Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-822-9_13

Chapter 13: Regulatory and Safety Challenges in Nano-Targeted Nutraceutical Development

Susovan Borat*[1], Shudesna Sarkar[2], Shipra Srivstava[3], Sonal Sharma[4], Subhajit Chakraborty[5], Akansha Bisht[1]

[1] *Jagannath University, Department of Pharmacy, NH-12, Chaksu Bypass Road, Tonk, Jaisinghpura, Rajasthan 303901, India.*
[2] *Dooars Institute of Pharmaceutical Sciences and Research (DIPSAR), Department of Pharmaceutical Chemistry, 31, Ghoksadanga, Unishbisha, West Bengal, 736171.*
[3]*Deparment of Naturopathy & Yogic Sciences, NH-12, Chaksu Bypass Road, Tonk, Jaisinghpura, Rajasthan 303901, India.*
[4]*Mahatma Gandhi College of Pharmaceutical Sciences, Jaipuer, Rajashthan, India.*
[5]*Department of Pharmacy, Tripura University, 799120, Tripura, India.*

Corresponding Author*
Mr. Susovan Borat
Email: *s.susovanborat@gmail.com*
Contact No: +91 8670441774

Abstract

Nanotechnology presents newer ways for nutraceutical preparation of site-specific delivery, stability, and bioavailability of the bioactive compounds. Nevertheless, they face the major regulatory and safety issues, therefore limiting their commercial and clinical application. Given some nanoscale properties such as altered pharmacokinetics, surface reactivity, and cellular absorption, traditional approaches of safety evaluation are questioned. Existing regulatory systems are disparate, without unified definitions, uniform testing criteria, and harmonized approval processes for nanomaterials in food and health foods. Issues of long-term toxicity, biodistribution, off-target toxicity, and cumulative exposure also add to complexity in risk assessment. The current paper critically assesses the gaps in regulation and safety concerns surrounding nano-targeted nutraceuticals, with a focus on the importance of coordinating globally aligned guidelines that include nanotoxicology, risk benefit considerations, and consumer protection. Creating strong, science-informed policies is key to maintaining a balance between innovation and safety, allowing for the safe development of nanotechnology in the nutraceutical industry.

Keyword: *Nano-targeted nutraceuticals, Regulatory frameworks, Nanotoxicology, Consumer safety.*

1. INTRODUCTION

1.1 Definition, Scope, and Importance:

Nano-targeted nutraceuticals are a novel approach of modern technology that combines nanotechnology with nutrition that are designed to develop the targeted delivery of bioactive compounds of food and their biological function in vivo (Barmherzig & Rajapakse, 2021). Nutraceuticals as such are products derived from food which offer extra health benefits in addition to the basic nutritional value present in food used to prevent or treat disease, a range of (commercially) marketable vitamins and supplements. Nanotechnology application to these formulations requires the development of carriers of nanoscale dimension (ranging typically from 1 to 100 nanometres) for the encapsulation or delivery of bioactive agents. The ability of nanoparticles to shield sensitive bioactive compounds from degradation due to environmental or enzymatic factors is another key advantage. This protection ensures that a greater fraction of the active ingredient reaches systemic circulation intact, ultimately translating into improved bioavailability and therapeutic efficacy (Makkar et al., 2020).

Nano-encapsulation strategies applied for nano-targeted delivery of nutraceuticals include nanocomposites, nano micelles, nano emulsions, lipidic carriers, etc., are being used in recent studies. Nanomicelles can encapsulate lipophilic molecules thanks to their core-shell structures, increasing their stability and bioactivity as well. In addition to enhancing absorption, nano-encapsulation permits tailoring of drug-release patterns and manipulation of tissue targeting, leading to improved safety and efficacy (Isola, 2020). Given these targeted and controlled release properties, such strategies not only improve the bioavailability of nutraceuticals but also the safety margin of the 'drugs.'

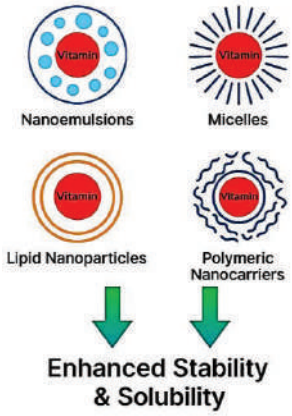


Figure 13.1. Schematic of Nano-Encapsulation Techniques

While the term 'nanoceutical' stems from the food science literature, it closely mirrors drug delivery principles by borrowing concepts from pharmacological discourse in terms of precisely manufactured products and selective localization. Thus, the nanoceuticals can be called 'pharmaceutical grade nutraceuticals' where the molecules are derived from natural food sources. Such modes of action can considerably raise the threshold effect by using nano-targeted delivery modalities to meaningfully counteract chronic pathological features driven by oxidative characteristics, gradient metabolic insults, or inflammatory underpinnings(Shields et al., 2023).

1.2 Current Trends and Market Growth:

The rising consumer awareness about health and wellness has fueled significant demand for functional foods and dietary supplements that deliver not only nutritional but also preventative and therapeutic benefits. This evolving consumer landscape has motivated the nutraceutical industry to adopt nanotechnology-based delivery systems, improving product performance in terms of absorption, efficacy, and stability. Industry

players, ranging from startups to multinational corporations, have increasingly invested in nano-engineering approaches aimed at differentiating products to capture market share by providing superior health outcomes(Martinović et al., 2020). Market analyses reveal robust growth trajectories for nano-nutraceuticals, driven by technological advancements in nanoparticle synthesis, encapsulation techniques, and characterization methods, alongside increasing consumer preference for natural yet efficacious health products. The global nano-nutraceutical market is expected to expand substantially over the coming decade, owing to rising prevalence of lifestyle-associated diseases, aging populations, and a growing preference for personalized nutrition. The integration of nanotechnology facilitates meeting these market demands through enhanced delivery systems that improve bioavailability of challenging bio actives such as polyphenols, carotenoids, and fat-soluble vitamins(Le et al., 2022). Economic benefits also follow improved therapeutic efficacy provided by nano-targeted delivery; this includes dose reduction possibilities, lowered manufacturing and distribution costs due to increased potency, and extended product shelf life. Moreover, the increasing trend for "clean label" and "natural ingredient" products propels demand for nano-enabled systems that maintain the natural character of nutraceutical ingredients while overcoming their physicochemical and pharmacokinetic limitations.

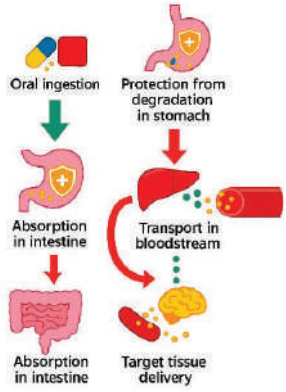


Figure 13.2. Mechanism of Targeted Delivery of Nano-Nutraceuticals

1.3 Regulatory and Safety Overview:

The development and marketing of nano-targeted nutraceuticals face complex regulatory and safety hurdles despite their promising potential. The special properties of nanoparticles which include increased reactivity and different ways of spreading into the body and their ability to break through bodily barriers create new challenges for standard safety evaluation methods. The standard testing methods employed for regular food supplements fail to identify all toxic effects that nanoparticles can produce which result in oxidative stress and inflammation and genotoxicity and immunotoxicity according to Aronson 2017.

The current situation faces a challenge because there are no standardized international regulations to govern nano-enabled food supplements which results in different countries establishing conflicting rules. The existing regulatory gap makes it difficult for manufacturers to enter international markets while it creates challenges for monitoring the safety of nano-nutraceuticals(Trischitta et al., 2024). The existing regulatory framework suffers from a lack of standardized methods which hinders agencies from conducting precise assessments of product contents and nanoparticle behavior in complex food systems(Rajapakse & Gantenbein, 2024). The scientific community still considers nanoparticle exposure to be a major issue because it leads to unknown health effects which develop over time due to continuous exposure. The existing risk assessment methods require updates that will enable them to handle unique nano-related aspects which include particle dimensions and structural characteristics and surface material properties and material breakdown patterns. Nanomaterial

regulations for nutraceuticals require the creation of new safety testing methods and market monitoring systems because policymakers need to balance their duty to protect consumers with their work to support product development(Chandra et al., 2022).

2. PHYSICOCHEMICAL PROPERTIES OF NANOPARTICLES AFFECTING SAFETY:

2.1 Particle Size, Shape, and Surface Characteristics:

Nanoparticles exhibit their biological behavior and safety assessment through their physicochemical characteristics which include their particle dimensions and their shape and their surface chemical composition. The nanometre particle size range of 1 to 100 nanometers leads to a substantial increase in surface area which improves both reactivity and functional capabilities while it affects how substances spread through the body and enter cells. The research by Crapanzano and colleagues in 2022 shows that smaller particles enable better body absorption through their ability to cross physiological barriers but this also results in a greater chance of unintentional body tissue accumulation.

The morphology of nanoparticles displays a broad range of shapes that includes spherical particles and rod-shaped particles and fiber-shaped particles and core-shell structures and advanced architectural designs. Each morphological type interacts distinctly within biological systems; for instance, fibrous nanoparticles induce different inflammatory responses because their shape and dimensions differ from those of spherical nanoparticles. The core-shell configuration of nanomicelles improves solubility and controls release but designers must exercise precision to prevent accidental immune system activation. The surface characteristics of materials encompass three parameters which include zeta potential as surface charge and functional group density and the presence of surface coatings or ligands. The features of these materials determine how they connect with proteins and cell membranes and immune cells which affects their ability to stay in the body and their rate of elimination and their ability to be detected by the immune system. The use of polymers or ligands for surface functionalization brings benefits for targeting accuracy but these materials create biocompatibility issues when they make immunogenic epitopes available for detection. The complete characterization of these surface properties is necessary to predict how nanomaterials will behave and what biological impacts they will create(Wang et al., 2022).

Table 13.1 . Physicochemical Properties of Nanoparticles Influencing Safety

Property	Range/Characteristic	Impact on Safety	Example Concern
Size	1–100 nm	Affects absorption, biodistribution	Smaller particles may cross BBB
Surface Charge	Positive/Negative	Influences interaction with cells, proteins	Cationic particles may induce toxicity
Shape	Spherical, rod-like, irregular	Alters uptake pathways	Rod-shaped may persist longer
Solubility	Hydrophobic/hydrophilic	Determines bioavailability & clearance	Poor solubility → accumulation risk
Stability	Colloidal stability in GI tract	Impacts release & degradation	Aggregation reduces efficacy

2.2 Stability and Solubility in Complex Nutraceutical Matrices:

Both stability and solubility problems represent major obstacles which hinder the implementation of nanoparticles in complex nutraceutical formulations. The nanoparticles experience three types of instability which include aggregation and oxidation and degradation when they face various environmental conditions which include temperature changes and pH shifts and gastrointestinal tract enzymatic activity. The protective functions which bioactive substances need from their stability become less effective because of this instability which leads to decreased bioactive protection and dangerous substance production through toxic degradation (Bender et al 2024).

The food matrix creates extra difficulties because it interacts with nanoparticles through both physical contact and chemical reactions. The proteins and lipids and carbohydrates and minerals present in the system will produce different effects on nanoparticle distribution and surface charge and aggregation processes which will affect solubility and absorption characteristics. The binding or entrapment of nanoparticles within matrix components will create a barrier which will slow their dissolution process and lead to decreased bioavailability (Lin et al 2020). The development of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as lipid nanoparticles demonstrates their superiority among different methods for improving solubility and stability because they possess biocompatibility and can effectively encapsulate hydrophobic nutraceuticals. The lipid-based nanocarriers enhance water dispersibility which creates protection for delicate bioactive substances against oxidation and enzymatic degradation while they enable intestinal absorption through their ability to mimic natural lipid digestion pathways. The need for toxicological evaluations arises from safety concerns about how these lipid carriers metabolize in the body and their possible accumulation in different tissues (B H Chen & Stephen Inbaraj 2018).

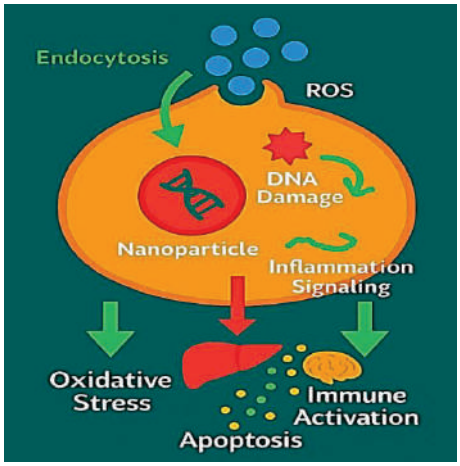
2.3 Surface Functionalization and Modification Techniques:

Surface functionalization needs nanoparticles to be treated with chemical groups and polymers and biological ligands in order to achieve better stability and targeting and biocompatibility. Researchers use chitosan, which comes from chitin, as the main biopolymer to create coatings for nanoparticles. Chitosan coatings enable mucoadhesive properties, which help track transmembrane transport, while the coatings also decrease inflammatory responses because they reduce gastrointestinal toxicity. The coatings provide protection to nanoparticles, which prevents their early destruction, while the nanoparticles exist within the digestive system (Field et al., 2011). The delivery of nutraceuticals to particular cells or organ systems achieves better therapeutic results, which also decreases unwanted systemic effects through functionalization with targeting ligands. The chemical alterations to nanoparticles create new surface patterns, which lead to immune detection and undesired interactions between plasma proteins and the particles. Functionalized surfaces interact with the immune system, which causes immunogenicity and opsonization that results in rapid clearance from the body, thus decreasing delivery efficiency and increasing safety risks (R. Liu et al., 2015). Engineers face a significant challenge when they must create safer products which need surface enhancements to achieve better delivery performance. Researchers need to use multidisciplinary methods that combine material science and toxicology with immunology to create safer and more effective surface changes for nano-nutraceuticals(Mittelheisser et al., 2022).

3. TOXICOLOGICAL CONCERNS OF NANO-TARGETED NUTRACEUTICALS:

3.1 Cellular and Molecular Mechanisms of Toxicity:

The use of nanoparticles for nutraceutical delivery results in cellular and molecular toxic effects which occur mainly through their ability to generate oxidative stress in living organisms. The process of reactive oxygen species (ROS) production results in damage to essential cellular components which include lipid membranes and intracellular proteins and genetic material. The oxidative damage process starts with lipid peroxidation which then results in mitochondrial dysfunction and DNA strand breaks followed by the activation of both pro-apoptotic and pro-inflammatory signaling pathways especially NF-kB and MAPK pathways which cause additional cellular damage and inflammation(Haghighatseir et al., 2025). These pathways enable transcriptional activation for genes that control immune responses with inflammation and apoptosis but their activity causes genotoxicity and immunotoxicity which some in vitro and in vivo studies have demonstrated. The ability of nanoparticles to persist in the body combined with their potential to accumulate in organs such as the liver and spleen and kidneys creates an increased risk of cytotoxic effects because they extend the time of bodily exposure while they harm vital organ functions. The accumulation of tissue damage results in systemic toxicity which negatively affects the health of the entire organism(Jaguezeski, Souza, et al., 2019). The complexity of these interactions underscores the importance of



mechanistic toxicological investigations to elucidate how nanoparticles influence cellular homeostasis and the immune system, guiding the design of safer formulations(Moradi et al., 2023).

Figure 13.3. Nanoparticle Interaction with Biological Systems

Table 13.2. Toxicological Concerns of Nano-Targeted Nutraceuticals

Toxicological Concern	Mechanism	Potential Health Impact
Oxidative Stress	ROS generation	DNA damage, apoptosis
Inflammation	Cytokine release	Chronic inflammatory conditions
Immunogenicity	Immune activation	Allergic responses, autoimmunity
Genotoxicity	DNA strand breaks	Mutagenesis, cancer risk
Bioaccumulation	Persistence in organs	Long-term toxicity

3.2 *In Vitro* and *In Vivo* Toxicity Assessment Challenges:

The existing testing models fail to provide dependable toxicity assessments for nano-targeted nutraceuticals because of their fundamental testing restrictions. The standard in vitro assays which toxicologists use in their work fail to simulate the actual multifactorial physiological processes which operate throughout the gastrointestinal system and the entire body circulation. The predictive capacity of these assays to simulate human biological responses shows limitations because of this specific restriction. The development of micro physiological systems through organ-on-chip platforms establishes an advanced method which can replicate both organ structure and organ-specific environmental conditions. The microfluidic devices operate with living cells which experience physiological shear stress conditions to create more precise nanoparticle absorption and metabolism and toxicity models which enhance safety evaluation processes. The use of these microfluidic devices in regulatory testing procedures is still at an early stage according to (Jalali-Jivan et al., 2022). Researchers continue to face difficulties in identifying suitable dosing methods for nanoparticles because they need to measure particle surface area and particle shape and particle aggregation state and effective concentration and mass concentrations. The different methods used to prepare nanoparticles and conduct experiments create challenges for achieving reproducible results which can be compared across different studies. The establishment of unified testing methods and exposure patterns becomes necessary for developing accurate toxicity assessments.

3.3 Long-Term Exposure, Bioaccumulation, and Cumulative Effects:

4. Researchers currently lack complete understanding about how people react to nano-encapsulated nutraceuticals which they consume through regular daily activities. The body of research shows that repeated particle ingestion over multiple months and years results in body tissue and organ nanoparticle accumulation, which leads to ongoing body inflammation and metabolic disorders and damage to specific

organs. The effects cannot be detected through acute toxicity testing, which requires researchers to conduct specific longitudinal studies(Raychaudhuri et al., 2020).

The current regulatory framework requires organizations to conduct chronic toxicity and bioaccumulation assessments, which should include post-market surveillance to assess safety throughout the product's complete life cycle. Health authorities are starting to demand companies provide complete safety documentation that covers all potential lifetime exposure scenarios while requiring organizations to maintain product safety updates and complete risk evaluations through each phase of the product development process(Dini, 2022).

5. REGULATORY FRAMEWORKS GOVERNING NANO-NUTRACEUTICALS:

4.1 Overview of Global Food and Drug Regulatory Systems

Nano-nutraceuticals are regulated under the auspices of various governmental bodies including the U.S. Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), and other international agencies. While these authorities acknowledge the distinctive challenges posed by nanomaterials, existing regulatory structures are mainly adapted from frameworks designed for bulk chemical substances and conventional food additives. This adaptation results in partial coverage of nano-specific considerations(Mohan Li et al., 2024).

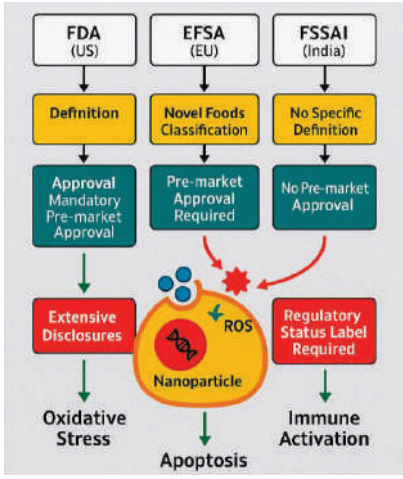


Figure 13.4. Comparative Regulatory Pathways Across Regions

Table 13.3. Global Regulatory Frameworks for Nano-Nutraceuticals

Region/Authority	Definition of Nanomaterial	Approval Process	Safety Evaluation Focus	Labeling Requirements
USA (FDA)	No fixed size definition; case-by-case assessment	Existing food/dietary supplement pathways	Toxicology, stability, exposure	Product-focused, must ensure safety
EU (EFSA)	<100 nm or novel properties	Premarket approval under Novel Food Regulation	Toxicokinetic, genotoxicity, chronic toxicity	Must disclose nanomaterial use on label
India (FSSAI)	Nano seen as “novel food”	Prior approval required	Safety dossier referencing global guidelines	Mandatory approval before commercialization

Different jurisdictions have established their own regulatory definitions of "nanomaterial" which they use to determine their own requirements for safety evaluation and product labeling and product approval processes. Some agencies need proof that researchers have determined nanoparticle size and conducted toxicology tests while other agencies use standard food additive regulations which do not include nano-specific requirements. This divergence complicates global product development and market access for manufacturersHoti et al.2022. Multiple regulatory decisions about nano-nutraceuticals demonstrate how safety assessment procedures and risk management practices differ from each other. The current regulatory landscape for nano-characteristics has various evolving frameworks yet it lacks a standardized framework which requires urgent harmonization together with specific guidance for nano-nutraceuticals.

4.2 Challenges in Nanomaterial Characterization and Standardization:

The regulatory process and product quality standards require complete assessment of nanomaterials used in nutraceutical products. The process of accurate measurement presents substantial challenges because it involves measuring particle size distribution and morphological features and surface chemistry and agglomeration state in food matrices that disrupt the analytical methods according to Sharifian et al. 2020 study. The research team uses three primary methods for material characterization which include transmission electron microscopy (TEM) dynamic light scattering (DLS) and different spectroscopic techniques. The methods prove useful yet they encounter problems which arise from sample preparation artifacts and they lack enough sensitivity to detect polydisperse samples and they cannot function in real product settings. The limitations established in this assessment process create obstacles which affect the evaluation of batch consistency and the tracking of product movement. The regulators require laboratories to develop validated analytical methods which must follow standard procedures for testing across different laboratory environments and production processes. The implementation of standardized methods establishes a framework which protects product safety while supporting legal requirements and maintaining consumer trust according to research by Si etal 2022.

4.3 Gaps and Needed Improvements in Regulatory Oversight:

Existing regulatory frameworks today fail to completely manage the particular characteristics and hazardous elements which accompany nanomaterials used in nutraceutical products. Existing risk assessment methods fail to evaluate nanoparticle risks because they do not account for enhanced surface reactivity and the potential for biological membrane translocation and environmental interactions (Maoyi Li et al. 2024). The labeling practices which describe nanomaterial content show considerable differences between products and do not provide sufficient information to support consumer decision-making while they make it difficult to monitor drug safety. The existing system of multiple agencies who control different areas of regulation prevents effective risk management because global standards do not exist. The proposed solutions for these issues recommend integrated governance structures which combine assessments of safety and efficacy together with environmental sustainability and ethical considerations. The establishment of complete databases and standardized testing procedures and transparent labeling standards requires cooperation between regulators and industry and academia to support safe development of nano nutraceuticals (W. Chen et al. 2025).

6. SAFETY EVALUATION METHODOLOGIES FOR NANO-TARGETED NUTRACEUTICALS:

6.1 Toxicity Testing Strategies and Protocols:

The process of evaluating nano-nutraceutical safety requires multiple testing methods which assess toxic effects across three different human consumption exposure periods. Animal models remain essential for evaluating systemic toxicity because they enable researchers to study how particular organs are affected and how animals process substances and how their immune systems react. The use of in vitro assays which use human cell lines and organotypic cultures needs to be combined with regular animal testing because of ethical issues and the differences between species (Rahmati et al., 2020). Advanced bioassays

which are designed to detect specific nanoparticle endpoints through their oxidative stress biomarkers and genotoxicity assays and cytokine profiles provide better hazard identification through their improved sensitivity and specificity. The ecological validity of data improves through testing which uses dose-relevant and exposure route-appropriate methods for oral administration that simulates dietary intake. The combination of various assay types creates a more comprehensive safety evaluation process which helps regulatory agencies determine the risks associated with nano-nutraceuticals(Y. Liu et al., 2025).

6.2 Analytical Techniques for Nanoparticle Detection and Quantification:

The basic requirements for safety assessment and regulatory adherence demand exact methods to find and measure nanoparticles in both nutraceutical products and biological samples. Scientists use transmission electron microscopy and scanning electron microscopy to obtain detailed images which show how nanoparticles look and their particle size distribution. Dynamic light scattering helps researchers quickly measure particle size but the method has two main problems because it cannot handle sample testing and it faces challenges from external factors which interfere with the process (Xu et al. 2025). The methods of spectroscopy support physical characterization through their ability to measure surface chemical composition and functional group identification. The analysis process becomes difficult because of two factors which include complex sample matrices and the possibility of nanoparticle aggregation. New biosensor technologies enable quick nanoparticle detection with high sensitivity and direct testing capabilities which could change how companies conduct quality tests and monitor their products after release. The analytical methods require complete validation which tests their ability to detect, identify, and produce repeatable results across different product categories before they can be used in regulatory processes. The improved analytical methods will enable manufacturers to produce their products consistently while scientists conduct in-depth safety research to ensure consumer safety.

Table 4. Emerging Analytical Techniques for Nanoparticle Detection in Nutraceuticals

Technique	Application	Advantages	Limitations
TEM/SEM	Morphology, size	High resolution imaging	Expensive, requires expertise
DLS	Particle size distribution	Quick, widely used	Sensitive to aggregates
Spectroscopy (UV-Vis, FTIR)	Functional groups, stability	Simple, non-destructive	Limited structural detail
Biosensors	Real-time detection	Portable, rapid	Still in early development
Chromatography-MS	Quantification, bio-distribution	Accurate, sensitive	High cost, complex sample prep

6.3 Integration of Bioavailability, Efficacy, and Safety Assessments:

The evaluation methods which assess complete systems require organizations to assess both bioavailability and performance data together with their safety assessments to establish a full understanding of nano-nutraceuticals. The research studies examine how nano formulations produce controlled release results which lead to distinct absorption and distribution and metabolic and excretory functions. The combination of in vitro and in vivo models together with controlled release kinetics produces efficacy metrics which determine the therapeutic window and dosing regimens. Safety assessments which use these efficacy data establish better risk-benefit evaluations which help formulation designs that achieve optimal health results with reduced off-target toxicity. The combined studies deliver scientific proof which supports regulatory choices because they demonstrate how nutraceutical products increase their benefits while yet maintaining consumer safety, which enables safe development of nano-enabled products.

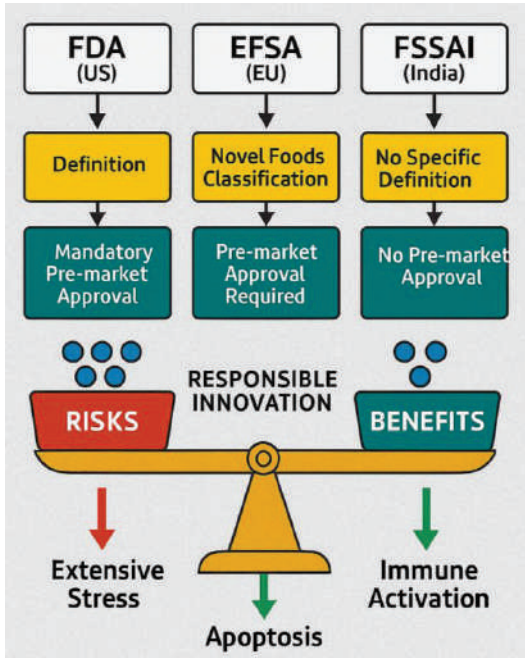


Figure 13.5. Risk–Benefit Balance Model in Nano-Nutraceutical Development

7. Risk Management and Mitigation Strategies:

7.1 Safe-by-Design Nanoparticle Engineering

The safe-by-design method requires scientists to implement safety measures during the first development phase of nanoparticle research because this practice helps to reduce downstream accident risks. The process requires researchers to choose biodegradable and biocompatible materials which include chitosan and other natural polymers in order to achieve their goal of decreasing harmful impacts and environmental persistence(Whelan et al. 2024). Design strategies work to enhance physicochemical properties through three methods which include reducing highly reactive surface areas and controlling particle size distribution and decreasing surface charge levels to stop biological interactions from occurring. Early safety assessments help researchers find and resolve toxic substances which expedites the regulatory process while building trust with consumers. The studies show that engineered nanocarriers which use these methods show lower immunogenicity and higher safety while delivering the needed results.

7.2 Post-Market Surveillance and Consumer Safety Monitoring:

The scientific uncertainties combined with the changing scientific evidence about nano-nutraceutical safety require complete post-market surveillance systems to manage risks effectively. The system continuously monitors for adverse events which enables prompt detection of unexpected safety problems that testing before market launch fails to identify. The regulatory authorities need companies to provide safety data updates at scheduled times while they have the power to initiate product recalls when required(Sumida et al., 2021). The healthcare professionals and consumers who participate in reporting systems improve the effectiveness of monitoring systems. The public trust relationship depends on organizations maintaining open communication about their monitoring findings which enables organizations to change their risk evaluations based on new information(Mazzoleni et al., 2024).

7.3 Public Awareness and Risk Communication:

The market for nano-enabled nutraceuticals requires effective communication which explains both their advantages and disadvantages to help consumers make informed choices. Consumers gain empowerment through clear product labeling which shows nanomaterial content together with scientific data that scientists have made available to them. The process of risk communication needs to maintain two objectives because it must provide complete information yet it should not create unnecessary panic through its risk assessment process that uses scientific evidence as its foundation which regulatory bodies and companies and scientists will share with the public(Fadah et al. 2025). Public engagement initiatives and educational campaigns combined with responsible media coverage create pathways for knowledge transfer which helps to debunk false beliefs while building public confidence. Through proactive communication methods companies can achieve safe innovation while they create opportunities for customers to be involved in their safety assessment process(Manore and Patton-Lopez 2022).

8. CASE STUDIES OF NANO-NUTRACEUTICAL APPLICATIONS:

8.1 Lipid-Based Nanoparticles for Polyphenols and Vitamins:

Researchers have found that lipid-based nanosystems which include solid lipid nanoparticles and nanostructured lipid carriers create effective delivery systems which enhance the solubility and stability and bioavailability of hydrophobic nutraceutical compounds that include polyphenols and fat-soluble vitamins and antioxidants. The carriers use their lipid matrix to create bioactive protection because they want to maintain their active components through hydrolysis and oxidation while controlling the release of their contents(Bartolomei et al., 2022). Preclinical evaluations demonstrate that such lipid nanoparticles enhance the pharmacokinetics of encapsulated nutraceuticals which provides targeted delivery while reducing systemic toxicity. The regulatory process demands complete analysis of lipid content and particle size distribution and immunological effects which each carrier system presents according to existing requirements. The development of products focuses on three main areas: manufacturing scalability and quality control and food-grade safety requirements.

8.2 Nanoencapsulation of Antioxidants and Phytochemicals:

Researchers use nanomicelles and nanocomposites to overcome the solubility and stability challenges that affect natural antioxidants and phytochemicals because these methods enhance their bioactive properties. Nanoencapsulation protects these compounds from premature degradation while helping their gastrointestinal absorption and enabling controlled release which improves therapeutic effects(Pugliese et al., 2018). The physical stability of nanoparticles in human body conditions together with their ability to generate immune responses through new surface chemical designs creates safety problems. The regulatory process now requires companies to provide extensive toxicology results which include both immunotoxicity information and details about systemic exposure risks, which leads to the need for better formulation methods that ensure both safety and effective product delivery.

8.3 Biopolymeric Nanocarriers: Chitosan and Derivatives:

Chitosan-based nanocarriers, because of their natural sources and their ability to decompose and their good compatibility with living organisms, serve as an effective method to deliver nutraceuticals. The system delivers targeted treatment while it safeguards the bioactive substances that it carries and its natural antimicrobial abilities serve useful purposes in food-related uses(Abbott et al., 1994). The regulations need manufacturers to create standardized production methods which test for allergenic properties and conduct complete toxic substance assessments to confirm product safety for extended consumption. The company must overcome obstacles to create production methods that can produce consistent product quality across all production units. Scientists dedicated their research to developing better functionalization methods while they

studied long-term safety results which would help obtain regulatory approval and make the product suitable for commercial use(Aguilar-Toalá et al., 2022).

9. Environmental and Ethical Considerations:

9.1 Environmental Impact of Production and Disposal:

The process of creating, using, and throwing away nano-nutraceuticals creates possible environmental hazards because nanoparticles can escape into both water and soil ecosystems. Life cycle assessments require organizations to assess environmental impacts which result from their solvent usage and energy consumption and the extended existence of nanoparticles in their operations (Dhokane et al., 2023). The green manufacturing protocols together with waste management strategies work to reduce the pollution of the environment. The development of environmental safety standards for nanomaterials should proceed through regulatory agencies which need to create standards that include monitoring methods for tracking their environmental movement to ensure protection of ecological health.

9.2 Ethical Issues in Development and Commercialization:

The ethical challenges in this field require researchers to develop nano-nutraceutical products which all socioeconomic groups can access while maintaining transparent product information and securing consumer knowledge through informed consent. The study shows that consumers need straightforward information which enables them to understand their exposure risks to nanomaterials(Lucarini et al., 2025). Public trust, which supports global health equity, depends on companies using responsible marketing strategies that avoid making false claims and on patenting policies which enable innovation while maintaining public access to products.

9.3 Sustainable Development and Green Nanotechnology Approaches:

The process of sustainable development requires the use of biodegradable renewable materials which scientists will apply to create nano formulations that need fewer harmful chemicals during the production of nanoparticles. Green nanotechnology supports its environmental and social goals through the development of safer sustainable products which produce less environmental impact according to Nieto et al. 2025. The development of these methods enables organizations to meet sustainability targets while improving the sustainable performance of their nano nutraceutical research.

10. Future Directions in Regulatory and Safety Science:

9.1 Advanced Analytical and Testing Technologies

Future advancements in safety science will increasingly leverage organ-on-chip and micro physiological models that replicate organ-specific responses with higher fidelity than traditional models. The combination of these platforms with omics and systems biology techniques will result in complete toxicity assessment because it will analyze detailed biological interactions(Fatima et al., 2025). The development of advanced nanoparticle detection technologies which offer improved sensitivity and specificity will enable precise safety evaluations while decreasing the need for animal testing to meet ethical and scientific advancement objectives.

9.2 Harmonization and Collaboration Among Regulatory Bodies:

The international system needs to create united safety standards for nanofood products which include both safety regulations and labeling rules and risk evaluation methods to support efficient regulatory operations and to promote worldwide trade. The creation of standard operating procedures will be expedited through shared data platforms together with unified policy efforts between international organizations. The collaboration will protect consumers through strong safety measures while it supports innovation development(Hansen, 2002).

9.3 Research Priorities and Knowledge Gaps:

Critical research domains include comprehensive toxicokinetic analyses of diverse nanoparticle materials, elucidation of long-term and cumulative exposure effects through epidemiological studies, and development of standardized toxicity protocols enhancing cross-study comparability. Multidisciplinary research incorporating nanotechnology, toxicology, nutrition, and regulatory science is vital to close existing knowledge gaps and enable evidence-based risk management(Vijayandran et al., 2025).

CONCLUSIONS

Nano-targeted nutraceuticals function as a groundbreaking approach which enables better stability and bioactive compound delivery and therapeutic benefits through their use. The unique properties of nano-targeted nutraceuticals establish various safety and regulatory challenges which existing regulatory frameworks fail to manage properly. The world currently needs immediate solutions for nano-enabled product regulations because these products can produce long-lasting toxic effects which lead to body accumulation and result in various regulatory classification problems. The field needs responsible innovation which requires better characterization tools and toxicity assessment models and safe-by-design strategies for ensuring safety. The nutraceutical industry needs clear labeling practices and post-market monitoring systems and proper risk information sharing to protect consumer trust. Researchers together with industry partners and regulatory bodies must collaborate to develop safe commercialization standards for nano-enabled nutraceuticals which follow sustainable and ethical practices. The nutraceutical industry will succeed in nanotechnology integration through finding equilibrium between product development and consumer safety measures.

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

All authors contributed equally to the conception, design, writing, and finalization of this work. Each author was actively involved in literature review, data interpretation, manuscript preparation, and critical revision. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

REFERENCES:

1. Abbott, C. A., McCaughan, G. W., Baker, E. & Sutherland, G. R. (1994). Genomic organization, exact localization, and tissue expression of the human CD26 (dipeptidyl peptidase IV) gene. *Immunogenetics*, *40*(5), 331–338. https://doi.org/10.1007/BF01246674
2. Aguilar-Toalá, J. E., Quintanar-Guerrero, D., Liceaga, A. M. & Zambrano-Zaragoza, M. L. (2022). Encapsulation of bioactive peptides: a strategy to improve the stability, protect the nutraceutical bioactivity and support their food applications. *RSC Advances*, *12*(11), 6449–6458. https://doi.org/10.1039/d1ra08590e
3. Aronson, J. K. (2017). Defining 'nutraceuticals': neither nutritious nor pharmaceutical. *British Journal of Clinical Pharmacology*, *83*(1), 8–19. https://doi.org/10.1111/bcp.12935
4. Ayseli, M. T., Çetinkaya, T. & Ayseli, Y. I. (2024). Innovative Food Safety Approaches and Nutraceuticals to Promote Children's Health on Future Outbreaks with the Reflection of COVID-19. *Advances in Experimental Medicine and Biology*, *1458*, 349–369. https://doi.org/10.1007/978-3-031-61943-4_23
5. 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.
6. Barmherzig, R. & Rajapakse, T. (2021). Nutraceuticals and Behavioral Therapy for Headache. *Current Neurology and Neuroscience Reports*, *21*(7). https://doi.org/10.1007/s11910-021-01120-3

7. Bartolomei, M., Capriotti, A. L., Li, Y., Bollati, C., Li, J., Cerrato, A., Cecchi, L., Pugliese, R., Bellumori, M., Mulinacci, N., Laganà, A., Arnoldi, A. & Lammi, C. (2022). Exploitation of Olive (Olea europaea L.) Seed Proteins as Upgraded Source of Bioactive Peptides with Multifunctional Properties: Focus on Antioxidant and Dipeptidyl-Dipeptidase-IV Inhibitory Activities, and Glucagon-like Peptide 1 Improved Modulation. *Antioxidants (Basel, Switzerland)*, *11*(9). https://doi.org/10.3390/antiox11091730
8. Bender, E. C., Sircar, A. J., Taubenfeld, E. K. & Suggs, L. J. (2024). Modulating Lipid-Polymer Nanoparticles' Physicochemical Properties to Alter Macrophage Uptake. *ACS Biomaterials Science and Engineering*, *10*(5), 2911–2924. https://doi.org/10.1021/acsbiomaterials.3c01704
9. Chandra, S., Saklani, S., Kumar, P., Kim, B. & Coutinho, H. D. M. (2022). Nutraceuticals: Pharmacologically Active Potent Dietary Supplements. *BioMed Research International*, *2022*. https://doi.org/10.1155/2022/2051017
10. Chen, B. H. & Stephen Inbaraj, B. (2018). Various physicochemical and surface properties controlling the bioactivity of cerium oxide nanoparticles. *Critical Reviews in Biotechnology*, *38*(7), 1003–1024. https://doi.org/10.1080/07388551.2018.1426555
11. Chen, W., Guo, Q., Li, H., Chi, X., Ma, X., Tang, Y., Liang, Q., Liu, Z., Liu, Y. & Li, J. (2025). Engineered Probiotics Mitigate Gut Barrier Dysfunction Induced by Nanoplastics. *Advanced Science*, *12*(22). https://doi.org/10.1002/advs.202417283
12. Crapanzano, R., Villa, I., Mostoni, S., D'Arienzo, M., Di Credico, B., Fasoli, M., Lorenzi, R., Scotti, R. & Vedda, A. (2022). Photo- and radio-luminescence of porphyrin functionalized ZnO/SiO2 nanoparticles. *Physical Chemistry Chemical Physics*, *24*(35), 21198–21209. https://doi.org/10.1039/d2cp00884j
13. Dhokane, D., Shaikh, A., Yadav, A., Giri, N., Bandyopadhyay, A., Dasgupta, S. & Bhadra, B. (2023). CRISPR-based bioengineering in microalgae for production of industrially important biomolecules. *Frontiers in Bioengineering and Biotechnology*, *11*, 1267826. https://doi.org/10.3389/fbioe.2023.1267826
14. Dini, I. (2022). Contribution of Nanoscience Research in Antioxidants Delivery Used in Nutricosmetic Sector. *Antioxidants (Basel, Switzerland)*, *11*(3). https://doi.org/10.3390/antiox11030563
15. Fadah, K., Mares, A. & Lange, R. A. (2025). Statin-Associated muscle symptoms and vitamin D supplementation. *Current Opinion in Cardiology*, *40*(4), 215–220. https://doi.org/10.1097/HCO.0000000000001222
16. Fatima, G., Khan, S., Shukla, V., Awaida, W., Li, D. & Gushchina, Y. S. (2025). Nutraceutical formulations and natural compounds for the management of chronic diseases. *Frontiers in Nutrition*, *12*, 1682590. https://doi.org/10.3389/fnut.2025.1682590
17. Field, J. A., Luna-Velasco, A., Boitano, S. A., Shadman, F., Ratner, B. D., Barnes, C. & Sierra-Alvarez, R. (2011). Cytotoxicity and physicochemical properties of hafnium oxide nanoparticles. *Chemosphere*, *84*(10), 1401–1407. https://doi.org/10.1016/j.chemosphere.2011.04.067
18. 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.
19. Haghighatseir, E., Heidari, R., Sabet-Eghlidi, N., Karimi, Z., Berenjian, A. & Ebrahiminezhad, A. (2025). Impacts of particles' aspect ratio on the efficacy of β-FeOOH nanorods as nano-based oral iron supplements. *Journal of Biological Inorganic Chemistry*, *30*(4–5), 345–357. https://doi.org/10.1007/s00775-025-02110-3
20. Hansen, E. B. (2002). Commercial bacterial starter cultures for fermented foods of the future. *International Journal of Food Microbiology*, *78*(1–2), 119–131. https://doi.org/10.1016/S0168-1605(02)00238-6
21. Hoti, G., Matencio, A., Pedrazzo, A. R., Cecone, C., Appleton, S. L., Monfared, Y. K., Caldera, F. & Trotta, F. (2022). Nutraceutical Concepts and Dextrin-Based Delivery Systems. *International Journal of Molecular Sciences*, *23*(8). https://doi.org/10.3390/ijms23084102
22. Ijinu, T. P., De Lellis, L. F., Shanmugarama, S., Pérez-Gregorio, R., Sasikumar, P., Ullah, H., Buccato, D. G., Di Minno, A., Baldi, A. & Daglia, M. (2023). Anthocyanins as Immunomodulatory Dietary Supplements: A Nutraceutical Perspective and Micro-/Nano-Strategies for Enhanced Bioavailability. *Nutrients*, *15*(19). https://doi.org/10.3390/nu15194152
23. Isola, G. (2020). The impact of diet, nutrition and nutraceuticals on oral and periodontal health. *Nutrients*, *12*(9), 1–6. https://doi.org/10.3390/nu12092724

24. Jaguezeski, A. M., Gündel, S. S., Favarin, F. R., Gündel, A., Souza, C. F., Baldissera, M. D., Cazarotto, C. C., Volpato, A., Fortuoso, B. F., Ourique, A. F. & Da Silva, A. S. (2019). Low-dose curcumin-loaded Eudragit L-100-nanocapsules in the diet of dairy sheep increases antioxidant levels and reduces lipid peroxidation in milk. *Journal of Food Biochemistry*, *43*(8). https://doi.org/10.1111/jfbc.12942

25. Jaguezeski, A. M., Souza, C. F., Perin, G., Reis, J. H., Gomes, T. M. A., Baldissera, M. D., Vaucher, R. A., de Andrade, C. M., Stefani, L. M., Gundel, S. S., Ourique, A. F. & Da Silva, A. S. (2019). Effect of free and nano-encapsulated curcumin on treatment and energetic metabolism of gerbils infected by Listeria monocytogenes. *Microbial Pathogenesis*, *134*. https://doi.org/10.1016/j.micpath.2019.103564

26. Jalali-Jivan, M., Rostamabadi, H., Assadpour, E., Tomas, M., Capanoglu, E., Alizadeh-Sani, M., Kharazmi, M. S. & Jafari, S. M. (2022). Recent progresses in the delivery of β-carotene: From nano/microencapsulation to bioaccessibility. *Advances in Colloid and Interface Science*, *307*. https://doi.org/10.1016/j.cis.2022.102750

27. Komolafe, K., Komolafe, T. R., Crown, O. O., Ajiboye, B., Noubissi, F., Ogungbe, I. V. & Graham, B. (2025). Natural Products in the Management of Gastroesophageal Reflux Disease: Mechanisms, Efficacy, and Future Directions. *Nutrients* , *17*(6). https://doi.org/10.3390/nu17061069

28. Le, Y., Wang, B. & Xue, M. (2022). Nutraceuticals use and type 2 diabetes mellitus. *Current Opinion in Pharmacology*, *62*, 168–176. https://doi.org/10.1016/j.coph.2021.12.004

29. Li, Maoyi, Liu, N., Zhu, J., Wu, Y., Niu, L., Liu, Y., Chen, L., Bai, B., Miao, Y., Yang, Y. & Chen, Q. (2024). Engineered probiotics with sustained release of interleukin-2 for the treatment of inflammatory bowel disease after oral delivery. *Biomaterials*, *309*. https://doi.org/10.1016/j.biomaterials.2024.122584

30. Li, Mohan, Mao, B., Tang, X., Zhang, Q., Zhao, J., Chen, W. & Cui, S. (2024). Lactic acid bacteria derived extracellular vesicles: emerging bioactive nanoparticles in modulating host health. *Gut Microbes*, *16*(1). https://doi.org/10.1080/19490976.2024.2427311

31. Lin, X., Sun, S., Wang, B., Zheng, B. & Guo, Z. (2020). Structural and physicochemical properties of lotus seed starch nanoparticles. *International Journal of Biological Macromolecules*, *157*, 240–246. https://doi.org/10.1016/j.ijbiomac.2020.04.155

32. Liu, R., Jiang, W., Walkey, C. D., Chan, W. C. W. & Cohen, Y. (2015). Prediction of nanoparticles-cell association based on corona proteins and physicochemical properties. *Nanoscale*, *7*(21), 9664–9675. https://doi.org/10.1039/c5nr01537e

33. Liu, Y., Huang, X., Jia, X., Huang, J., Cao, R., Yu, F., Xue, K., Hui, H. & Lu, J. (2025). Biosynthesis of Melanin with Engineered Probiotics for Oral Treatment of Ulcerative Colitis. *ACS Nano*, *19*(23), 21333–21347. https://doi.org/10.1021/acsnano.4c17942

34. Lucarini, E., Schettino, A., Marigliano, N., Ciampi, C., Smimmo, M., Romano, F., Paolillo, A., Izzo, L., Begum, J., Mansour, A. A., Iaccarino, N., Randazzo, A., Greco, K. V., Scarpa, R., Caso, F., Iqbal, A. J., Bucci, M., Ghelardini, C., Mannelli, L. D. C., … Maione, F. (2025). Exploring the dual role of Mangifera indica L. in regulating immune response and pain persistence in inflammatory bowel disease. *Pharmacological Research*, *217*. https://doi.org/10.1016/j.phrs.2025.107773

35. Makkar, R., Behl, T., Bungau, S., Zengin, G., Mehta, V., Kumar, A., Uddin, M. S., Ashraf, G. M., Abdel-Daim, M. M., Arora, S. & Oancea, R. (2020). Nutraceuticals in neurological disorders. *International Journal of Molecular Sciences*, *21*(12), 1–19. https://doi.org/10.3390/ijms21124424

36. Manore, M. M. & Patton-Lopez, M. (2022). Should Clinicians Ever Recommend Supplements to Patients Trying to Lose Weight? *AMA Journal of Ethics*, *24*(5), E345–E352. https://doi.org/10.1001/amajethics.2022.345

37. Martinović, L. S., Peršurić, Ž. & Pavelić, K. (2020). Nutraceuticals and metastasis development. *Molecules*, *25*(9). https://doi.org/10.3390/molecules25092222

38. Mazzoleni, B., Ferrari, G., Caccialanza, R., Cattani, D., Savioni, F., Ferrante, S., Lopane, D., Dacomi, A., Coldani, C., Tomaiuolo, G., Anastasi, G. & Mancin, S. (2024). Pharmacological strategies and nutritional supplements for managing dysgeusia among chemotherapy patients: A systematic review. *Clinical Nutrition ESPEN*, *63*, 20–30. https://doi.org/10.1016/j.clnesp.2024.05.026

39. Mittelheisser, V., Coliat, P., Moeglin, E., Goepp, L., Goetz, J. G., Charbonnière, L. J., Pivot, X. & Detappe, A. (2022). Optimal Physicochemical Properties of Antibody–Nanoparticle Conjugates for Improved Tumor Targeting. *Advanced Materials*, *34*(24). https://doi.org/10.1002/adma.202110305

40. 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.

41. Moradi, S., Ashouri, S., Pirani, F., Johari, S. A., Kim, H. P., Yu, I. J. & Ghaderi, E. (2023). Nutritional and ameliorative effects of dietary curcumin and its nano-silica and nano-zeolite encapsulated forms on growth, biochemical and fatty acid profile of common carp (Cyprinus carpio). *Fish Physiology and Biochemistry*, *49*(4), 599–612. https://doi.org/10.1007/s10695-023-01209-1

42. Nieto, Á. V. A., Diaz, A. H. & Hernández, M. (2025). Are there Effective Vegan-Friendly Supplements for Optimizing Health and Sports Performance? a Narrative Review. *Current Nutrition Reports*, *14*(1). https://doi.org/10.1007/s13668-025-00633-4

43. Pugliese, R., Fontana, F., Marchini, A. & Gelain, F. (2018). Branched peptides integrate into self-assembled nanostructures and enhance biomechanics of peptidic hydrogels. *Acta Biomaterialia*, *66*, 258–271. https://doi.org/10.1016/j.actbio.2017.11.026

44. Rahmati, F., Hosseini, S. S., Mahuti Safai, S., Asgari Lajayer, B. & Hatami, M. (2020). New insights into the role of nanotechnology in microbial food safety. *3 Biotech*, *10*(10), 425. https://doi.org/10.1007/s13205-020-02409-9

45. Rajapakse, T. & Gantenbein, A. R. (2024). Nutraceuticals in migraine. *Handbook of Clinical Neurology*, *199*, 125–144. https://doi.org/10.1016/B978-0-12-823357-3.00001-X

46. Raychaudhuri, R., Naik, S., Shreya, A. B., Kandpal, N., Pandey, A., Kalthur, G. & Mutalik, S. (2020). Pullulan based stimuli responsive and sub cellular targeted nanoplatforms for biomedical application: Synthesis, nanoformulations and toxicological perspective. *International Journal of Biological Macromolecules*, *161*, 1189–1205. https://doi.org/10.1016/j.ijbiomac.2020.05.262

47. Sharifian, P., Yaslianifard, S., Fallah, P., Aynesazi, S., Bakhtiyari, M. & Mohammadzadeh, M. (2020). Investigating the effect of nano-curcumin on the expression of biofilm regulatory genes of pseudomonas aeruginosa. *Infection and Drug Resistance*, *13*, 2477–2484. https://doi.org/10.2147/IDR.S263387

48. Shields, A., Ly, S., Wafae, B., Chang, Y. F., Manjaly, P., Archila, M., Heinrich, C., Drake, L., Mostaghimi, A. & Barbieri, J. S. (2023). Safety and Effectiveness of Oral Nutraceuticals for Treating Acne: A Systematic Review. *JAMA Dermatology*, *159*(12), 1373–1382. https://doi.org/10.1001/jamadermatol.2023.3949

49. Si, W., Liang, H., Bugno, J., Xu, Q., Ding, X., Yang, K., Fu, Y., Weichselbaum, R. R., Zhao, X. & Wang, L. (2022). Lactobacillus rhamnosus GG induces cGAS/STING- dependent type i interferon and improves response to immune checkpoint blockade. *Gut*, *71*(3), 521–533. https://doi.org/10.1136/gutjnl-2020-323426

50. Sumida, K., Lau, W. L., Kovesdy, C. P., Kalantar-Zadeh, K. & Kalantar-Zadeh, K. (2021). Microbiome modulation as a novel therapeutic approach in chronic kidney disease. *Current Opinion in Nephrology and Hypertension*, *30*(1), 75–84. https://doi.org/10.1097/MNH.0000000000000661

51. Trischitta, P., Tamburello, M. P., Venuti, A. & Pennisi, R. (2024). Pseudovirus-Based Systems for Screening Natural Antiviral Agents: A Comprehensive Review. *International Journal of Molecular Sciences*, *25*(10). https://doi.org/10.3390/ijms25105188

52. Vijayandran, K., Abdo, A. I. K., Wong, M. T. J., Balakrishnan, V., Nordin, F., Wan Kamarul Zaman, W. S., Lim, C. S. Y. & Tye, G. J. (2025). Nanobodies targeting cytokines for the amelioration of autoimmune diseases. *International Immunopharmacology*, *164*. https://doi.org/10.1016/j.intimp.2025.115368

53. Wang, M., He, H., Liu, D., Ma, M. & Zhang, Y. (2022). Preparation, Characterization and Multiple Biological Properties of Peptide-Modified Cerium Oxide Nanoparticles. *Biomolecules*, *12*(9). https://doi.org/10.3390/biom12091277

54. Whelan, K., Ford, A. C., Burton-Murray, H. & Staudacher, H. M. (2024). Dietary management of irritable bowel syndrome: considerations, challenges, and solutions. *The Lancet Gastroenterology and Hepatology*, *9*(12), 1147–1161. https://doi.org/10.1016/S2468-1253(24)00238-3

55. Xu, X., Tang, Q., Gao, Y., Chen, S., Yu, Y., Qian, H., McClements, D. J., Cao, C. & Yuan, B. (2025). Recent developments in the fabrication of food microparticles and nanoparticles using microfluidic systems. *Critical Reviews in Food Science and Nutrition*, *65*(12), 2199–2213. https://doi.org/10.1080/10408398.2024.2329967

56. 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

57. 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.

58. 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.