polyphenols for anti-aging and photoprotection[90].

5.6 Carotenoids in Nanosystems

Carotenoids are fat-soluble pigments naturally found in fruits, vegetables, and microorganisms. They exhibit potent antioxidant properties and play key roles in human health by supporting immune function, eye health, cardiovascular protection, and cancer prevention. Common carotenoids include beta-carotene, lycopene, lutein, zeaxanthin, and astaxanthin. Despite their biological importance, carotenoids face challenges such as poor water solubility, chemical instability, and limited bioavailability.

Challenges in Carotenoid Delivery

- **Poor water solubility:** Carotenoids are highly lipophilic, leading to low dispersion in aqueous gastrointestinal fluids.
- **Chemical instability:** Susceptible to degradation by light, heat, oxygen, and acidic environments.
- **Low bioavailability:** Limited absorption and isomerization reduce systemic exposure.
- **Sensitivity to processing and storage:** Leads to loss of activity in food and supplement products[91].

Nanotechnology Solutions: Carotenoids in Nanosystems

Nanotechnology provides effective strategies to overcome carotenoids' limitations by improving solubility, stability, absorption, and controlled delivery.

Types of Nanocarriers for Carotenoids

Lipid-Based Nanocarriers

- **Nanoemulsions:** Oil-in-water emulsions with nanoscale droplets (<200 nm) improve solubilization and intestinal absorption.
- **Liposomes:** Phospholipid bilayer vesicles encapsulating carotenoids protect them from oxidation and enhance cellular uptake.
- **Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):** Provide solid lipid matrices that stabilize carotenoids and enable controlled release.

Polymeric Nanoparticles

- Biodegradable polymers such as PLGA, chitosan, and alginate entrap carotenoids, offering sustained release and improved stability.
- Surface modification facilitates targeted delivery and mucoadhesion.

Nanocrystals and Nanosuspensions

- Pure carotenoid crystals or suspensions reduced to nanometer size enhance dissolution rates and bioavailability.

Inorganic Nanoparticles

- Silica and gold nanoparticles functionalized for carotenoid delivery improve stability and can offer theranostic potential.

Advantages of Carotenoid Nanosystems

- Enhanced water dispersibility and solubility promote improved gastrointestinal absorption.
- Increased chemical and photostability protect carotenoids from degradation during processing and storage.
- Improved bioavailability through enhanced dissolution and lymphatic transport.
- Controlled release profiles optimize bioefficacy.
- Potential for targeted delivery to tissues such as the retina or skin.

Nutraceutical and Therapeutic Applications

- **Eye health:** Carotenoid nanosystems enhance delivery of lutein and zeaxanthin to the retina for macular degeneration prevention.
- **Antioxidant and anticancer:** Enhanced systemic antioxidant activity from improved carotenoid bioavailability.
- **Skin protection:** Topical nanosystems provide photoprotection and anti-aging benefits through improved skin penetration.
- **Cardiovascular support:** Delivery of lycopene and beta-carotene via nanocarriers supports vascular health.
- **Immune modulation:** Improved delivery strengthens immune responses[92].

5.7 Brain-Targeted Nutraceutical Nanodelivery

The brain is a critical organ vulnerable to oxidative stress, neuroinflammation, and neurodegenerative diseases such as Alzheimer's and Parkinson's. Nutraceuticals with neuroprotective properties, including curcumin, resveratrol, and omega-3 fatty acids, have shown promise for brain health. However, effective delivery to the brain is severely limited by the blood-brain barrier (BBB), which restricts the passage of most molecules, including many beneficial nutraceuticals.

Nanotechnology enables the design of brain-targeted nanodelivery systems that can cross the BBB and deliver nutraceuticals efficiently, enhancing therapeutic outcomes for neurological conditions.

Blood-Brain Barrier: A Major Challenge

- The BBB is composed of tightly packed endothelial cells supported by astrocytes and pericytes, forming a highly selective barrier.
- It restricts penetration of hydrophilic and large molecules, allowing only certain nutrients to pass via specific transport mechanisms.
- This protective barrier limits the brain bioavailability of many neuroprotective nutraceuticals when administered conventionally.

Strategies for Brain-Targeted Nanodelivery of Nutraceuticals

1. Nanocarrier Design for BBB Penetration

- **Size and surface properties:** Nanoparticles sized between 10–200 nm with surface modifications avoid rapid clearance and improve BBB penetration.
- **Surface modification:** Functionalization with targeting ligands (e.g., transferrin, lactoferrin, peptides) facilitates receptor-mediated transcytosis across the BBB.
- **Charge:** Slightly positive or neutral surface charge enhances cellular uptake without toxicity.
- **Stealth properties:** PEGylation reduces opsonization and prolongs circulation time, increasing BBB interaction.

2. Types of Brain-Targeted Nanocarriers

- **Lipid-based nanocarriers:** Liposomes, solid lipid nanoparticles, and nanostructured lipid carriers protect nutraceuticals and improve brain delivery.
- **Polymeric nanoparticles:** Biodegradable polymers such as PLGA and chitosan form nanoparticles with modifiable surfaces for targeting.
- **Dendrimers and micelles:** Offer controlled release and BBB crossing abilities.
- **Inorganic nanoparticles:** Gold, silica, and magnetic nanoparticles can be engineered for targeted delivery and imaging.
- **Exosomes:** Natural nanovesicles inherently capable of crossing the BBB, used for delivering nutraceutical payloads.

3. Routes of Administration

- **Intranasal delivery:** Provides direct nose-to-brain transport bypassing the BBB, reducing systemic exposure.
- **Intravenous injection:** Requires effective targeting ligands and stealth coatings to cross the BBB.
- **Oral delivery:** Challenging due to degradation and BBB barriers, but nanoparticle encapsulation improves stability and absorption[93].

Examples of Brain-Targeted Nutraceutical Nanodelivery

- **Curcumin nanoparticles:** Functionalized with transferrin or lactoferrin for receptor-mediated BBB transport; demonstrated improved neuroprotective effects in Alzheimer's models.
- **Resveratrol-loaded liposomes:** Enhanced brain uptake and antioxidant activity after intranasal administration.
- **Omega-3 nanocarriers:** Facilitate BBB crossing and accumulation in brain tissue, supporting cognitive enhancement and neuroinflammation reduction.
- **Quercetin nanoparticles:** Improved BBB penetration and anti-inflammatory effects in neurodegenerative disease models.

Advantages of Brain-Targeted Nanodelivery

- Overcomes the restrictive BBB for effective nutraceutical delivery.
- Enhances bioavailability and accumulation of neuroprotective agents in the brain.
- Enables targeted therapy, reducing systemic side effects.
- Offers controlled and sustained release to maintain therapeutic concentrations.
- Potential for combination therapies integrating imaging and therapeutic modalities (theranostics).

Challenges and Limitations

- Complexity in nanoparticle design and scale-up manufacturing.
- Potential toxicity and immunogenicity concerns with nanocarriers.
- Variability of BBB integrity and receptor expression in disease states affecting delivery efficiency.
- Regulatory hurdles for clinical translation require extensive safety and efficacy data.

5.8 Gut-Targeted Nutraceutical Nanodelivery

The gastrointestinal tract plays a central role in nutrient absorption, immune function, and host-microbiome interactions. Targeted delivery of nutraceuticals to specific gut regions enhances therapeutic efficacy in gastrointestinal diseases, improves systemic bioavailability, and supports gut health. However, the harsh and variable environment of the gut (acidic gastric juices, enzymes, microbial flora) challenges the stability and efficacy of many nutraceuticals.

`Nanotechnology-enabled gut-targeted delivery systems have been developed to overcome these limitations by protecting nutraceuticals from premature degradation, enabling controlled release, and enhancing site-specific uptake.

Challenges in Gut-Targeted Nutraceutical Delivery

- **Acidic gastric environment:** Many nutraceuticals degrade or lose activity in the stomach.
- **Enzymatic degradation:** Proteases and other digestive enzymes can degrade bioactives before absorption.

- **Poor targeted release:** Conventional formulations often release nutraceuticals diffusely along the GI tract.
- **Limited absorption:** Low permeability and efflux transporters reduce bioavailability.
- **Microbiota interaction:** Complex gut microbiome interactions can affect nutraceutical stability and effects[94].

Nanotechnology Approaches for Gut-Targeted Delivery

1. pH-Responsive Nanoparticles

- Exploit the pH gradient along the GI tract (acidic stomach, neutral to alkaline intestine).
- Nanocarriers coated with pH-sensitive polymers (e.g., Eudragit, chitosan derivatives) remain intact at low pH and release contents in the higher pH of the intestine.
- Protect nutraceuticals such as curcumin, polyphenols, and probiotics from stomach acid.

2. Enzyme-Responsive Nanocarriers

- It utilizes polymers or materials cleaved specifically by enzymes abundant in the gut (e.g., proteases, glycosidases).
- It offers site-specific release triggered by enzymatic activity.

3. Mucoadhesive Nanoparticles

- Polymers such as chitosan provide adhesive properties, promoting prolonged residence time on the intestinal mucosa.
- Enhance localized delivery and absorption of nutraceuticals.

4. Microbiome-Responsive Nanocarriers

- Designed to respond to metabolites or enzymes produced by gut microbiota.
- Enable targeted release in colon or specific gut regions.
- Support synergistic interaction between microbiome and nutraceuticals.

5. Lipid-Based and Polymeric Nanocarriers

- Liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles protect sensitive nutraceuticals.
- Enhance uptake and bioavailability through enterocyte absorption or paracellular pathways.
- Facilitate co-delivery of probiotics and prebiotics (synbiotics)[95].

Examples of Gut-Targeted Nutraceutical Nanodelivery

- **Curcumin-loaded pH-sensitive nanoparticles:** Protect curcumin from gastric degradation, releasing in the intestines for anti-inflammatory effects.

- **Probiotic encapsulated nanoparticles:** Enhance survival and colonization by shielding against stomach acid and bile salts.
- **Polyphenol-loaded mucoadhesive nanocarriers:** Prolong local retention, improving antioxidant and anti-inflammatory actions.
- **Omega-3 fatty acid nanocarriers:** Improve oral absorption and protect from oxidation in the GI tract.

Advantages of Gut-Targeted Nanodelivery

- Protects nutraceuticals from harsh gastric and enzymatic conditions.
- Allows site-specific delivery to desired gut regions (small intestine, colon).
- Enhances absorption and bioavailability.
- Supports modulation of gut microbiota and immune response.
- Enables controlled and sustained release minimizing dosing frequency.
- Improves stability and shelf-life of nutraceutical formulations[96].

6. ADVANTAGES OF NANO-NUTRACEUTICAL DELIVERY SYSTEMS

Nano-nutraceutical delivery systems offer several significant advantages over conventional formulations by improving the way bioactive compounds are protected, absorbed, and utilized in the body. These systems use nanosized carriers such as nanoparticles, liposomes, nanoemulsions, micelles, and nanocapsules to enhance the performance of nutraceuticals.

6.1. Enhanced Solubility and Stability

The primary advantage of nanotechnology in delivering nutraceuticals through delivery systems is its ability to enhance nutrient absorption and bioavailability. Bioactive compounds present in nutraceuticals exhibit three major challenges which include poor water solubility and instability and restricted gastrointestinal tract absorption. Nanotechnology enables the development of nanosized materials which allow the body to better dissolve and absorb these compounds. The process of reducing particles to their nanometer size results in a substantial increase of surface area which boosts the compound's ability to dissolve in biological fluids. According to the Noyes–Whitney equation, smaller particles dissolve faster, leading to higher concentrations of the active compound available for absorption. The intestinal lining directly benefits from this improved dissolution process which enhances uptake through the intestinal lining[97]. The scientists developed nanocarriers which included nanoparticles and liposomes and nanoemulsions and micelles to achieve improved biological membrane interaction which increased their ability to transport active compounds through cellular barriers. The intestinal cells have tight junctions which some nanocarriers can open while other nanocarriers enter cells through endocytosis to enhance bioactive compound delivery into the bloodstream. The use of nanotechnology protects sensitive nutraceutical ingredients from gastrointestinal tract degradation which includes stomach acid and enzymes and oxidation because the compound reaches the absorption site without damage. Lipid-based systems which include nanoemulsions and solid lipid nanoparticles provide enhanced lipophilic compound absorption through lymphatic transport which bypasses the liver to increase systemic bioavailability. [98].

6.2. Improved Absorption and Bioavailability

The use of nanotechnology in nutraceutical delivery systems provides two major advantages through its ability to enhance both absorption and bioavailability. The bioactive compounds present in nutraceuticals, which include curcumin, resveratrol, coenzyme Q10, and omega-3 fatty acids, experience difficulties during gastrointestinal absorption because of their dual problems of poor water solubility and unstable chemical nature. Nanotechnology enables the solution of these challenges through the conversion of these substances into nanosized materials which the body can more efficiently dissolve and absorb and utilize. The process of

reducing particle size to the nanometer range results in an increased surface area which enables the compound to dissolve better and reach higher dissolution rates in biological fluids. The Noyes–Whitney equation shows that smaller particles dissolve at faster rates which results in increased active compound concentration that becomes available for absorption[99]. The intestinal lining enhancement directly results from better dissolution which occurs through improved dissolution process. The nanocarriers which include nanoparticles and liposomes and nanoemulsions and micelles enable better contact with biological membranes which results in higher permeability to active substances that can now penetrate cell barriers. The bioactive compound has more systemic circulation access because certain nanocarriers can either open tight junctions between intestinal cells or enter the body through endocytosis. Nanotechnology safeguards delicate nutraceutical components from digestive system destruction which includes stomach acid and enzymes and oxidation because the compound must reach the absorption area unbroken. The lymphatic system enables lipophilic compounds to be absorbed more effectively from lipid-based systems which include nanoemulsions and solid lipid nanoparticles because this method skips the liver and first-pass metabolism process which results in increased systemic bioavailability.[100]

6.3. Controlled and Sustained Release

Nanotechnology-based systems provide their primary benefit through their capability to deliver substances in a controlled manner through sustained release. The method creates bioactive compounds which exist as nanocarrier-encapsulated substances that control their body release schedule. The system provides controlled release which delivers active ingredients throughout an extended period instead of providing instant product delivery. The system maintains stable blood levels of the compound which leads to better treatment results and needs less medicine and causes fewer unwanted effects. The bioactive compound exits the nanocarrier matrix through three different methods which include diffusion and erosion and swelling. Some systems use specific physiological stimuli which include pH and temperature and enzyme activity to release the nutrient only when certain conditions exist. The system protects delicate substances from early breakdown in the gastrointestinal tract while it guarantees that the nutrient will be delivered at the exact necessary moment and location. The process of controlled and sustained release leads to improved nutraceutical stability and bioavailability and better functional performance of nutraceuticals[101].

6.4. Site-Specific and Precision Nutrition Benefits

Nanotechnology enables targeted nutrient delivery which aligns with precision nutrition that delivers nutrients to specific body parts according to individual requirements. The surface of nanocarriers gets modified through ligand targeting which uses peptides and polysaccharides and antibodies to deliver nutraceuticals to specific body locations including intestines and liver and particular cell receptors. The targeted method delivers active compounds to their most effective locations which helps to decrease negative effects while improving operational productivity. The development of personalized nutraceutical formulations through nanotechnology allows for precise dietary recommendations based on an individual's genetic information and metabolic characteristics and health conditions. This approach ensures that nutrients get used most effectively which results in better therapeutic results. Site-specific and precision delivery systems enhance nutrient bioefficacy while they help prevent diseases and maintain optimal health through precise nutritional assessments.[102]

7. SAFETY, REGULATORY, AND ETHICAL CONSIDERATIONS

The application of nanotechnology in nutraceuticals shows significant promise but it creates multiple safety issues and regulatory challenges and ethical problems. The safety assessment process evaluates how nanoparticles interact with human health through their toxicity and biocompatibility and their long-lasting impacts because some nanomaterials will build up in body tissues and create unexpected health effects. Before companies can start selling their products to consumers, they need to conduct proper risk assessment and toxicology research.Currently, the field of nano-nutraceuticals lacks standardized international regulating protocols which should address this emerging market. The FDA and EFSA mandate companies to conduct in-depth material testing and safety assessments and product classification when dealing with nanomaterials because these procedures protect both product quality and consumer rights. Manufacturers must implement good manufacturing practices (GMP) while proving their products achieve safety and effectiveness standards through credible evidence. The main ethical issues surround three aspects which include transparent product

labeling and the ability of consumers to make informed choices and the need to protect the environment. The ethical application of the technology requires proper use of nanotechnology to benefit human health while avoiding deceptive marketing practices[103].

7.1 Nanotoxicity and Long-Term Safety

Nanotoxicity and long-term safety represent vital aspects which must be assessed throughout all stages of developing and using nanotechnology-based nutraceuticals. The advantages of nanotechnology include better solubility and improved absorption together with precise delivery systems, yet its nanoparticles present health dangers because of their tiny dimensions and high reactivity. Nanoparticles possess the ability to traverse biological barriers which enable them to access cells and form connections with DNA and proteins and lipids found within cells. The uncontrolled interactions between these substances and the body may result in oxidative stress and tissue destruction which leads to inflammation and damage. Certain nanoparticles have the potential to build up in organs such as the liver and kidneys and brain which can result in toxic effects from extended exposure. The safety profile of nanoparticles depends on their chemical makeup and particle dimensions and particle shapes and surface electrical charge and particle dosage. The safety of nano-nutraceuticals requires assessment because their ongoing consumption creates a risk of building up nanoparticles and causing metabolic disruptions. The existing research about nanomaterials shows limited information about their long-term effects and their ability to break down in the human body since most nanomaterials have emerged only recently. The process requires thorough toxicological assessments together with practical research and evaluation of extended effects before any product can proceed to market launch. The testing procedures must meet established standards, while the product information needs to provide precise details and safety information needs to be presented clearly to protect consumers, according to regulatory authorities [104].

7.2 Regulatory Frameworks for Nano-Nutraceuticals

Nanotoxicity and long-term safety serve as essential requirements for developing and implementing nanotechnology-based nutraceuticals. Nanotechnology enables substantial advantages because it enhances solubility and absorption together with providing precise delivery methods, however, nanoparticles present danger to health because of their extremely small dimensions and their ability to react with other substances. Nanoparticles possess the capability to traverse biological boundaries, which enables them to penetrate cells and engage with essential cellular elements, including DNA and proteins and lipids. The uncontrolled system leads to oxidative stress and inflammation together with cellular harm. The accumulation of certain nanoparticles in organs, including the liver and kidneys and brain, results in potential toxicity risks, which increase with extended exposure. The safety profile of nanoparticles depends on their chemical composition together with their particle size, shape, surface charge, and administered dose. The permanent safety of nano-nutraceuticals constitutes a risk because their continuous or repeated intake leads to nanoparticle buildup and metabolic disorders. The human body lacks comprehensive data about new nanomaterials because most of them exist as recent innovations with unknown chronic effects and biodegradability patterns. The approval of products requires extensive toxicological evaluations together with in vivo tests and monitoring of results over extended time periods. To protect consumers, regulatory authorities require standardized testing methods together with clear labeling and transparent safety data disclosure.

7.3 Consumer Awareness and Acceptance

The successful introduction of nanotechnology-based nutraceuticals depends on two factors which are consumer awareness and consumer acceptance. The public lacks understanding about how nanotechnology functions in food and nutrition products despite the technology providing multiple benefits which include better absorption and ability to deliver specific health advantages. Many consumers may be skeptical or cautious due to safety concerns which include toxic effects and incomplete information about long-term safety. Businesses need to create educational content about their product development procedures which helps them build consumer trust by showing the benefits and safety of their nano-nutraceuticals. Businesses and regulatory agencies must disclose complete information about the specific nanomaterials they use and their intended functions and the results of their safety assessments. This helps consumers make informed choices while it decreases common misunderstandings. People develop opinions based on their ethical and

environmental values which extend to their views about how nanoparticles affect human health and the balance of nature. The public needs to develop trust through three specific practices which include thorough testing and responsible marketing and meeting safety standards.[106]

8. FUTURE PERSPECTIVES AND CHALLENGES

Future advancements in nano-nutraceuticals will focus on smarter, more precise delivery systems, improved safety profiles, and personalized nutrition based on individual needs. Emerging technologies such as stimuli-responsive nanoparticles and AI-driven formulation design will enhance efficacy and targeted release. However, key challenges remain, including long-term toxicity concerns, high production costs, regulatory uncertainties, consumer acceptance issues, and the need for standardized testing methods. Balancing innovation with safety, affordability, and transparency will be essential for future progress.

8.1 Smart and Personalized Nutraceutical Delivery

The delivery system for nutraceuticals provides smart personalized delivery of nutrients and bioactive compounds through its specialized method which matches the unique needs of each individual. The new concept uses scientific tools which include nanotechnology and biosensors and genetic profiling and digital health monitoring to create personalized nutrient solutions while traditional nutraceuticals deliver fixed doses to all users. The systems maintain proper nutraceutical delivery to the body by supplying the correct amount at scheduled times to designated body locations which need the substance. Smart delivery systems use advanced carriers which include nanoparticles and nanoemulsions and liposomes and hydrogels to protect delicate components while enhancing their absorption and bioavailability. The smart carriers respond to changes in internal body conditions which include pH levels and enzyme concentrations and oxidative stress and inflammation to release nutrients at necessary times. The process leads to better nutrient absorption and fewer side effects and more effective treatment outcomes. The system creates personalized results through examination of a person's genetic makeup and metabolic processes and their daily routines and intestinal microbiome. The combination of wearable devices and mobile health applications supports personalized nutrition through its continuous monitoring of physical activity and heart rate and glucose levels and sleep patterns. Nutraceuticals require customized formulations which match the health objectives of each user based on the information they provide.

8.2 Green Nanotechnology and Sustainable Approaches

Green nanotechnology refers to the design, production, and application of nanomaterials and nanodevices which use environmentally friendly and safe and sustainable methods of manufacturing. The research aims to decrease the ecological effects of nanotechnology by decreasing energy requirements and eliminating hazardous substances and advancing the use of sustainable energy resources. The goal of green nanotechnology is to achieve environmentally friendly nanomaterial production methods which maintain sustainability throughout the complete life cycle from material creation to final disposal. Green nanotechnology uses natural biological systems to create nanoparticles which serve as its main method of nanoparticle production. The process uses plants and microorganisms and algae and enzymes and biodegradable polymers as reducing and stabilizing agents to create nanoparticles without dangerous chemical substances. The process decreases environmental contamination while producing biocompatible and safer nanomaterials which scientists use in medical and food and agricultural and environmental protection fields108. The sustainable methods support microwave-assisted and ultrasonic and solvent-free synthesis methods which create energy-efficient products while reducing waste and resource needs. Green nanotechnology helps create nanomaterials which can be fully recycled or biodegradable thus preventing environmental persistence and protecting ecosystems from extended damage.Green nanotechnology enables environmental cleanup through its development of nanomaterials which function to purify water and eliminate contaminants and collect heavy metals and enhance soil quality. The eco-friendly nanodevices support cleaner ecosystems while combating global issues such as water scarcity and pollution109.

8.3 Integration with Artificial Intelligence and Biosensors

Artificial intelligence (AI) and biosensor technology have created a new paradigm for nutraceutical delivery systems because these systems now enable continuous tracking of health data while delivering

personalized health information and managing the exact timing of active compound release. Biosensors operate as testing devices which can identify biological signals through their ability to measure glucose concentration and oxidative stress and inflammation indicators and pH values and essential nutrient shortages. The sensors deliver uninterrupted precise physiological monitoring when their data streams are analyzed by AI technology. AI algorithms can process the vast amount of data generated by wearable and implantable biosensors to identify patterns which let them predict nutritional requirements with high accuracy. The system creates customized nutraceutical plans which match the specific metabolic and lifestyle and health objectives of each user. Smart delivery systems use biosensor technology to release nutraceuticals only after specific environmental changes reach a particular threshold which helps to optimize nutrient absorption and distribution[110]. The AI system assists researchers in developing new formulations by creating optimal nano-carrier systems which allow them to determine product stability and bioavailability and safety assessments. The system helps precision nutrition researchers to make better choices because it combines genomic data with metabolomic information and gut microbiome research and daily health status updates.

8.4 Pathways for Commercialization

The term pathways for commercialization describes the specific processes and strategic methods which organizations need to follow in order to develop scientific discoveries or nutraceutical innovations into products that reach commercial markets. The process validates that the product meets scientific standards while achieving economic viability and consumer acceptance and maintaining safety and regulatory compliance. The first step of research validation requires scientists to prove through laboratory studies and pilot-scale trials that the nutraceutical formulation provides functional benefits while maintaining safety and stability. The subsequent phase after validation requires companies to establish intellectual property protection through patents and trademarks and licensing agreements which protect their technology and create market advantage[111]. The product enters the regulatory approval process after the organization has established its intellectual property protection, which verifies that the product meets all national and international standards. The market requires organizations to meet FSSAI and FDA and EFSA guidelines, which depend on their specific operational requirements. Companies implement their plans to increase production capacity by transitioning from laboratory synthesis to industrial manufacturing while preserving product quality and reproducibility and maintaining cost efficiency. Organizations need to establish partnerships with manufacturing units and ingredient suppliers and technology providers during this stage. The next pathway requires market analysis and product positioning, which involves identifying target consumers and competitive products and pricing strategies and branding. The marketing team promotes the product through its distinctive characteristics, which include nano-encapsulation and smart delivery and personalized formulations. The organization creates distribution channels through online platforms and pharmacies and health stores and clinical networks to achieve effective product distribution.

Post-market surveillance activities serve as the final essential component which enables organizations to achieve successful commercialization.

CONCLUSION

Nanotechnology provides an enabling platform for the overcoming of the limitations of traditional nutraceutical delivery systems. With enhanced bioavailability, stability, and targeted and controlled release, nano-based strategies have unmatched promise to drive the design of functional foods, dietary supplements, and therapeutic nutrition. The destiny of nano-nutraceuticals is the development of smart, safe, and sustainable nanocarriers that can facilitate personalized nutrition and disease prevention programs. Through further innovations and harmonization of regulation, nanotechnology for nutraceutical delivery has the potential to transform the healthcare and functional food sectors.

Acknowledgement

The authors would like to express their sincere gratitude to Deep Science Publishers for providing the opportunity to contribute to this work. Their continuous support, guidance, and commitment to academic

excellence are highly appreciated. The authors also acknowledge all contributors whose efforts and cooperation made this work possible.

Authors' Contributions

The authors would like to thank the Editors and Deep Science Publishers for providing this valuable opportunity. The authors also sincerely acknowledge Priya Singh for their contributions toward drafting, grammatical modification, and overall quality improvement of the manuscript.

REFERENCES

1. Mehta, J., Pathania, K., & Pawar, S. V. (2025). Recent overview of nanotechnology based approaches for targeted delivery of nutraceuticals. *Sustainable Food Technology*, 3(4), 947–978.
2. Ramani, M. S. (2025). Nanoemulsions in Drug Delivery and Biomedical Applications: Regulatory Challenges, Guidelines and Future Directions. *International Journal of Pharmaceutical Sciences*, 3(8), 2614–2628.
3. Elsewedy, A. A., et al. (2025). Insights of Nanoemulsion as a Drug Delivery System: An Overview of Current Trends and Applications. *Indian Journal of Pharmaceutical Education and Research*, 59(2), 472–483.
4. Dharme, J., et al. (2025). Nanosuspension Innovations: Expanding Horizons in Drug Delivery Techniques. *Nanomedicine*, 19(1), 101–114.
5. Teli S, Shah TM. Design solid lipid nanoparticle solid lipid nanoparticle (SLNs) of dapagliflozin for enhanced oral bioavailability and controlled release in type 2 diabetes. African Journal of Biological Sciences. 2022;4(1):287-306.
6. Vidyadhari, J., et al. (2023). Nanosuspensions: A Strategy to Increase the Solubility and Bioavailability of Poorly Water-Soluble Drugs. *Asian Journal of Pharmaceutical and Clinical Research*, 16(5), 33–40.
7. Vasanth S, Mishra R, Sahoo S, Parveen S, Khan Z, Mumtaz, Ruqaiya, Pal R. Advancing Mitochondrial Health in Huntington Disease (HD): Small Molecule Therapies and Neurodegeneration. Current aging science. 2025.
8. Pandey, S., & Pandey, M. K. (2025). Advancement in nanobubble technology: enhancing drug and nutraceutical delivery with focus on bioavailability, targeted therapy, safety, and sustainability. *Frontiers in Nanotechnology*, 6(13), 1548593.
9. Al-Musawi, S., et al. (2025). Stimuli-Responsive (Smart) Drug Delivery Systems: An In-Depth Review. *Journal of Drug Delivery Science and Technology*, 106, 104711.
10. Li, T., et al. (2024). Application of Nanoparticles in Human Nutrition: A Review. *Nutrients*, 16(5), 636.
11. Huang Q, Yu L. Bioavailability and Delivery of Nutraceuticals Using Nano-Delivery Systems. J Food Sci. 2010;75(1):R1-R8.
12. Gupta U, Kosey S, Pal R. Advancements in nanotechnology-based targeted drug delivery systems for glioblastoma chemotherapy: A comprehensive review. Journal of Drug Delivery Science and Technology. 2025 Sep 1;111:107181.
13. Patil S, Chaudhari B, Acharya M. Emerging Nano-Formulation Strategies for Nutraceutical Delivery. Adv Food Process Technol. 2023;4:127.
14. Pateiro M, et al. "Nanoencapsulation of Promising Bioactive Compounds to Improve Their Absorption, Stability and Bioavailability." Molecules. 2021;26(12):3630.
15. Lelis C.A., et al. "A Systematic Review on Nanoencapsulation Natural Bioactive Compounds: Techniques, Wall Materials and Release Mechanisms." *Int. J. Mol. Sci.* 2021;22(21):12055.
16. "Review: Recent Advancement in Nanoencapsulation." J. Pharm. Res. Appl. 2023;8(2):1218-1227.
17. Kamble M.G., Singh A., et al. "Nanotechnology for Encapsulation of Bioactive Components: A Review." Discover Food. 2025;5:116.
18. Suganya V., Anuradha V. "Microencapsulation and Nanoencapsulation: A Review." IJPCR. 2017;9(3):233–239.
19. Arshad R., et al. "Nanotechnology: A novel tool to enhance the bioavailability of micronutrients." *Food Sci Nutr.* 2021;9(4):1514-1524.
20. Altemimi A.B., Farag H.A.M., Salih T.H., et al. "Application of Nanoparticles in Human Nutrition: A Review." Nutrients. 2024;16(5):636.
21. Mishra R, Pal R, Khan Z, Sahoo S, Chawra HS, Kumar D. Solid lipid nanoparticles (SLNPs): a state-of-the-art formulation strategy and their applications against tuberculosis (TB) and analgesic effects. Nanoscience & Nanotechnology-Asia. 2025 Jun;15(3):E22106812379362.

22. Mehta J., Pathania K., Pawar S.V. "Recent overview of nanotechnology-based approaches for targeted delivery of nutraceuticals." *Sustainable Food Technol.* 2025;3:947-978.

23. Sultana A., Uddin M.A., Maseera R., Ahmed M.G. "Scope of nanotechnology in nutraceuticals, cosmeceuticals and dentistry – Review." Int J Pharm Sci & Res. 2023;14(1):56-61.

24. Sana, S. S., & Li, Y. (2020). "Smart Stimuli-Responsive Nanocarriers for Controlled Release." Advanced Drug Delivery Reviews, 156, 36–51.

25. Duarte, J., Pereira, C., Dias, J. R., & Gil, M. H. (2025). Polymeric Nanoparticles in Targeted Drug Delivery: Unveiling the Impact of Polymer Characterization and Fabrication. *Polymers*, 17(7), 833.

26. Singh, R. P., et al. (2023). Recent Advances in Polymeric Nanoparticles for Oral Delivery of Biologics: A Pharmaceutics Perspective. *Journal of Pharmaceutical Research in Modern Sciences*, 1(1), 1-15.

27. Karantonis, C., Moreno-Rojas, J. M., Tang, C.-H., Chen, H.-L., & Dong, J.-R. (2023). Solid Lipid Nanoparticles {SLNs} and Nanostructured Lipid Carriers {NLCs} as Food-Grade Nanovehicles for Hydrophobic Nutraceuticals or Bioactives. *Applied Sciences*, 13(3), 1726.

28. Pal R, Pandey P, Chawra HS, Singh RP. Niosomal as potential vesicular drug nano-carriers for the treatment of tuberculosis (TB). Nanoscience & Nanotechnology-Asia. 2025 Feb;15(1):E22106812323829.

29. Ashfaq, R., Rasul, A., Asghar, S., Kovács, A., Berkó, S., & Budai-Szűcs, M. (2023). Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. *International Journal of Molecular Sciences*, 24(21), 15764.

30. López, K. L., Ravasio, A., González-Aramundiz, J. V., & Zacconi, F. C. (2023). Solid Lipid Nanoparticles and Nanostructured Lipid Carriers Prepared by Microwave and Ultrasound-Assisted Synthesis: Promising Green Strategies for the Nanoworld. *Pharmaceutics*, 15(5)1333.

31. Chand, P., et al. (2025). Nanostructured lipid carriers {NLCs}: A comprehensive review of drug delivery advancements. *Journal of Applied Pharmaceutical Research*, 13(2), 23-34.

32. Elbialy, N. S., & Zaid, S. S. (2023). Liposomes: a promising delivery system for active ingredients in food and nutrition. *International Journal of Food Science and Technology*, *58*(11), 6061-6072.

33. Pachani, Sachin & Shah, Tapaskumar. (2021). Formulation of Paclitaxel-Encapsulated Polymeric Micelles For Targeted Breast Cancer Therapy. Journal of Population Therapeutics and Clinical Pharmacology. 28. 936-951. 10.53555/m318xt37.

34. S. Chauhan, P. Chand, & T. Parashar. (2025). Lipid-based Nanoparticles: Strategy for Targeted Cancer Therapy. *Bio-Integration*.

35. Duarte, A., et al. (2025). Non-Ionic Surfactant Vesicles (Niosomes) for Nutraceutical Delivery: Formulation, Optimization, and Future Trends. *Journal of Functional Foods*, 22(4), 1060-1075.

36. Pal R, Pandey P, Chawra HS, Khan Z. Nano drug delivery carriers (Nanocarriers): A promising targeted strategy in tuberculosis and pain treatment. Pharmaceutical Nanotechnology. 2025 Mar 7.

37. Hassan, H. M., & El-Setouhy, D. A. (2023). Niosomes: Versatile Nanocarriers for Enhanced Bioavailability and Targeted Delivery of Phytochemicals. *International Journal of Pharmaceutics*, 648, 126135.

38. Ramani, M. S., et al. (2025). Nanoemulsions in Drug Delivery and Biomedical Applications: Regulatory Challenges, Guidelines and Future Directions. *International Journal of Pharmaceutical Sciences*, 3(8), 2614–2628.

39. Ahmad, A., et al. (2024). Advances in Nanoemulsion Technology for Enhanced Oral Bioavailability of Lipophilic Nutraceuticals. *Foods*,13(12), 1850.

40. Pachani, Raj & Shah, Tapaskumar & Soni, Dhruv. (2021). Advances In Peptide-And Antibody-Targeted Nanocarriers For Cancer Therapy And Imaging. 28. 392-419. 10.53555/3sadmc24.

41. Morais, L., & Pinto, A. M. (2024). Microemulsions as Versatile Systems for Encapsulation of Natural Active Compounds. *Separation and Purification Technology*, 335(4), 125950.

42. Priyadarshini, M., & Thangam, R. (2024). Recent Advances in Microemulsion-Based Delivery Systems for Enhanced Solubility and Bioavailability of Curcumin. *Current Drug Delivery*, 21(1), 43-56.

43. Jafari, S. M., et al. (2023). Challenges and Future Prospects of Microemulsions in Food and Pharmaceutical Applications.

44. Li, C., et al. (2024). Zein-Caseinate Composite Nanoparticles for Improved Stability and Enhanced Bioavailability of Curcumin: A Food-Grade Delivery System. *Food Chemistry*,445, 138760.

45. Chai, X., et al. (2023). New Perspective on Natural Plant Protein-Based Nanocarriers for Bioactive Ingredients Delivery. *Foods*,12(12), 2383.

46. Zhang, Y., & Liu, X. (2024). Natural Polysaccharide-Based Nanodrug Delivery Systems for Treatment of Metabolic Disorders. *Polymers*,16(1), 33.

47. Amar K, Sahoo S, Mishra R, Dutta P, Ghosh B, Pal R. Lipidic nanocarriers (liposomes): A potential targeting strategy for cosmeceutical and therapeutic applications—an in-depth review. Curr Nanomed. 2026;16:e24681873411316. doi:10.2174/0124681873411316251118051648.

48. Patil, S., et al. (2023). Emerging Nano-Formulation Strategies for Nutraceutical Delivery: Focus on Nanohydrogels and Nanoemulgels. *Journal of Pharmaceutical Research in Modern Sciences*, $2(1)$, 1-12.

49. Singh, R., et al. (2025). Stimuli-Responsive Nanogels: Tailoring Release Kinetics for Enhanced Bioavailability of Phytochemicals. *ACS Nano*, $19(4)$, 3012-3028.

50. Karimi-Nami, H., et al. (2024). Electrospun Nanofibers for the Delivery of Bioactive Food Components: Current Trends and Future Opportunities. *Trends in Food Science & Technology*, 143, 106366.

51. Shahriar, M. S., et al. (2023). Core-Shell Electrospun Nanofibers: Design Strategies for Controlled and Sustained Release of Nutraceuticals. *Journal of Controlled Release*, 364, 540-557.

52. Gheorghita, R., et al. (2024). Natural and Synthetic Polymeric Nanofibers in Transdermal Drug Delivery Systems: A Critical Review. *Polymers*, 16(2), 238.

53. Hassan, F., et al. (2024). Advances in Mesoporous Silica Nanoparticles {MSNs}for Enhanced Oral Delivery of Poorly Soluble Nutraceuticals. *International Journal of Pharmaceutics*, 654, 126909.

54. Shukla, V., et al. (2023). Magnetic Nanoparticles for Targeted Delivery of Phytochemicals in Cancer Therapy and Imaging: A Theranostic Approach. *Advanced Drug Delivery Reviews*, 201, 114002.

55. Shah, Tapaskumar. (2020). Advancing Formulation Science in Diabetes and Migraine: From Conventional Therapies to Precision Drug Delivery. Journal of Cardiovascular Disease Research. 11. 358-372.

56. Zhu, Y., et al. (2023). Toxicity and Safety Assessment of Inorganic Nanoparticles in Food and Biomedical Applications. *Environmental Science: Nano*, 10(9), 3450-3465.

57. Chao N, Yan Y, Li S, et al. Enhancement of EPR Effect for Passive Tumor Targeting: Current Status and Future Perspectives. *Appl Sci*. 2024; 15(6):3189.

58. Rai R, Gidwani B, Shukla S, Singh V, Kaur CD. Emerging Nano-Formulation Strategies for Nutraceutical Delivery. *Adv Food Process Technol*. 2023; 4: 127.

59. Koli M, Shah TM, Dutta P, Patel N, Patel AK, Ghosh B, Singh A, Pal R. Non-Ionic Surfactants (NIOs) in Niosome Drug Delivery: In-Depth Review of Clinical Trials, Patents in Tuberculosis (TB) and Oncology. Current Nanomedicine. 2025. doi:10.2174/0124681873413153251014082026

60. Ventola CL. Nanomedicine in Drug Delivery and Cancer Therapy: Applications, Challenges, and Clinical Translation. *P T*. 2022; 47(11):620-624.

61. Reverchon E, Sessa M, Iannuzzo F, Della Porta G. Recent Developments in Nanocarrier-Based Nutraceuticals for Therapeutic Purposes. *Crit Rev Food Sci Nutr*. 2020;37(4).

62. Zhu Y, Liu X, Jiang C, et al. Different Targeting Ligands-Mediated Drug Delivery Systems for Tumor Therapy. *Pharmaceutics*. 2024;16(2):248.

63. Agwa MM, Marzouk RE, Sabra SA. Advances in active targeting of ligand-directed polymeric nanomicelles via exploiting overexpressed cellular receptors for precise nanomedicine. *RSC Adv*. 2024;14(32):23520-23542.

64. Agama I, Pinho J, Gomes C, et al. Folic Acid-Decorated Nanocrystals as Highly Loaded Trojan Horses to Target Cancer Cells. *Mol Pharmaceut*. 2024;21(6):2740-2750.

65. Wang P, Gao S, Wang D, et al. Surface Functionalization of Nanocarriers with Anti-EGFR Ligands for Cancer Active Targeting. *Nanomaterials*. 2024;15(3):158.

66. Zulfiqar F, Anjum S, Awasthi A, et al. Significance of Ligand-Anchored Polymers for Drug Targeting in the Treatment of Colonic Disorders. *Front Pharmacol*. 2020;10:1628.

67. Gomila-Vila G, Valls M, Pîrvu C, Fàbregas D. Next-Generation Drug Delivery for Neurotherapeutics: The Promise of Stimuli-Triggered Nanocarriers. *Biomedicines*. 2024;12(6):1464.

68. Mali S, Kulkarni A, Kulkarni D, Kulkarni V. "Smart" drug delivery: A window to future of translational medicine. *Front Chem*. 2022;10:1095598.

69. Agwa MM, Elgendy K, Marzouk RE, Sabra SA. 2D materials for nutraceutical delivery and smart packaging: multifunctional, sustainable, and responsive applications. *RSC Adv*. 2025;15(42):35233–35252.

70. Abdelrahman M, Aboelmagd M, Farghaly A, et al. Current Advances in Stimuli-Responsive Hydrogels as Smart Drug Delivery Carriers. *Gels*. 2023; 9(10):838.

71. Ansari MJ, Ansari M, Tabish M, et al. Nanomaterials as Delivery Systems for Phytochemicals: Recent Advances and Future Perspectives. *Pharmaceutics*. 2021; 13(11):1858.

72. Dhasmana, A., & Gupta, P. K. (2020). Nanotechnology in nutraceuticals: a comprehensive review of its applications, challenges, and future prospects. *Drug Delivery and Translational Research*, *10*(6), 1612-1634.

73. Weiss, J., Takhistov, P., & McClements, D. J. (2006). Functional materials in food nanotechnology. *Journal of Food Science*, *71*(9), R107-R116.

74. Mozafari, M. R. (2010). Nanocarrier technologies for the delivery of food ingredients and nutraceuticals. *Trends in Food Science & Technology*, *21*(9), 417-432.

75. Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: problems and promises. *Molecular Pharmaceutics*, *4*(6), 807-818. (Supports the challenges section on Curcumin's poor bioavailability).

76. Garg, V., Khan, R., & Singh, P. K. (2021). Curcumin nanoformulations: A comprehensive review of their development and application in cancer therapy. *Drug Delivery and Translational Research*, *11*(4), 1362-1383.

77. Kumari, A., Yadav, S. K., Yadav, S. C., & Singh, M. (2020). Curcumin nanoformulations in neurodegenerative disorders: A comprehensive review. *International Journal of Nanomedicine*, *15*, 2491-2508.

78. Amri, B., Chaumeil, J. C., Sfar, S., & Devissaguet, J. P. (2012). Administration of resveratrol: what formulation strategies should be followed? *Journal of Controlled Release*, *158*(1), 1-12. (Supports the challenges section on Resveratrol's low bioavailability).

79. Zhang, H., Gao, X., Zhao, Y., & Li, F. (2018). Resveratrol-loaded lipid nanocarriers: A review on their development, characterization, and applications. *Molecules*, *23*(3), 666.

80. Vyas, A., Singh, A., & Jain, N. K. (2016). Solid lipid nanoparticles (SLNs) as a novel carrier for enhanced brain delivery of resveratrol. *Drug Development and Industrial Pharmacy*, *42*(7), 1146-1153.

81. McClements, D. J., & Gumus, C. E. (2016). Nanotechnology approaches for increasing the effectiveness of nutraceuticals. *Annual Review of Food Science and Technology*, *7*, 437-458. (Relevant for nanoemulsions for lipid-soluble components).

82. Pouton, C. W. (2006). Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *European Journal of Pharmaceutical Sciences*, *29*(3-4), 278-287.

83. Bhatt, P. B., & Jain, N. K. (2018). Nanotechnology in the delivery of omega-3 fatty acids: advantages and applications. *Expert Opinion on Drug Delivery*, *15*(1), 77-88.

84. Yilmaz, S., & Gümüsay, O. A. (2020). Nanoencapsulation of probiotics and its applications in functional foods. *Food Bioscience*, *38*, 100782.

85. Gandomi, H., Abbaszadeh, S., Misaghi, A., Basti, A. A., & Bokaei, S. (2016). Effect of chitosan–alginate encapsulation on the viability of *Lactobacillus acidophilus* during exposure to simulated gastrointestinal conditions and heat treatment. *LWT - Food Science and Technology*, *69*, 365-371.

86. Hossain, S. M., Al-Ghamdi, H., Areeshi, M. Y., & Ashraf, S. M. (2023). Nanocarriers for targeted delivery of probiotics. *Journal of Drug Delivery Science and Technology*, *84*, 104523.

87. Teng, F., Fan, Y., & Zhong, Q. (2019). Nano-encapsulation of polyphenols for enhanced stability and bioavailability. *Current Opinion in Food Science*, *28*, 33-39.

88. Dabestani, S., & Khandani, A. A. (2020). Enhancing the bioavailability of carotenoids using nanotechnology: A systematic review. *International Journal of Food Science and Technology*, *55*(2), 481-492.

89. Jafari, S. M., Maleki, H., & Kadkhodaee, R. (2017). Nano-encapsulation of natural food colorants and antioxidants in nanostructured lipid carriers. *Trends in Food Science & Technology*, *66*, 129-143.

90. Ambani, J., Gendelman, H. E., & Mosley, R. L. (2014). Nanotechnology for CNS drug delivery and neurological disorders. *Journal of Controlled Release*, *190*, 25-31. (Supports Brain-Targeted delivery).

91. Li, P., Zhu, X., Huang, J., Guo, J., Li, T., & Wu, C. (2020). Gastrointestinal tract-targeted delivery of nutraceuticals using nanoparticles. *Advanced Drug Delivery Reviews*, *159*, 164-184. (Supports Gut-Targeted delivery).

92. Patel, A., et al. (2019). "pH-Sensitive Nanoparticles for Oral Delivery of Nutraceuticals." Journal of Controlled Release, 294, 268–299.

93. Sogias, I. A., et al. (2008). "Chitosan Derivatives and Their Applications in Drug Delivery." Carbohydrate Polymers, 74(4), 813–821.

94. McClements, D. J. (2020). Nanoencapsulation Technologies for Nutraceuticals. Elsevier.

95. Goyal, R., & Macri, L. (2021). "Eudragit-Based pH-Controlled Release Nanocarriers." International Journal of Pharmaceutics, 606, 120899.

96. Li, J., & Mooney, D. J. (2016). "Designing Biodegradable Hydrogels for Controlled Release." Nature Reviews Materials, 1, 16071.

97. McClements, D. J. (2017). "Enhancing Nutrient Bioavailability with Nanotechnology." Annual Review of Food Science and Technology, 8, 105–125.

98. Jafari, S. M. (Ed.). (2017). Nanoencapsulation of Food Bioactive Ingredients: Principles and Applications. Elsevier.

99. Acosta, E. (2009). "Bioavailability of Nanoparticles in the gastrointestinal Tract." Journal of Pharmaceutical Sciences, 98(9), 3497–3509.

100. Khoo, Y. C., et al. (2019). "Lipid-Based Nanocarriers Enhance Oral Bioavailability via Lymphatic Transport." Advanced Drug Delivery Reviews, 142, 108–126.

101. Rizvi, S. A. A., & Saleh, A. M. (2018). "Applications of Nanoparticles in Controlled Drug Delivery." Saudi Pharmaceutical Journal, 26(1), 64–70.

102. Sperling, R. A., & Parak, W. J. (2010). "Surface Functionalization and Targeting of Nanoparticles." Philosophical Transactions of the Royal Society A, 368, 1333–1383.

103. Fadeel, B., et al. (2018). "Safety Assessment of Engineered Nanomaterials: A Focus on Nanotoxicology." *Advanced Drug Delivery Reviews*, 143, 3–20.

104. U.S. Food and Drug Administration (FDA). (2014). Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology.

105. Gupta, N., et al. (2013). "Consumer Attitudes Toward Nanotechnology in Food." Journal of Food Science, 78(10), R1771–R1780.

106. Frewer, L. J., et al. (2014). "Consumer Perceptions of Emerging Technologies: Nanotechnology in Food." Trends in Food Science & Technology, 40(2), 211–225.

107. Iravani, S. (2011). "Green synthesis of metal nanoparticles using plants." Green Chemistry, 13(10), 2638–2650.

108. Kumar, A., Dixit, C. K. (2017). "Methods for synthesis of green nanoparticles and their applications." In: Biosensors Nanotechnology. Springer, pp. 1–22.

109. Wang, Y., Chen, Z., & Zhang, D. (2021). "Artificial intelligence–integrated biosensors for personalized healthcare and smart delivery systems." Biosensors and Bioelectronics, 176, 112—120.

110. Bordini, D. R., et al. (2020). "Intellectual property and commercialization strategies for nutraceutical innovations." Journal of Functional Foods, 72, 104—116.

111. Bagchi, D., & Nair, S. (2019). Developing New Functional Food and Nutraceutical Products. Academic Press.

112. Weiss, J., Takhistov, P., & McClements, D. J. (2006). Functional materials in food nanotechnology. *Journal of Food Science*, *71*(9), R107-R116.