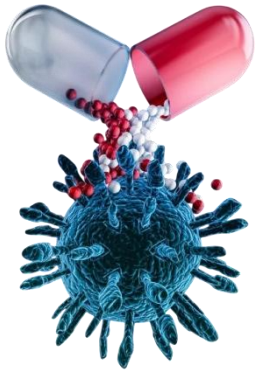
CHAPTER 21

Nanotechnology-Based Delivery of Natural Products



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ABSTRACT: Natural products are derived from plants, animals and microorganisms. They are an indispensable source of biologically active compounds that have diverse therapeutic and pharmacological effects i.e. anticancer, antiviral, antimicrobial, antioxidant, neuroprotective and anti-inflammatory properties. However, clinical applications of bioactive compounds are hindered by various challenges including instability, rapid metabolism, lesser bioavailability and poor solubility. Nanotechnology has emerged as an innovative platform to overcome challenges by enabling the design of various nanocarriers, such as nano-emulsions, dendrimers, polymeric nanoparticles, green-synthesized metallic nanoparticles, and solid lipid nanoparticles. These nano-carriers increase bioavailability, controlled release, improve stability and solubility as well as minimize the side effects and boost the therapeutic efficiency of natural products. Furthermore, nanotechnology is applicable in agriculture and aquaculture for plant growth enhancement, pest control, detoxifying pollutants and boosting immunity in fish. Green nanotechnology highlights environment friendly plant-based synthesis of nanomaterials, contributing to a sustainable way for the management of environment and health of fish. This chapter describes a comprehensive overview of nanotechnology-based delivery systems of natural products, nanoformulation techniques, and applications of natural products in agriculture and aquaculture sectors.

Background on Natural Products

Natural products are complex molecules derived from animals, plants or microorganisms, and have been major source of therapeutic agents, pharmaceuticals and traditional medicines. In other words, natural products consist of any substance or compound produced by living organisms (Coman et al., 2012). Natural products have unique biological and pharmacological roles due to natural selection. These are also used for discovery of drugs with minimum side effects and enhanced bioavailability. Natural products are classified into primary and secondary metabolites. Organic molecules that have an intrinsic function that is necessary to the existence of producers are called primary metabolites. These include amino acids, nucleic acids, fatty acids, sugars that are essential for making proteins, DNA, RNA, carbohydrates and lipids. Secondary metabolites are those organic molecules that have extrinsic function and they affect other organisms instead of the producers.

Importance in Nutraceuticals, Pharmaceuticals and Agriculture

Nutraceuticals are defined as the substances or food that have physiological benefits and provide health and medical benefits (Puri et al., 2022). Pharmaceuticals are used to treat, cure or prevent chronic diseases whereas agriculture is the practice of farming. There has been a renewed focus on natural products because of their synergistic effects, less toxicity and biocompatibility. They are generally used as an alternative to the synthetic drugs and eco-friendly agents in agriculture (Puri et al., 2022).

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Challenges in Natural Product Delivery (Solubility, Bioavailability, Stability)

Natural products are the compounds extracted from plants and animals. These products have structural diversity and possess numerous compounds such as alkaloids, flavonoids, sterols, saponins and terpenoids (Tang et al., 2023). Most of these compounds are used for signal transmission, adapting to the environment and resisting invasion. A number of natural products have bioactive functions, acting as medicines with widely different bioactivities (Zhao et al., 2021). For example, artemisinin, that is extracted from *Artemisia annua*, is used in antimalarial treatment (Lyu et al., 2021). Lots of bioactive natural products are discovered, however some challenges associated with natural products delivery such as poor solubility, less permeability, poor bioavailability and rapid degradation. Solubility, stability and lack of target specificity are the major challenges in natural products delivery (Gandhi et al., 2022).

NANOTECHNOLOGY IN DRUG DELIVERY

Definition and Fundamentals of Nanotechnology

Nanotechnology deals with the design, synthesis and manipulation of nano-sized particles, typically the size of 1 to 100 nm for the utilization of smaller structures for different applications (Solomon, 2018). The term nanotechnology was first used by late Norio Taniguchi in 1974. At the nanometer scale, materials have distinctive physical, chemical and biological properties including more surface area, permeability and reactivity. In milieu of natural product delivery, nanotechnology focuses on the formation of nanocarriers that can protect, encapsulate and release bioactive compounds in an efficient way (Singh & Naveen, 2014). These nanoscale carriers improve the delivery of natural products to specific cells, tissues in addition to preserving the integrity of sensitive natural products as shown in Fig. 1 (Dhand et al., 2016).

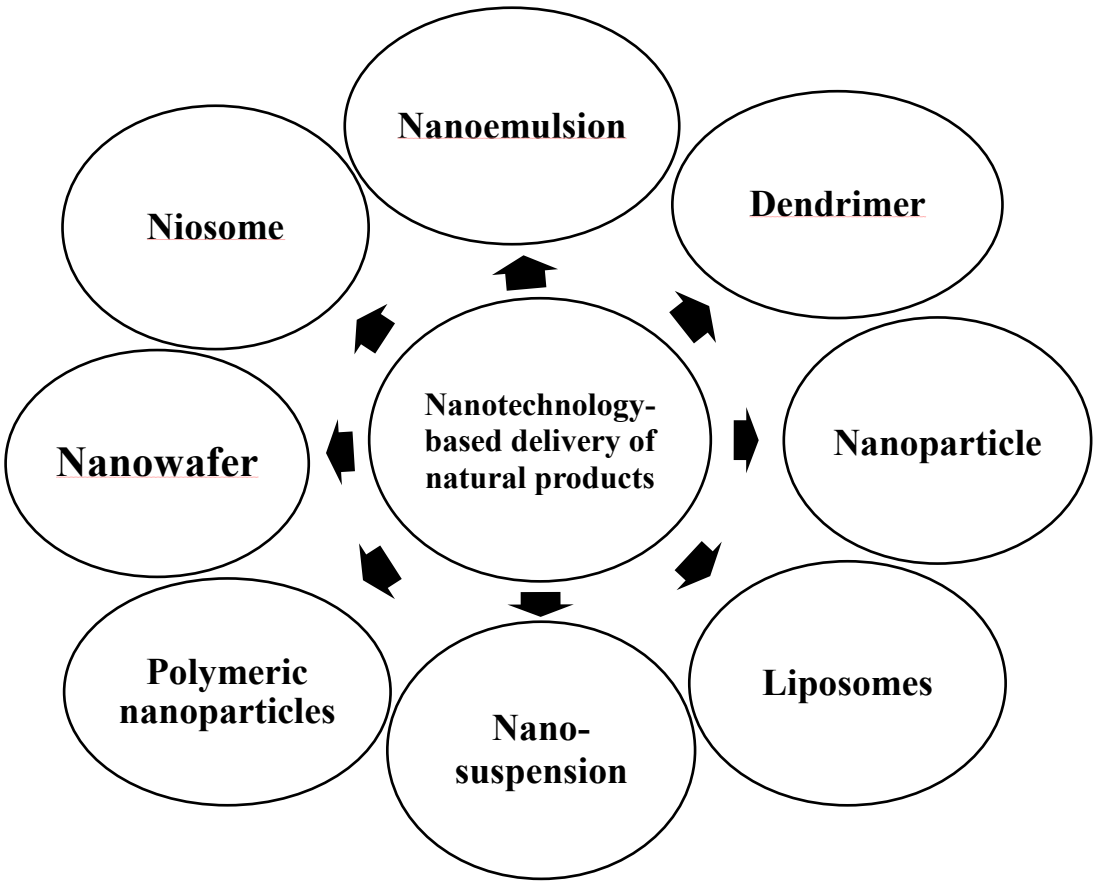

Fig 1. Nanotechnology-based drug delivery systems of natural products

Advantages of Nano-Delivery Systems

Nanotechnology-based delivery systems have potential for the treatment of various diseases such as tuberculosis. The most important advantages of nanotechnology are improved bioavailability and solubility of natural products, e.g. quercetin, high carrier capacity, high stability (Gelperina et al., 2005). Surface modifications of natural products enable active targeting to specific tissues or cells and less doses of these products reduce toxicity (Ashraf et al., 2025).

Nanocarriers

Nanocarriers are nanomaterial or nanoparticles widely used for the transportation of therapeutic agent to a target site (Chamundeeswari et al., 2019). Size of nanoparticles range from 1 to 100 nm in diameter while the microcapillaries of the body are 200 nm due to which therapeutic application of nanocarrier to be less than 200 nm (Qian et al., 2012). Nanocarriers have unique characteristics that are distinct from conventional carriers. These characteristics include (How et al., 2013) decrease in toxicity, continuous medication administration, improved stability, pharmacokinetics and biodistribution, and enhanced solubility

TYPES OF NANOCARRIERS USED FOR NATURAL PRODUCTS

Nanocarriers are formed at the nanoscale used to encapsulate, transport and release biologically active natural compounds. The composition of nanocarriers affects the efficiency of drug delivery system. Various types of nanocarriers, their size, properties and applications are given in Table 1.

Polymeric nanocarriers

They are colloidal solid nanoparticles derivatives of synthetic polymers such as polyglycolic acid, polylactic acid and natural polymers including alginate and chitosan. They are classified into biodegradable and non-biodegradable and their size ranges from 10 to 100 nm (Jafernik et al., 2023).

Solid Lipid Nanocarriers

Solid Lipid Nanocarriers are used as a suitable carrier for transporting lipophilic drugs (Lingayat et al., 2017). These are formed by dispersion of melted solid lipid in water and stabilized by emulsifiers through high pressure homogenization or micro-emulsification. Solid lipid nanoparticles have been used to transport berberine and thymoquinone (Malam et al., 2009).

Metallic nanocarriers

Metallic nanoparticles refer to nanosized metals with sizes of 1 to 100 nm and their existence was first recognized by Faraday. Quantitative description of color of metallic nanoparticles was given in 1908 by Mie (Mody et al., 2010). Features of these nanoparticles are large surface area to volume ratio and surface energies, quantum confinement as well as transition among metallic and molecular states (Kumar et al., 2018).

Nanoemulsions

Nanoemulsions or mini-emulsions are basically transparent or translucent, thermodynamically stable dispersions of water and oil, stabilized by surfactant and cosurfactant molecules with droplets less than 100 nm size. Nanoemulsions are of three types i.e., oil in water, water in oil and bicontinuous nanoemulsions. These are characterized by clarity and stability and used as delivery systems to improve drug efficacy, thus minimizing the side effects (Patel & Joshi, 2012).

Dendrimers

Dendrimers are macromolecules having branched structures that consist of an initiator core and terminal arms or active groups. These are produced by sugar molecules, amino acids or nucleotides (Gillies & Frechet, 2005). They are highly branched, multivalent with particle sizes of 1 to 100 nm and dendrimers uniqueness depends on their well-defined globular structure, molecular weight, branching and multivalency (Mignani et al., 2018). These are used a coating agent to protect the drugs, and other applications are DNA, gene transport, catalysis and biomimetics (Ochekpe et al., 2009).

Mesoporous Silica nanocarriers

These nanoparticles possess a porous honeycomb structure that allows the incorporation

of more drug molecules into it. It can protect the hydrophilic and hydrophobic drugs, which can be attached to a ligand molecule for specific targeted drug delivery (Rosenblum et al., 2018). The characteristics of mesoporous silica nanoparticles include their biocompatibility, thermochemical stability and high surface area (Wang et al., 2015).

Liposomes

Liposomes are artificial small vesicles of size range from 50 to 100 nm, formed from phospholipids including phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine and phosphatidylglycerol (Moussaoui et al 2002). They mimic the biological membranes, enhance stability and solubility. Moreover, they are biodegradable and less toxic. Applications include carrier for drug delivery, transdermal drug delivery and ocular drug delivery (Pattni et al., 2015).

NATURAL PRODUCTS DELIVERED VIA NANOTECHNOLOGY

Alkaloids

Alkaloids are nitrogenous organic compounds derived from amino acids and extracted from plants. They are classified into quinoline, pyridine, isoquinoline and indole alkaloids based on their core structure (Souza et al., 2020). Pharmacological characteristics of alkaloids include antiviral, anti-inflammatory and ant-cancer properties. However,

Table 1. Types of nanocarriers, their size, and mode of synthesis, properties and application

Types of Nanocarriers	Size (nm)	Synthesis mode	Properties	Applications	References
Polymeric Nanocarriers	10-100	Emulsification, polymerization, nanoprecipitation, supercritical fluid technology	Biodegradable, stability in blood stream and permeability of cell membrane	Higher concentration of bioactive natural products, enhanced stability and solubility	Jafernik et al., 2023
Solid lipid nanocarriers	50-100	Hot and cold homogenization, solvent emulsification, ultrasonication	Biodegradable, better stability, colloidal carrier, burst release	Targeted drug delivery, antitubercular hemotherapy, gene vector carrier	Malam et al., 2009; Lingayat et al., 2017; Chamundeeswari et al., 2019
Metallic nanocarriers	1-100	Microemulsion, thermal decomposition, chemical reduction	High surface area to volume ratio, enhanced reactivity, strong plasma absorption	Targeted drug delivery	Mody et al., 2010; Kumar et al., 2018
Nanoemulsions	20-200	Microfluidization, phase inversion emulsification, ultrasonication	Thermodynamically stable, transparent, translucent	Drug delivery, pharmaceuticals and material synthesis	Patel & Joshi, 2012
Dendrimers	1-10	Self-assembly, convergent or divergent reactions	High drug loading capacity, multifunctional surface modification, homogeneous, symmetric	Specific target drug delivery, gene delivery neutron capture therapy	Gillies & Frechet, 2005; Ochekpe et al., 2009
Mesoporous silica nanocarriars	1-100	Self-assembly, aerogel method, hard and soft templating	Porous honeycomb structure, biocompatibility, good chemical and thermal stability	Protein and peptide delivery, drug delivery	Yoo et al., 2005; Rosenblum et al., 2018
Liposomes	50-100	Detergent removal method, solvent dispersion	Biocompatible, less toxic, biodegradable	Entrap both hydrophobic and hydrophilic drug, biologically active agent transport	Chamundeeswari et al., 2019; Pattni et al., 2015

due to certain challenges alkaloids often modified by nano-based drug delivery system and encapsulated to protect drugs from degradation (Bregoli et al., 2016).

Flavonoids

Flavonoids have a C15 backbone structure with phenyl rings and are acknowledged for therapeutic applications such as their ability to alleviate aging process in different organs. They are also known for their preventive role against Alzheimer's disease, cancer and cardiovascular disease (Alhabib et al., 2024; Ahmed et al., 2025). However, many flavonoids interact with other compounds and modify their bioavailability and stability. These challenges can be overcome by developing nano-carrier systems to target specific organs and transport flavonoid compounds (Selvakumar et al., 2020). Nano-formulations of flavonoids such as gambogic acid that have clinical applications against colon, breast cancers (Lin et al., 2020).

Polyphenols

Polyphenols are plant based secondary metabolites with potent anti-inflammatory and antioxidant properties. These compounds are valuable for the management of various chronic diseases. Polyphenols are characterized by aromatic rings with hydroxyl group (Zhang et al., 2021). Nano-drug delivery systems have been developed to overcome their instability, solubility challenges and less bioavailability. Curcumin and Resveratrol are natural polyphenols with antioxidant properties. These compounds can be modified by encapsulating them in biocompatible and biodegradable nanoparticles (Han et al., 2020).

Terpenoids

Terpenoids are used in different industries such as food and medicine and consist of many C_5H_8. Terpenoids have a range of pharmacological activities including antimicrobial, anti-cancerous and anti-inflammatory effects (Ge et al., 2022). Thymoquinone in the form of nano emulsion and solid lipid nanocarriers possess antioxidant, anti-inflammatory and anti-cancerous activities (Ballout et al., 2018).

METHODS FOR NANO-FORMULATION OF NATURAL PRODUCTS

Green Synthesis Techniques

Green synthesis method of nano formulation of natural products is also known as biological method, which is a substitute of physical and chemical methods. This method provides eco-friendly ways to synthesize nanoparticles, non-toxic, expensive and harmful chemical agents (Nadaroglu et al., 2017a). Synthesis can be done in one step by using biological agents including bacteria, plants, algae and actinobacteria. Molecules in these biological agents synthesize NPs via reduction as shown in Fig. 2 (Nadaroglu et al., 2017b).

Supercritical Fluid Technology

Supercritical fluid technology has been used since 19th century for the isolation of chemicals. CO_2 is used as mobile phase due to its low critical point, and the chromatographic path flow is pressurized. A fluid is called supercritical, when its temperature and pressure above their critical value, at which point distinct liquid and gas phases no longer exist (Parhi et al., 2013). It is not possible to liquefy a gas by pressure increasing, when temperature is above critical point. Critical temperature and pressure increase with the increase of density, intermolecular forces and molecular weight. The unique features are viscosity, density and diffusivity. CO_2 is non-inflammable and non-toxic solvent used specifically in nano-formulation. For the nano-formulation, natural products firstly dissolved in supercritical fluid and then depressurization results in nanoprecipitation (Ventosa et al., 2003).

Surface Functionalization and Targeting

Nanoparticles can be functionalized by ligands such as peptides and folic acid to intensify targeting toward specific cells. Functionalization of nanoparticles influences their colloidal stability, dispersion and controlled assembly. Surface functionalization provides selective recognition and targeted delivery in medicine. Strategies for functionalization of nanoparticles are through electrostatic interactions, supramolecular affinity and intrinsic surface engineering.

Solvent Evaporation and Emulsification

This is one of the most widely used methods for the formulation of nanoparticles. This technique involves two main steps, first is the polymer solution emulsification into aqueous phase and in second step, solvent is evaporated. Nanoparticles after precipitation, collected by ultracentrifugation and washed with distilled water to remove residue and lyophilized for storage. Solvent evaporation and emulsification method has high encapsulation efficiency, capable for use in industries and have controlled particle size (Jaiswal et al., 2004).

APPLICATION IN HEALTH AND DISEASE

Antioxidant and Anti-inflammatory Applications

Natural products extracted from plants and other living organisms primarily consist of bioactive compounds including terpenoids, polyphenols, flavonoids, essential oils and possess health promoting roles (Xu et al., 2020). These bioactive compounds are widely utilized for their ability to cure various inflammatory conditions and improve physical health. Bioactive compounds also have antioxidant and anti-inflammatory properties that inhibit the oxidative stress markers (Pradubyat et al., 2024). Quercetin, myricetin and orientin have been extensively used as medicine to treat various diseases due to their antioxidant and anti-inflammatory benefits (Mu et al., 2024).

Anticancer Therapy

Natural products such as alkaloids and flavonoids have potent anticancer effects and are successfully applicable in cancer treatment. Vinca Alkaloid family extracted from *Catharanthus roseus* that responsible for the treatment of cancer, leukemia and Hodgkin's disease (Da Rocha et al., 2001). Similarly, quercetin liposomes, curcumin and camptothecin dendrimers are agents derived from natural sources used in clinical practice (Ali et al., 2022).

Antimicrobial and Antiviral Uses

Due to increased side effects of chemical or synthetic drugs, the use of herbal medicines or natural products having antimicrobial and antiviral properties increases. Herb medicines are used as a substitute of nanosilver, as nanosilver influences the reactive oxygen species mediated mechanisms and in turn increases the oxidative stress (Parham et al., 2020). Therefore, synthetic drugs replaced by natural products with antiviral and antimicrobial activities. *Aeromonas* in clinical and aquaculture can be inhibited by allicin (Nano-garlic oil) while curcumin nanoparticles are used against SARS-CoV-2 (Joshi et al., 2020).

Neuroprotective and Cardioprotective Delivery

Natural products which are extracted and isolated from plants, fungi, microorganisms or animals have been extensively used for the treatment of various diseases including diabetes, reproductive, cardiovascular or neurodegenerative disorders (Mohd Sairazi & Sirajudeen, 2020). Quercetin, bioactive secondary metabolite, involves the treatment of neurological and cardiovascular disorders (Bhat & Bhat, 2021). Honey is bee-hive product that has therapeutic potential and consists of various bioactive compounds such as polyphenols. So, honey has been recognized as antioxidant, neuroprotective, cardioprotective agent and anti-inflammatory (Bogdanov et al., 2008).

APPLICATIONS IN AGRICULTURE AND AQUACULTURE

Nano-encapsulated Biopesticides

Biopesticides play an important role in agriculture as pest management. These are derived

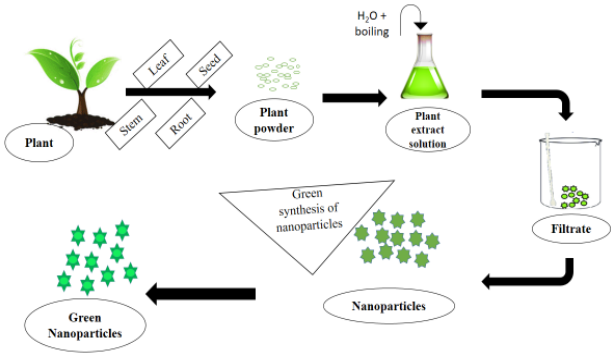

Fig 2. Green synthesis of Nanoparticles

from plants and other biological organisms, exhibit rapid decomposition, less toxicity and overcome the bioaccumulation. Biopesticides are eco-friendly substitutes of synthetic chemicals, effectively controlling pests in agriculture and aquaculture. Nano-biopesticides are pioneering revolutions in agriculture manipulating nanotechnology to boost the stability, specificity, sustainability and efficiency of pest management (Pan et al., 2023). Nano-biopesticides are the formulations that contain bioactive compounds with nanomaterials (nanoparticles) to selectively target pests (Sharma et al., 2012). Aquaculture is the food production system both in terms of food security and economic impact. Nanotechnology based systems are applied to enhance the efficiency, sustainability and management of fish and dietary supplementation through neutraceuticals (Fajardo et al., 2022).

Plant growth enhancement

Use of synthetic chemicals or hormones to enhance the growth of plants raises issues due to their effects on humans and the environment. On the other hand, natural products are eco-friendly, non-toxic and safe for plant growth enhancement (Singh et al., 2024). Various plant extracts such as garlic, moringa leaf extract, ginger, *Aloe vera*, and cinnamon powder containing hormones cytokinin, auxin and gibberllins, enhance the growth of plants (Mirihagalla & Fernando, 2020). Aloe vera leaves contain hormones, glycoproteins, lignin, enzymes and polysaccharides. These components have anitifungal, antioxidant and immunity enhancing effects (Aryan et al., 2023). Seaweed extracts are also rich of bioactive compounds that have the ability to promote plant growth, metabolism and photosynthesis (Massoud et al., 2017).

Mitigation of Water Pollutants via Nano-remediation

Water is an essential source to sustain life on earth and is also an important source for the survival of aquatic organisms. Excessive use of metals contaminates water and becomes a serious problem all over the world. Moreover, the excessive use of pesticides and fertilizers also add impurities in water (Mathur et al., 2022). Nanoremediation is a process using nanomaterials like nanoparticles and nanotubes to remove pollutants from water, and nanoparticles are particularly useful due to their high surface area, efficiency, and features such as stability, high recycling capacity, and lower toxicity (Gupta et al., 2013).

CHALLENGES AND LIMITATIONS

Nanotechnology has been extensively applied to drug development, as nanoparticles have unique characteristics at molecular, cellular and atomic levels. Several challenges limit the nano-delivery systems such as nanoformulations face stability and scale up difficulties, moreover, they may cause toxicity due to their accumulation in different organs (Desai, 2012). Various biological barriers stop natural products from targeting specific tissues as blood-brain barrier hinders the efficiency of nanotechnology-based delivery of natural products (Alonso, 2004). Reproducibility in the *in situ* formation of nanomedicines is a significant challenge, while high costs and a lack of clear guidance also limit the commercialization of nanobased natural products. (Feng et al., 2004). These challenges may be overcome through the development of nanocarriers responsive to stimuli, emphasis on green and sustainable nanotechnology and combining nanomedicines with AI-based drug and proteomics (Patra et al., 2018).

CONCLUSION

Nanotechnology-based delivery of natural products represents a revolution in drug delivery, environmental health and agricultural innovations. Nanoformulations including liposomes, polymeric nanoparticles, solid-lipid nanoparticles and green synthesized metallic nanoparticles allow controlled release, enhanced therapeutic effects and targeted delivery in various heath conditions such as cardiovascular disorders, neurodegeneration, cancer, hypertension and other infectious disorders. Nanotechnology shows great promise in aquaculture and agriculture; specifically, nano-biopesticides and nano-fertilizers can enhance plant growth and crop productivity, while nano-herbal products can improve fish health, boost immunity, and increase growth. Although nanoformulations play a key role in different fields, challenges still persist with reference to long term toxicity,

bioavailability, cost and commercialization. These challenges may be countered by sustainable green synthesis of nanocarriers, stimuli-responsive nanoparticles and artificial intelligence, which may improve the efficiency of bioactive compounds delivery.

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