

FUTURE DIRECTIONS IN UTILIZING POLYMERIC NANOFORMULATIONS FOR PLANT BIOACTIVES AND EXTRACTS

Abstract

Polymeric nano formulations hold great promise for enhancing the efficacy and targeted delivery of plant bioactives in various agricultural applications. This review covers future directions, including advancements in nanoencapsulation techniques, stability improvement, bioavailability enhancement, tailoring formulations to specific plant applications and safety assessment. Advances in nanoencapsulation techniques have transformed the delivery of plant bio actives, including pesticides, growth regulators, and beneficial microorganisms. Biocompatible and biodegradable polymers ensure safety and eco-friendliness. Stimuli-responsive nanoparticles enable controlled release, optimizing dosing while minimizing environmental impact. Enhancing the stability and bioavailability of plant bioactives is crucial for maximizing their effectiveness. Polymeric nanoformulations protect compounds from degradation, improve solubility, and enable sustained release, leading to prolonged exposure and enhanced nutrient uptake. Tailored polymeric nanoformulations in precision agriculture enable targeted delivery to specific plant tissues, enhancing disease management, stress tolerance, and nutrient supply. Combination therapies with multiple bioactives provide personalized solutions for diverse plant-related challenges. Safety is crucial for polymeric nanoformulations. Nanotoxicity studies and safety evaluations guide responsible formulation design and regulatory approvals. Long-term safety assessments and environmental impact evaluations ensure sustainable agricultural practices.

Future research focuses on personalized plant treatments, smart nanoparticles,

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and innovative applications such as nanoscale vaccines, wound healing, and environmental remediation. Overcoming challenges in scale-up, cost, and public acceptance is crucial for successful implementation. Interdisciplinary collaboration and ongoing research will unleash the full potential of polymeric nanoformulations in sustainable agriculture and plant-related industries.

Keywords: Nanoformulations , Plant bioactives, Stability, Nanotoxicity

I. INTRODUCTION

Nanoformulations have emerged as a promising field in the realm of drug delivery, offering unprecedented opportunities to enhance the efficacy and safety of therapeutic agents. Polymeric nanoformulations, in particular, have garnered significant attention due to their versatility, tunability, and ability to encapsulate a wide range of bioactive compounds.[1]

Polymeric nanoformulations involve the encapsulation of bioactive substances within polymeric nanoparticles, which are typically in the range of 1 to 100 nanometers in size. [1] These nanoparticles can be fabricated from a variety of biocompatible and biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polyethylene glycol (PEG), and polycaprolactone (PCL).[2] [3]The choice of polymer depends on factors such as the desired release profile, stability requirements, and compatibility with the target application.

One of the key advantages of polymeric nanoformulations is their ability to protect bioactive compounds, such as plant extracts and phytochemicals, from degradation and premature release.[3] The polymeric matrix acts as a barrier, shielding the encapsulated bioactives from environmental factors, such as light, oxygen, and enzymatic degradation. This protection ensures enhanced stability and prolonged shelf life, which is particularly crucial for plant-based bioactives that are prone to degradation.

Furthermore, polymeric nanoformulations offer improved bioavailability and targeted delivery of plant bioactives. The small size and high surface area-to-volume ratio of polymeric nanoparticles allow for efficient cellular uptake and transport across biological barriers.[4] This enables better penetration of bioactives into specific tissues or cells, maximizing their therapeutic potential. Moreover, the controlled release capabilities of polymeric nanoformulations can be tailored to achieve sustained or triggered release profiles, allowing for optimized dosage regimens and minimizing side effects.[5]

In addition to their biomedical applications, polymeric nanoformulations have shown great promise in the field of plant science. By encapsulating plant bioactives and extracts, these nanoformulations can protect them from degradation during storage, transportation, and application. Furthermore, they can improve the solubility and dispersibility of hydrophobic plant compounds, enhancing their absorption and bioavailability in plant systems. This opens up new avenues for utilizing polymeric nanoformulations in areas such as agriculture, horticulture, and plant-based therapeutics.[6]

The advent of polymeric nanoformulations represents a significant advancement in the field of drug delivery and plant science. These nanostructures hold immense potential for improving the stability, bioavailability, and targeted delivery of plant bioactives and extracts. As research continues to evolve in this area, it is expected that polymeric nanoformulations will revolutionize the utilization of plant-based compounds, enabling their effective application in various sectors ranging from healthcare to sustainable agriculture.[6]

Polymeric nanoformulations fall under the broader category of pharmaceutical formulations. They are specifically classified as nanoparticulate drug delivery systems. Within the field of pharmaceuticals, polymeric nanoformulations can be further categorized based on their composition, structure, and intended application. Some common classifications include:

- 1. Polymeric Nanoparticles:** These are nano-sized particles composed of polymeric materials, such as PLGA (poly lactic-co-glycolic acid), chitosan, PEG (polyethylene glycol), or PCL (polycaprolactone). They are used for encapsulating drugs or bioactive compounds and are designed to improve drug stability, solubility, and targeted delivery.
- 2. Polymeric Micelles:** Micelles are self-assembled structures composed of amphiphilic block copolymers. They form nanosized spherical structures with a hydrophobic core and a hydrophilic shell. Polymeric micelles are used to encapsulate hydrophobic drugs and improve their solubility and targeted delivery.
- 3. Polymeric Lipid Hybrid Nanoparticles:** These nanoformulations combine polymeric materials and lipids to create hybrid nanoparticles. The lipid component provides stability and enhanced drug encapsulation, while the polymeric component offers control over drug release and stability.
- 4. Dendrimers:** Dendrimers are highly branched polymeric nanoparticles with a well-defined structure. They have a spherical shape and can encapsulate drugs within their interior or attach them to their surface. Dendrimers are known for their high drug-loading capacity and controlled release properties.
- 5. Polymer-Drug Conjugates:** In this type of nanoformulation, the drug molecule is covalently attached to a polymeric carrier. The polymer acts as a carrier, providing stability and controlled release of the drug, while also facilitating targeted delivery.

Furthermore, various combinations and modifications of polymeric materials can be employed to create hybrid or multifunctional nanoformulations. The classification of polymeric nanoformulations is dynamic and continually evolving as new materials and strategies are developed for drug delivery applications.

II. IMPORTANCE OF UTILIZING POLYMERIC NANOFORMULATIONS FOR PLANT BIOACTIVES AND EXTRACTS

Plant bioactives and extracts have gained significant attention due to their potential health benefits and wide-ranging applications in various industries. However, the effective utilization of these bioactive compounds is often hindered by challenges related to their stability, bioavailability, and targeted delivery. Polymeric nanoformulations have emerged as a valuable tool to overcome these limitations, offering numerous advantages for enhancing the utilization of plant bioactives and extracts. One of the key importance of utilizing polymeric nanoformulations lies in their ability to protect plant bioactives and extracts from degradation. Many bioactive compounds found in plants are highly sensitive to environmental factors, such as light, oxygen, heat, and enzymatic degradation. These factors can cause a loss of potency and reduced shelf life, limiting their effectiveness.[7] Polymeric nanoformulations act as protective carriers, encapsulating plant bioactives and extracts within a polymeric matrix. This encapsulation shields the bioactive compounds from degradation, preserving their structural integrity, and maintaining their bioactivity over extended periods. By enhancing stability, polymeric nanoformulations enable the utilization of plant bioactives and extracts in various applications, ranging from pharmaceuticals to nutraceuticals and functional foods.[8]

Another significant advantage of polymeric nanoformulations is their ability to improve the bioavailability of plant bioactives and extracts. Many bioactive compounds have poor solubility in water and low permeability across biological barriers, limiting their absorption and therapeutic efficacy. Polymeric nanoparticles can encapsulate hydrophobic plant compounds and enhance their solubility in aqueous media. The small size and high surface area-to-volume ratio of polymeric nanoparticles facilitate efficient cellular uptake and transport across biological barriers, such as the gastrointestinal tract or skin. This improved bioavailability enhances the therapeutic potential of plant bioactives and extracts, allowing for lower doses, reduced side effects, and increased efficacy.[9]

Polymeric nanoformulations offer the opportunity for targeted delivery of plant bioactives and extracts. The design of polymeric nanoparticles can be tailored to achieve site-specific delivery, ensuring that the bioactive compounds reach the intended target tissues or cells. Surface modifications of nanoparticles with ligands or antibodies enable active targeting, directing the nanoparticles to specific receptors or cellular markers. This targeted delivery approach improves the efficiency of bioactive compounds, reduces off-target effects, and increases the selectivity of their action. Polymeric nanoformulations thus enable the development of more precise and personalized approaches for utilizing plant bioactives and extracts in various therapeutic and agricultural applications.[9] The utilization of polymeric nanoformulations is of paramount importance in harnessing the full potential of plant bioactives and extracts. These nanoformulations offer protection against degradation, enhance bioavailability, and enable targeted delivery. By addressing the challenges associated with stability, solubility, and site-specific delivery, polymeric nanoformulations facilitate the development of innovative plant-based products and therapies.

III. ADVANCES IN POLYMERIC NANOENCAPSULATION TECHNIQUES

Nanoencapsulation refers to the process of enclosing active substances or payloads within nanoscale polymeric carriers, often termed nanoparticles. These nanoparticles can protect the encapsulated materials, enhance their stability, control their release, and improve their bioavailability. This article provides a detailed overview of the recent advances in polymeric nanoencapsulation techniques, highlighting their potential applications in various industries, particularly in pharmaceuticals and biomedical sciences.

- 1. Stimuli-Responsive Nanoencapsulation:** Researchers have made significant strides in developing stimuli-responsive polymeric nanoparticles. These nanoparticles can release their payloads in response to specific environmental cues, such as pH, temperature, enzymes, or light. By harnessing these triggers, researchers can achieve on-demand drug release, providing personalized and efficient therapy for various diseases.[10][11]
- 2. Surface Modification and Targeting:** Surface modification of polymeric nanoparticles has been a game-changer in achieving site-specific targeting and controlled drug release. Techniques like PEGylation, ligand conjugation, and biofunctionalization enable nanoparticles to evade the immune system, prolong circulation, and actively target specific cells or tissues. This has immense potential in cancer therapy, where targeted delivery can minimize side effects and improve treatment efficacy.[12]

3. **Biodegradable Polymers:** Biodegradable polymers have gained significant attention due to their potential in reducing environmental impact and improving safety for biomedical applications. Recent advancements have led to the development of new biodegradable polymers with tunable properties for nanoencapsulation, enabling controlled drug release and reduced toxicity.[13]
4. **Hybrid Nanomaterials:** Combining different types of polymers or incorporating other nanomaterials, such as lipids or inorganic nanoparticles, has shown enhanced stability and functionality of the nanoencapsulation systems. These hybrid nanomaterials can be engineered to have specific properties tailored to the desired application.[14]
5. **Nanogels:** Nanogels are three-dimensional polymeric networks that can encapsulate therapeutic agents. Recent advances have enabled the fabrication of nanogels with precise control over size, shape, and drug release kinetics, making them attractive for drug delivery and tissue engineering applications.[15]
6. **Self-Assembled Nanoparticles:** Utilizing self-assembly processes, researchers have been able to create nanoparticles with high encapsulation efficiency and stability. By allowing the polymers to self-assemble into organized structures, such as micelles or vesicles, it is possible to encapsulate drugs or other bioactive molecules more efficiently.[16]
7. **Targeting Strategies:** Surface modification of polymeric nanoparticles with ligands, peptides, or antibodies has become more sophisticated, allowing for improved targeting and specific delivery to diseased tissues or cells. Active targeting strategies help enhance the selectivity and efficiency of therapeutic delivery.[17]

IV. ENHANCING STABILITY AND BIOAVAILABILITY OF PLANT BIOACTIVES AND EXTRACTS

Plant bioactives are natural substances found in fruits and vegetables that influence cellular and physiological processes in humans and animals after consumption. They include plant sterols, carotenoids, tannins, betalains, anthocyanins, flavonoids, and glucosinolates, showcasing activities like anti-inflammatory, antioxidant, and anti-carcinogenic properties, protecting against various illnesses and metabolic disorders.[18] However, their stability can be influenced by factors such as temperature, light (especially UV light), oxygen, pH, and moisture. High temperatures and UV light can speed up degradation and reduce potency. Oxygen can create free radicals damaging bioactives, and moisture can lead to hydrolysis, reducing their effectiveness. Therefore, proper storage, processing, and utilization are essential for maintaining plant bioactives' stability. [19] [20]

1. **Challenges In Stabilizing And Delivering Plant Bioactives And Extracts** Growing interest in plant bioactives and extracts, natural compounds found in plants, is driven by their potential health benefits. These compounds show antioxidant, anti-inflammatory, anticancer, and antimicrobial properties, leading to increased research and development efforts to incorporate them into food, pharmaceutical, and cosmetic products. However, utilizing plant bioactives and extracts in commercial applications faces challenges, particularly in stabilizing and delivering these compounds effectively.[21][22] [23] Therefore

this note highlights some of the key challenges encountered in stabilizing and delivering plant bioactives and extracts.

- **Chemical Instability:** Plant bioactives often exhibit inherent instability, making them susceptible to degradation from factors like light, heat, oxygen, and pH fluctuations. This degradation can result in a loss of their beneficial properties, diminishing the effectiveness of the end product.[24]
 - **Solubility Issues:** Enhancing the solubility of bioactive compounds from plants is crucial to improve their bioavailability and efficacy. However, this poses a significant challenge in developing effective delivery systems for better absorption in the body. [25]
 - **Bioavailability and Absorption:** The successful delivery of plant bioactives into target tissues or cells is a challenging task. The body's intricate physiological processes can impede the absorption and bioavailability of these compounds, limiting their therapeutic potential. [26]
 - **Interactions with Other Ingredients:** Interactions between plant bioactives and other ingredients in formulations can impact stability and efficacy. Compatibility challenges with excipients or active pharmaceutical ingredients are significant concerns in various formulations. [27]
 - **Regulatory Hurdles:** Incorporating plant bioactives into commercial products involves complying with stringent regulatory guidelines. The lengthy and costly approval process can act as a barrier, impeding the development of products utilizing these compounds. [27]
 - **Standardization and Quality Control:** The chemical composition of plant extracts can vary considerably due to factors such as growing conditions, harvesting methods, and extraction processes. To deliver reliable and effective products, ensuring consistency and standardization of bioactive content in plant extracts is crucial. [28]
 - **Delivery System Selection:** Developing suitable delivery systems that safeguard plant bioactives during storage and transportation, while enabling controlled release at the desired location, is a complex task. [29]
 - **Cost Considerations:** The production and extraction of plant bioactives, especially from rare or low-yield sources, can be costly, limiting their commercial viability and accessibility to consumers. [30]
2. **Role of Polymeric Nanoformulations in Improving Stability and Bioavailability:** Polymeric nanoformulations play a crucial role in enhancing the stability and bioavailability of plant bioactives and extracts. By encapsulating and protecting the bioactive compounds within a stable polymeric matrix, these nanoformulations offer numerous advantages over conventional delivery systems.[31]
- **Protection against Degradation:** Polymeric nanoformulations create a protective barrier around the encapsulated bioactive compounds, safeguarding them from environmental factors like light, heat, oxygen, and pH fluctuations. This protection prevents degradation, preserving the bioactive's chemical integrity, and enhancing its stability during storage and transportation. [32]
 - **Enhanced Solubility:** Polymeric nanoformulations improve the solubility of hydrophobic plant bioactives by encapsulating them within hydrophilic polymers. This en-

hancement enables better absorption and distribution in the body upon ingestion or application, addressing the issue of poor water solubility and increasing their bioavailability and effectiveness. [33]

- **Controlled Release:** Polymeric nanoformulations enable controlled release of bioactive compounds by adjusting the properties of the polymer matrix. This tailored release matches specific therapeutic needs, preventing sudden spikes in bioactive concentrations and ensuring sustained efficacy over an extended period. [34]
- **Increased Bioavailability:** The small size of polymeric nanoparticles enhances the cellular uptake and absorption of plant bioactives. These nano-sized carriers can pass through biological barriers like the gastrointestinal tract and cell membranes, leading to increased bioavailability of the encapsulated compounds. [4]
- **Targeted Delivery:** Functionalization of polymeric nanoparticles allows for targeted delivery of plant bioactives to specific tissues or cells. Ligands or receptors can be attached to the nanoparticle surface, guiding them to the desired site of action, minimizing off-target effects, and improving therapeutic outcomes.[35]
- **Stability during Processing:** Polymeric nanoformulations play a protective role during the formulation of products with plant bioactives. They safeguard these compounds from degradation caused by processing conditions, like heating or blending, which could otherwise compromise their stability.[36]
- **Compatibility with Formulations:** Polymeric nanoformulations offer easy incorporation into diverse product formulations, such as food, pharmaceuticals, and cosmetics. Their compatibility with different matrices ensures efficient delivery of plant bioactives without compromising the properties of the final product.[37]
- **Reduced Dose and Side Effects:** The improved bioavailability and targeted delivery of polymeric nanoformulations allow for the use of lower doses of bioactives while achieving the desired therapeutic effects. This can minimize potential side effects associated with higher dosages.[38]
- **Long-term Stability:** Well-designed polymeric nanoformulations offer long-term stability to plant bioactives, prolonging their shelf life and enhancing the overall efficacy of products incorporating these compounds.[36]

V. TAILORING POLYMERIC NANOFORMULATIONS FOR SPECIFIC PLANT APPLICATIONS

1. **Customizing Polymeric Nanoformulations for Targeted Delivery and Efficacy:** Polymeric nanoformulations have shown immense promise in the field of plant sciences by enabling targeted delivery of bioactive compounds to specific plant tissues and improving their efficacy. These nanoformulations involve the encapsulation of plant bioactives, such as pesticides, fertilizers, growth regulators, and beneficial microorganisms, within nanoscale polymeric carriers. Following are the key strategies for customizing polymeric nanoformulations to achieve targeted delivery and enhance efficacy for specific plant applications.

- **Selection of Biocompatible and Biodegradable Polymers:** The choice of polymer is crucial in designing polymeric nanoformulations. Biocompatible and biodegradable polymers are preferred to ensure that the nanoparticles are safe for plants and do not cause environmental harm. Polymers like poly(lactic-co-glycolic acid) (PLGA), chito-

san, starch, and cellulose derivatives are commonly used due to their biocompatibility and ability to degrade into non-toxic byproducts.[39]

- **Surface Modification for Targeting:**Surface modification of polymeric nanoparticles allows for active targeting to specific plant tissues or cell types. Ligands, antibodies, or peptides can be conjugated to the nanoparticle surface to recognize and bind to receptors present on the target cells. This approach enhances the accumulation of nanoparticles in the desired plant parts and reduces off-target effects.[40]
- **Stimuli-Responsive Nanoparticles:**Stimuli-responsive polymeric nanoparticles respond to specific environmental cues, such as pH, temperature, enzymes, or light. These nanoparticles can release their payload in response to these stimuli, allowing for controlled and triggered drug release. For plant applications, such nanoparticles can be designed to release bioactive compounds in response to specific plant physiological conditions or pest/disease presence.[41]
- **Encapsulation Of Multiple Bioactives:**Polymeric nanoformulations allow for the encapsulation of multiple bioactive compounds in a single nanoparticle. This capability is particularly beneficial for combination therapies, where different compounds can work synergistically to enhance plant growth, protection, or nutrient uptake. By controlling the ratios of different bioactives, the formulation can be tailored for optimal effects.[42]
- **Nanoencapsulation of Beneficial Microorganisms:**Polymeric nanoparticles can encapsulate beneficial microorganisms, such as mycorrhizal fungi and plant growth-promoting bacteria. These nanoparticles protect the microorganisms during application, improve their survival and colonization in the rhizosphere, and enhance their beneficial effects on plant growth, nutrient uptake, and stress tolerance.[43]
- **Release Kinetics and Sustained Delivery:**By carefully selecting the polymer composition and formulation parameters, the release kinetics of the encapsulated bioactives can be tailored. Sustained release over an extended period ensures a continuous supply of the active compounds to the plants, reducing the need for frequent applications and enhancing the overall efficacy.[40]
- **Size and Surface Charge:**The size and surface charge of nanoparticles influence their cellular uptake and distribution within plant tissues. Smaller nanoparticles generally have better cellular penetration, while surface charge affects their interaction with plant cell membranes. Customizing these parameters can optimize the uptake and distribution of the nanoformulations within plants.[40]

2. **Suitable Natural Polymers for Polymeric Nano Formulations:** Several natural polymers have been commonly used in polymeric nano formulations due to their biocompatibility, biodegradability, low toxicity, and ease of processing. These natural polymers have found various applications in drug delivery, tissue engineering, and nanomedicine. Some of the commonly used natural polymers are discussed below.

- **Chitosan:** Chitosan is derived from chitin, a polysaccharide found in the exoskeleton of crustaceans such as shrimp and crab. It is biocompatible, biodegradable, and has excellent mucoadhesive properties, making it suitable for drug delivery systems, especially for oral, nasal, and ocular administration.[44][45]

- **Alginate:** Alginate is extracted from brown seaweeds and is widely used for the preparation of nanoparticles and hydrogels. It forms a gel upon exposure to divalent cations, such as calcium ions, making it suitable for controlled release of drugs and encapsulation of cells.[46][47]
- **Hyaluronic Acid (HA):** HA is a glycosaminoglycan naturally present in the extracellular matrix of connective tissues. It is biocompatible, non-immunogenic, and has high water-binding capacity. HA-based nanoformulations are used in drug delivery, wound healing, and tissue engineering applications.[48]
- **Gelatin:** Gelatin is a denatured form of collagen, obtained from animal sources like bovine or porcine skin and bones. It has been used in the development of nanostructured delivery systems for drugs, proteins, and genes due to its biodegradability and biocompatibility.[49]
- **Starch:** Starch is a natural carbohydrate polymer obtained from plant sources like corn, wheat, or potatoes. It has been used in nanoparticulate systems for drug delivery and encapsulation due to its availability, low cost, and biodegradability.[50][51]
- **Cellulose and Derivatives:** Cellulose is the main component of the plant cell wall. Cellulose derivatives like methylcellulose, hydroxypropyl cellulose, and carboxymethyl cellulose have been utilized in various nanoformulations for drug delivery and other biomedical applications.[52][53]
- **Dextran:** Dextran is a glucose-based polymer produced by bacteria during the fermentation of sucrose. It has been used in the formulation of nanoparticles for drug delivery and imaging applications.[54]
- **Polyhydroxyalkanoates (PHAs):** PHAs are naturally occurring biodegradable polymers synthesized by certain bacteria as energy storage compounds. These polymers have gained attention in nanoformulations for drug delivery and tissue engineering applications.[55]

3. Polymeric Nano Formulations for Specific Plant Applications

- **Polymeric Nano herbicides:** Weeds compete with crops for water, light, and nutrients, leading to the use of herbicides in crop fields. While herbicides are essential for maximizing agricultural productivity, their indiscriminate use has negative environmental and health impacts. To address these concerns, polymeric nanocarriers for herbicides have been developed, offering enhanced effectiveness against target organisms, biodegradability, low toxicity, and reduced environmental impact. For instance, metribuzin combined with PCL nanoparticles showed increased efficacy against weeds without affecting soil or environmental persistence. Atrazine-loaded PCL nanocapsules also demonstrated greater post-emergent herbicidal action than traditional atrazine, allowing for a ten-fold reduction in application dose and minimizing environmental damage. [56] [57][58][59].
- **Polymeric nano fungicides:** There is a pressing need for novel, highly effective anti-fungal medicines due to fungi posing a serious threat to plant production.[60] Disease management for food crops is crucial, and fungicides play a key role in protecting crops from pests and diseases. Pests cause about 35% of global crop losses, with poorer nations experiencing a higher rate of 48%. Plant diseases caused by bacteria, fungus, and viruses account for about one-third of these losses, impacting product quality and both human and animal health. Nano fungicides, with their unique physio-

chemical properties, can combat plant ailments by delivering active ingredients in a controlled manner and improving their bioavailability.[61] Their effectiveness, gradual release, and compatibility with fertilizers enhance plant development and resilience against various challenges. Improved nanoparticle qualities offer a promising solution for reducing the environmental impact of undesirable compounds, especially in the case of plant protectants. For example, when compared to bulk materials, nano-sulfur has been shown to be more effective in controlling the growth of the okra fungus *Erysiphe cichoracearum* at a concentration of 1000 parts per million. In fact, nano-sulfur outperforms regular sulfur fungicides and commercial formulations, enabling its use in smaller, more efficient doses to effectively combat powdery mildew illness.[62]

- **Polymeric nano insecticide:** Insects are the most diverse organisms on Earth, with over one million documented species. While some insects provide beneficial services like pollination and pest control, others harm crop production and storage. To combat harmful insects, pesticides are commonly used, but they can also be hazardous to non-target organisms. To address this, researchers have developed polymeric nanoparticles carrying insecticides, known as nano insecticides, which offer increased efficiency and lower toxicity. These nano formulations have advantages over conventional insecticides, including higher efficacy, increased solubility, and systemic activity.[63] There is a growing interest in replacing synthetic insecticides with natural alternatives, such as botanical insecticides derived from plant extracts and essential oils. Neem essential oil, extracted from *Azadirachta indica*, is one of the widely used botanical insecticides due to its effectiveness against insects and low toxicity to non-target organisms.[64] Nanotechnology could further enhance the application of natural insecticides. Studies have shown that chitosan nanoparticles and neem oil-loaded PCL nanocapsules exhibited promising effects in controlling harmful insects like *Helicoverpa armigera* and *Plutella xylostella*, respectively.[65]
- **Polymeric nanoparticles containing plant growth regulators:** Plant growth regulators (PGRs) play a crucial role in facilitating plant survival under adverse conditions by regulating growth, development, and physiological processes.[66] PGRs encompass various hormones like auxins, cytokinins, gibberellins, ethylene, abscisic acid, brassinosteroids, and nitric oxide (NO).[67] However, excessive application of PGRs can be phytotoxic, necessitating controlled release methods for their optimal use. Recent groundbreaking research focused on polymeric nanoparticles as carrier systems for PGRs, showing the effectiveness of chitosan/tripolyphosphate nanoparticles encapsulating the NO donor S-nitroso-mercaptosuccinic acid (S-nitroso-MSA) in protecting maize plants from salt stress. These nanoparticles exhibit continuous NO release due to strong electrostatic interactions with the chitosan core, enabling their application in diverse biomedical and agricultural contexts.[68] Similarly, alginate/chitosan and chitosan/tripolyphosphate nanoparticles have been developed as controlled release systems for gibberellic acid (GA3), leading to improved plant growth and overcoming seed dormancy. The nanocarrier systems offer slow release, increased solubility, and protection of GA3 from degradation, making them promising tools for agricultural applications.[69][70]

VI. NANOTOXICITY AND SAFETY CONSIDERATIONS

Nanotoxicology aims to assess the adverse impacts of nanomaterials on human health and the environment. Employing a multidisciplinary team approach, it combines expertise from toxicology, biology, chemistry, physics, material science, geology, exposure assessment, pharmacokinetics, and medicine to establish and detect the harmful effects of manmade nanomaterials.[71]

In nanomaterial toxicity assessment, factors like exposure time, dose, aggregation and concentration, particle size and shape, and surface area and charge are crucial.[72] Smaller nanomaterials have increased surface area, facilitating more molecule attachment and raising their harmful impact. Additionally, different-sized particles can accumulate in various lung regions and be expelled at different rates.[73] Particle surface, surface chemistry, and charge are critical properties influencing the interaction of nanomaterials with the biological micro-environment. Nanomaterials may have coatings with positive or negative charges based on their function. Evaluating surface chemistry can be achieved using electron and atomic force microscopes for topographic characterization. Studies have indicated that these factors significantly impact the toxicity rate of nanoparticles.[74] Inhaling nanomaterials can lead to dose-dependent hazardous consequences. Relying solely on mass concentration measurement in toxicological dosage evaluation may produce inaccurate results and fails to fully explain the connection between nanomaterials and exposed tissue, as per recent research findings.[75]

Assessment of Potential Risks and Toxicity Associated with Polymeric Nanoformulations

- 1. Physicochemical Characterization:** One of the fundamental steps in risk assessment is the comprehensive physicochemical characterization of the polymeric nanoformulations. This includes determining particle size, shape, surface charge, surface chemistry, and aggregation state. These characteristics play a crucial role in their biological interactions and potential toxicity.[76][77][78]
- 2. Cellular uptake and Biodistribution:** Understanding the cellular uptake and biodistribution of polymeric nanoparticles is critical to assessing their potential toxicity. Studies should investigate how these nanoparticles interact with different cell types and tissues and whether they accumulate in specific organs or cross biological barriers.[79][80]
- 3. In Vitro Cytotoxicity Studies:** In vitro studies are conducted to assess the cytotoxicity of polymeric nanoformulations using various cell lines. These studies help identify the potential adverse effects of nanoparticles on cell viability, proliferation, and cellular processes. Additionally, they can indicate the impact of nanoparticle properties on their toxicity.[81]
- 4. In Vivo Toxicity Studies:** In vivo toxicity studies are essential to evaluate the systemic effects of polymeric nanoformulations in living organisms. These studies involve administering nanoparticles to animal models to assess their acute and chronic toxic effects on different organs and systems. It helps determine the maximum tolerated dose and potential accumulation in organs.[82]

5. **Immunotoxicity Assessment** Polymeric nanoformulations can interact with the immune system, leading to immunomodulatory effects. Immunotoxicity assessment is crucial to understanding how these nanoparticles may influence immune responses and whether they trigger inflammatory or allergic reactions.[83]
6. **Genotoxicity and Mutagenicity Studies:**Genotoxicity and mutagenicity studies assess whether polymeric nanoformulations have the potential to damage DNA or induce mutations. These studies are vital to evaluating the long-term safety of nanoparticles.[84]
7. **Biotransformation and Metabolism:** Investigating the biotransformation and metabolism of polymeric nanoformulations provides insights into how they are processed and cleared by the body. Understanding these processes helps predict potential accumulation and persistence in different organs.[85][86]
8. **Environmental Impact Assessment:** Apart from human health concerns, the environmental impact of polymeric nanoformulations should also be assessed. Studies should investigate nanoparticle behavior in the environment, potential bioaccumulation, and their effects on non-target organisms.[87][88]

VII. INTEGRATION OF POLYMERIC NANOFORMULATIONS IN SUSTAINABLE AGRICULTURE

Sustainable agriculture aims to meet the current and future demands for agricultural products while preserving the environment and promoting the well-being of farmers and consumers. Traditional agricultural practices often involve the excessive use of agrochemicals, leading to environmental pollution, development of resistance in pests and pathogens, and health hazards for farmers. The integration of polymeric nanoformulations in agriculture offers a solution to mitigate these issues by improving the efficacy and eco-friendliness of agrochemicals. Polymeric nanoparticles are constructed using biodegradable and biocompatible polymers. They have unique properties, such as high surface area, tunable release kinetics, and the ability to encapsulate various agrochemicals.[89] The contributions of polymeric nanoformulations to sustainable agriculture are numerous and include:

1. **Enhanced Targeted Delivery:** Polymeric nanoformulations enable precise and targeted delivery of agrochemicals to specific plant tissues or pests. By reducing off-target effects, farmers can use lower amounts of pesticides and fertilizers, minimizing environmental pollution and preserving biodiversity. [90]
2. **Controlled Release of Agrochemicals:** Polymeric nanoparticles offer controlled-release capabilities, delivering agrochemicals gradually over an extended period. This sustained release ensures prolonged efficacy and reduces the frequency of application, thereby saving resources and minimizing potential risks to the environment and human health.[91]
3. **Minimization of Soil Contamination:** The targeted delivery and controlled release of pesticides through nanoformulations reduce their accumulation in soil, preventing long-term contamination and promoting soil health.[92]

4. **Resistance Management:** By utilizing polymeric nanoformulations, the development of resistance in pests and diseases to agrochemicals can be mitigated. The precise delivery of active ingredients hampers the development of resistance, maintaining the effectiveness of these inputs for longer periods.[93]
5. **Water Conservation:** Nanoformulations aid in increasing water use efficiency in crops. Controlled release of water-absorbing polymers helps retain moisture in the soil, reducing irrigation requirements and conserving water resources.[94]
6. **Biodegradability and Environmental Safety:** Most polymeric nanoformulations are biodegradable and pose minimal risk to the environment. As a result, they are less harmful to beneficial organisms and ecosystems, aligning with sustainable agriculture principles.[95]

7. Applications in Crop Protection

- **Pesticides and Insecticides:** Polymeric nanoformulations can encapsulate pesticides and insecticides, reducing their off-target drift and providing controlled release, which prolongs their effectiveness and minimizes the environmental impact.[63]
- **Fungicides:** Nanoformulations can protect crops from fungal diseases more efficiently, leading to reduced application frequency and lower chemical load in the environment.[60]
- **Herbicides:** Controlled release of herbicides through nanoformulations ensures prolonged weed control while minimizing herbicide usage.[58]

8. Nutrient Delivery

- **Fertilizers:** Polymeric nanoparticles can enhance nutrient uptake by plants and reduce nutrient leaching, leading to improved crop yields and minimized environmental pollution.[96]
- **Micronutrients:** Nanoformulations enable targeted delivery of essential micronutrients to specific plant tissues, optimizing nutrient utilization.[97]

Environmental Impact and Regulatory Aspects of Polymeric Nanoformulation

The integration of polymeric nanoformulations in sustainable agriculture holds great promise in revolutionizing farming practices, offering enhanced crop protection, controlled nutrient delivery, and improved water and soil management.[98] However, as with any emerging technology, it is crucial to assess their potential environmental impact and address regulatory aspects to ensure their safe and responsible use.[99]

Environmental Impact:

- **Nanoparticle Fate and Behavior:** Understanding how polymeric nanoparticles behave in the environment is essential to determine their potential impacts. Research should focus on nanoparticle mobility, persistence, and interactions with soil, water, and living organisms to identify any long-term effects on ecosystems. [100]

- **Ecotoxicity and Non-Target Effects:** Evaluating the ecotoxicity of polymeric nanoformulations is vital to determine their effects on non-target organisms such as beneficial insects, aquatic life, and soil microorganisms. Studying their impact on ecosystem health and biodiversity helps mitigate unintended consequences.[101]
- **Soil and Water Contamination:** The release of nanoparticles into agricultural fields may lead to soil and water contamination. Investigating the potential accumulation of nanoparticles in the food chain and their implications for human health and the environment is essential.[102]
- **Bioaccumulation:** Understanding the potential bioaccumulation of nanoparticles in plants and animals is critical to assessing the safety of using polymeric nanoformulations in agriculture and preventing long-term accumulation in the food chain.[101]

Regulatory Aspects:

- **Risk Assessment:** Conducting robust risk assessments is necessary to evaluate the environmental and health risks associated with polymeric nanoformulations. This aids in determining appropriate usage guidelines and ensuring their safe application.[103]
- **Labeling and Reporting:** Implementing clear labeling and reporting requirements for products containing polymeric nanoformulations is crucial to inform farmers and consumers about their use and potential risks.[104]
- **Regulation of Environmental Release:** Regulations should be in place to control the deliberate release of nanoparticles into the environment and set thresholds for permissible levels in soil and water systems.[105]
- **International Cooperation:** Collaborative efforts between countries to set regulatory standards will promote global harmonization and ensure uniform safety measures for polymeric nanoformulations in sustainable agriculture.[106]
- **Monitoring and Surveillance:** Implementing monitoring and surveillance programs can track the behavior and impact of nanoparticles in the environment over time, enabling informed decision-making and adaptive regulatory measures.[107]

VIII. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Polymeric nanoformulations show great promise and potential in diverse fields, including medicine, agriculture, cosmetics, and industry. Despite their current applications, there are still numerous unexplored opportunities for these nanomaterials. Ongoing research is likely to drive significant progress in targeted drug delivery, combination therapies, immunotherapies, brain drug delivery, personalized medicine, and agricultural applications.[108][109]

The treatment of neurodegenerative diseases, like Alzheimer's and Parkinson's, remains challenging due to the blood-brain barrier. However, polymeric nanoformulations offer a new approach by enabling the delivery of therapeutic agents directly to the brain, potentially managing these debilitating conditions more effectively.[110]

Immunotherapies have shown remarkable success in cancer treatment, but their effectiveness varies among patients. Using polymeric nanoformulations to deliver immune check-

point inhibitors and other immunotherapy enhancers could enhance patient response rates and reduce adverse effects.[111]

In the agricultural sector, beyond their current applications, polymeric nanoformulations present exciting possibilities for precision agriculture. By facilitating targeted delivery of nutrients, growth regulators, and pesticides tailored to specific plant and soil conditions, these formulations could revolutionize farming practices.

Furthermore, polymeric nanoformulations hold potential for environmental remediation. They could be employed to deliver compounds that degrade pollutants, capture heavy metals, or promote the growth of beneficial microorganisms, restoring ecological balance in polluted environments. With careful consideration of safety and environmental impact, polymeric nanoformulations have the capacity to transform healthcare and enhance the quality of life for millions of people worldwide. [112]

IX. DISCUSSION & CONCLUSION

The advances in polymeric nanoencapsulation techniques have provided powerful tools to encapsulate a wide range of plant bioactives, enhancing their stability, controlled release, and targeted delivery. These techniques enable the formulation of bioactive-loaded nanoparticles with tailored physicochemical properties, promoting their efficient interaction with plants for optimal effects. Enhancing the stability and bioavailability of plant bioactives and extracts through polymeric nanoformulations addresses critical challenges in their application. Nanoencapsulation protects these bioactives from degradation and improves their solubility, ensuring their sustained release and prolonged activity in plant tissues. This advancement allows for efficient nutrient delivery, enhanced pest management, and improved stress tolerance, ultimately leading to increased crop productivity and sustainability in agriculture.

Tailoring polymeric nanoformulations for specific plant applications is an exciting prospect. Surface modifications and nanoparticles that respond to stimuli present opportunities for precise delivery, ensuring the bioactive compounds are localized within plants effectively while reducing unintended effects on non-target areas. By formulating the nanoparticles to match specific growth stages, environmental stresses, and nutrient needs of plants, precision agriculture can be achieved, leading to a transformative approach in managing crops. As research progresses, nanotoxicity and safety considerations remain of utmost importance. Understanding the potential risks and interactions of polymeric nanoparticles with plants and the environment is crucial for responsible implementation. Comprehensive toxicity assessments and standardized safety protocols will ensure the sustainable use of these nanoformulations, promoting safe and environmentally friendly agricultural practices. Future perspectives and research directions in this field are vast. Exploring unexplored opportunities, such as non-invasive plant treatments, microbiome modulation, and nanoscale vaccines for plants, presents exciting possibilities for further advancements. Additionally, interdisciplinary collaborations, technological innovations, and regulatory guidance will play vital roles in harnessing the full potential of polymeric nanoformulations for plant bioactives and extracts.

In summary, the integration of polymeric nanoformulations with plant bioactives and extracts opens up a new era of innovative solutions in agriculture and plant sciences. By capi-

talizing on the advances in polymeric nanoencapsulation techniques, enhancing stability, targeting specific plant applications, addressing nanotoxicity concerns, and considering future perspectives, we can propel agricultural practices towards sustainability, increased crop yields, and improved global food security. This multidisciplinary field offers exciting opportunities to revolutionize agriculture, mitigating challenges faced by modern farming and paving the way for a greener and more productive future.

REFERENCES

- [1] D. Khiev *et al.*, “Emerging Nano-Formulations and Nanomedicines Applications for Ocular Drug Delivery,” *Nanomaterials*, vol. 11, no. 1, p. 173, Jan. 2021, doi: 10.3390/nano11010173.
- [2] C. Igwe Idumah, “Emerging trends in Poly(lactic-co-glycolic) acid bionanoarchitectures and applications,” *Clean. Mater.*, vol. 5, p. 100102, Sep. 2022, doi: 10.1016/j.clema.2022.100102.
- [3] A. Zielińska *et al.*, “Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology,” *Molecules*, vol. 25, no. 16, p. 3731, Aug. 2020, doi: 10.3390/molecules25163731.
- [4] B. Begines *et al.*, “Polymeric Nanoparticles for Drug Delivery: Recent Developments and Future Prospects,” *Nanomaterials*, vol. 10, no. 7, p. 1403, Jul. 2020, doi: 10.3390/nano10071403.
- [5] N. Kamaly, B. Yameen, J. Wu, and O. C. Farokhzad, “Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release,” *Chem. Rev.*, vol. 116, no. 4, pp. 2602–2663, Feb. 2016, doi: 10.1021/acs.chemrev.5b00346.
- [6] H. S. Han, S. Y. Koo, and K. Y. Choi, “Emerging nanoformulation strategies for phytochemicals and applications from drug delivery to phototherapy to imaging,” *Bioact. Mater.*, vol. 14, pp. 182–205, Aug. 2022, doi: 10.1016/j.bioactmat.2021.11.027.
- [7] A. Kyriakoudi, E. Spanidi, I. Mourtzinou, and K. Gardikis, “Innovative Delivery Systems Loaded with Plant Bioactive Ingredients: Formulation Approaches and Applications,” *Plants*, vol. 10, no. 6, p. 1238, Jun. 2021, doi: 10.3390/plants10061238.
- [8] G. L. Zabot *et al.*, “Encapsulation of Bioactive Compounds for Food and Agricultural Applications,” *Polymers (Basel)*, vol. 14, no. 19, p. 4194, Oct. 2022, doi: 10.3390/polym14194194.
- [9] M. Elmowafy *et al.*, “Polymeric Nanoparticles for Delivery of Natural Bioactive Agents: Recent Advances and Challenges,” *Polymers (Basel)*, vol. 15, no. 5, p. 1123, Feb. 2023, doi: 10.3390/polym15051123.
- [10] S. B. K. Dlodla, L. T. Mashabela, B. Ng’andwe, P. A. Makoni, and B. A. Witika, “Current Advances in Nano-Based and Polymeric Stimuli-Responsive Drug Delivery Targeting the Ocular Microenvironment: A Review and Envisaged Future Perspectives,” *Polymers (Basel)*, vol. 14, no. 17, p. 3580, Aug. 2022, doi: 10.3390/polym14173580.
- [11] E. K. Efthimiadou, M. Theodosiou, G. Toniolo, and N. Y. Abu-Thabit, “Stimuli-responsive biopolymer nanocarriers for drug delivery applications,” in *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, Volume 1*, Elsevier, 2018, pp. 405–432.
- [12] Y. V Pathak, Ed., *Surface Modification of Nanoparticles for Targeted Drug Delivery*. Cham: Springer International Publishing, 2019.
- [13] A.-C. Albertsson and S. Karlsson, “Biodegradable Polymers,” in *Comprehensive Polymer Science and Supplements*, Elsevier, 1989, pp. 285–297.
- [14] W. Park, H. Shin, B. Choi, W.-K. Rhim, K. Na, and D. Keun Han, “Advanced hybrid nanomaterials for biomedical applications,” *Prog. Mater. Sci.*, vol. 114, p. 100686, Oct. 2020, doi: 10.1016/j.pmatsci.2020.100686.
- [15] K. S. Soni, S. S. Desale, and T. K. Bronich, “Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation,” *J. Control. Release*, vol. 240, pp. 109–126, Oct. 2016, doi: 10.1016/j.jconrel.2015.11.009.
- [16] J. López-Sagasetta, E. Malito, R. Rappuoli, and M. J. Bottomley, “Self-assembling protein nanoparticles in the design of vaccines,” *Comput. Struct. Biotechnol. J.*, vol. 14, pp. 58–68, 2016, doi: 10.1016/j.csbj.2015.11.001.
- [17] Z. Zhao, A. Ukidve, J. Kim, and S. Mitragotri, “Targeting Strategies for Tissue-Specific Drug Delivery,” *Cell*, vol. 181, no. 1, pp. 151–167, Apr. 2020, doi: 10.1016/j.cell.2020.02.001.
- [18] M. Samtiya, R. E. Aluko, T. Dhewa, and J. M. Moreno-Rojas, “Potential Health Benefits of Plant Food-Derived Bioactive Components: An Overview,” *Foods*, vol. 10, no. 4, p. 839, Apr. 2021, doi: 10.3390/foods10040839.

- [19] D. Dahiya, A. Terpou, M. Dasenaki, and P. S. Nigam, "Current status and future prospects of bioactive molecules delivered through sustainable encapsulation techniques for food fortification," *Sustain. Food Technol.*, vol. 1, no. 4, pp. 500–510, 2023, doi: 10.1039/D3FB00015J.
- [20] B. Vieira da Silva, J. C. M. Barreira, and M. B. P. P. Oliveira, "Natural phytochemicals and probiotics as bioactive ingredients for functional foods: Extraction, biochemistry and protected-delivery technologies," *Trends Food Sci. Technol.*, vol. 50, pp. 144–158, Apr. 2016, doi: 10.1016/j.tifs.2015.12.007.
- [21] H. Nisa, A. N. Kamili, I. A. Nawchoo, S. Shafi, N. Shameem, and S. A. Bandh, "Fungal endophytes as prolific source of phytochemicals and other bioactive natural products: A review," *Microb. Pathog.*, vol. 82, pp. 50–59, May 2015, doi: 10.1016/j.micpath.2015.04.001.
- [22] A. Khanal, H. P. Devkota, S. Kaundinyayana, P. Gyawali, R. Ananda, and R. Adhikari, "Culinary herbs and spices in Nepal: A review of their traditional uses, chemical constituents, and pharmacological activities," *Ethnobot. Res. Appl.*, vol. 21, Jun. 2021, doi: 10.32859/era.21.40.1-18.
- [23] M. I. Dias, I. C. F. R. Ferreira, and M. F. Barreiro, "Microencapsulation of bioactives for food applications," *Food Funct.*, vol. 6, no. 4, pp. 1035–1052, 2015, doi: 10.1039/C4FO01175A.
- [24] N. Oladzadabbasabadi, A. Mohammadi Nafchi, M. Ghasemlou, F. Ariffin, Z. Singh, and A. . Al-Hassan, "Natural anthocyanins: Sources, extraction, characterization, and suitability for smart packaging," *Food Packag. Shelf Life*, vol. 33, p. 100872, Sep. 2022, doi: 10.1016/j.fpsl.2022.100872.
- [25] H. Hosseini and S. M. Jafari, "Introducing nano/microencapsulated bioactive ingredients for extending the shelf-life of food products," *Adv. Colloid Interface Sci.*, vol. 282, p. 102210, Aug. 2020, doi: 10.1016/j.cis.2020.102210.
- [26] R. F. S. Gonçalves, J. T. Martins, C. M. M. Duarte, A. A. Vicente, and A. C. Pinheiro, "Advances in nutraceutical delivery systems: From formulation design for bioavailability enhancement to efficacy and safety evaluation," *Trends Food Sci. Technol.*, vol. 78, pp. 270–291, Aug. 2018, doi: 10.1016/j.tifs.2018.06.011.
- [27] N. Khandelwal *et al.*, "Budding trends in integrated pest management using advanced micro- and nano-materials: Challenges and perspectives," *J. Environ. Manage.*, vol. 184, pp. 157–169, Dec. 2016, doi: 10.1016/j.jenvman.2016.09.071.
- [28] Kunle, "Standardization of herbal medicines - A review," *Int. J. Biodivers. Conserv.*, vol. 4, no. 3, Mar. 2012, doi: 10.5897/IJBC11.163.
- [29] Z.-L. Wan, J. Guo, and X.-Q. Yang, "Plant protein-based delivery systems for bioactive ingredients in foods," *Food Funct.*, vol. 6, no. 9, pp. 2876–2889, 2015, doi: 10.1039/C5FO00050E.
- [30] *Water Extraction of Bioactive Compounds*. Elsevier, 2017.
- [31] S. Sonkaria, S.-H. Ahn, and V. Khare, "Nanotechnology and its Impact on Food and Nutrition: A Review," *Recent Patents Food, Nutr. Agric.*, vol. 4, no. 1, pp. 8–18, Apr. 2012, doi: 10.2174/2212798411204010008.
- [32] M. Pateiro *et al.*, "Nanoencapsulation of Promising Bioactive Compounds to Improve Their Absorption, Stability, Functionality and the Appearance of the Final Food Products," *Molecules*, vol. 26, no. 6, p. 1547, Mar. 2021, doi: 10.3390/molecules26061547.
- [33] L. Li, Y. Zeng, M. Chen, and G. Liu, "Application of Nanomicelles in Enhancing Bioavailability and Biological Efficacy of Bioactive Nutrients," *Polymers (Basel)*, vol. 14, no. 16, p. 3278, Aug. 2022, doi: 10.3390/polym14163278.
- [34] K. Ulbrich, K. Holá, V. Šubr, A. Bakandritsos, J. Tuček, and R. Zbořil, "Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies," *Chem. Rev.*, vol. 116, no. 9, pp. 5338–5431, May 2016, doi: 10.1021/acs.chemrev.5b00589.
- [35] S. Bhatia, "Nanoparticles Types, Classification, Characterization, Fabrication Methods and Drug Delivery Applications," in *Natural Polymer Drug Delivery Systems*, Cham: Springer International Publishing, 2016, pp. 33–93.
- [36] B. S. Munteanu and C. Vasile, "Encapsulation of Natural Bioactive Compounds by Electrospinning—Applications in Food Storage and Safety," *Polymers (Basel)*, vol. 13, no. 21, p. 3771, Oct. 2021, doi: 10.3390/polym13213771.
- [37] K. N. C. Murthy, P. Monika, G. K. Jayaprakasha, and B. S. Patil, "Nanoencapsulation: An Advanced Nanotechnological Approach To Enhance the Biological Efficacy of Curcumin," 2018, pp. 383–405.
- [38] M.-L. Laracuento, M. H. Yu, and K. J. McHugh, "Zero-order drug delivery: State of the art and future prospects," *J. Control. Release*, vol. 327, pp. 834–856, Nov. 2020, doi: 10.1016/j.jconrel.2020.09.020.
- [39] I. Armentano *et al.*, "Nanocomposites Based on Biodegradable Polymers," *Materials (Basel)*, vol. 11, no. 5, p. 795, May 2018, doi: 10.3390/ma11050795.

- [40] A. Yusuf, A. R. Z. Almotairy, H. Henidi, O. Y. Alshehri, and M. S. Aldughaim, "Nanoparticles as Drug Delivery Systems: A Review of the Implication of Nanoparticles' Physicochemical Properties on Responses in Biological Systems," *Polymers (Basel)*, vol. 15, no. 7, p. 1596, Mar. 2023, doi: 10.3390/polym15071596.
- [41] M. Grzelczak, L. M. Liz-Marzán, and R. Klajn, "Stimuli-responsive self-assembly of nanoparticles," *Chem. Soc. Rev.*, vol. 48, no. 5, pp. 1342–1361, 2019, doi: 10.1039/C8CS00787J.
- [42] L. Pachuau, Laldinchhana, P. K. Roy, J. H. Zothantluanga, S. Ray, and S. Das, "Encapsulation of Bioactive Compound and Its Therapeutic Potential," 2021, pp. 687–714.
- [43] A. Balla, A. Silini, H. Cherif-Silini, A. Chenari Bouket, F. N. Alenezi, and L. Belbahri, "Recent Advances in Encapsulation Techniques of Plant Growth-Promoting Microorganisms and Their Prospects in the Sustainable Agriculture," *Appl. Sci.*, vol. 12, no. 18, p. 9020, Sep. 2022, doi: 10.3390/app12189020.
- [44] V. Zargar, M. Asghari, and A. Dashti, "A Review on Chitin and Chitosan Polymers: Structure, Chemistry, Solubility, Derivatives, and Applications," *ChemBioEng Rev.*, vol. 2, no. 3, pp. 204–226, Jun. 2015, doi: 10.1002/cben.201400025.
- [45] A. Bernkop-Schnürch and S. Dünnhaupt, "Chitosan-based drug delivery systems," *Eur. J. Pharm. Biopharm.*, vol. 81, no. 3, pp. 463–469, Aug. 2012, doi: 10.1016/j.ejpb.2012.04.007.
- [46] A. Ahmad *et al.*, "A Critical Review on the Synthesis of Natural Sodium Alginate Based Composite Materials: An Innovative Biological Polymer for Biomedical Delivery Applications," *Processes*, vol. 9, no. 1, p. 137, Jan. 2021, doi: 10.3390/pr9010137.
- [47] H. Daemi and M. Barikani, "Synthesis and characterization of calcium alginate nanoparticles, sodium homopolymannuronate salt and its calcium nanoparticles," *Sci. Iran.*, vol. 19, no. 6, pp. 2023–2028, Dec. 2012, doi: 10.1016/j.scient.2012.10.005.
- [48] B. Xiao *et al.*, "Hyaluronic acid-functionalized polymeric nanoparticles for colon cancer-targeted combination chemotherapy," *Nanoscale*, vol. 7, no. 42, pp. 17745–17755, 2015, doi: 10.1039/C5NR04831A.
- [49] A. O. Elzoghby, "Gelatin-based nanoparticles as drug and gene delivery systems: Reviewing three decades of research," *J. Control. Release*, vol. 172, no. 3, pp. 1075–1091, Dec. 2013, doi: 10.1016/j.jconrel.2013.09.019.
- [50] M. Odeniyi, O. Omoteso, A. Adepoju, and K. Jaiyeoba, "Starch nanoparticles in drug delivery: A review," *Polym. Med.*, vol. 48, no. 1, pp. 41–45, Jan. 2019, doi: 10.17219/pim/99993.
- [51] S. Bel Haaj, A. Magnin, C. Pétrier, and S. Boufi, "Starch nanoparticles formation via high power ultrasonication," *Carbohydr. Polym.*, vol. 92, no. 2, pp. 1625–1632, Feb. 2013, doi: 10.1016/j.carbpol.2012.11.022.
- [52] K. Peranidze, T. V. Safronova, and N. R. Kildeeva, "Electrospun Nanomaterials Based on Cellulose and Its Derivatives for Cell Cultures: Recent Developments and Challenges," *Polymers (Basel)*, vol. 15, no. 5, p. 1174, Feb. 2023, doi: 10.3390/polym15051174.
- [53] H. Seddiqi *et al.*, "Cellulose and its derivatives: towards biomedical applications," *Cellulose*, vol. 28, no. 4, pp. 1893–1931, Mar. 2021, doi: 10.1007/s10570-020-03674-w.
- [54] I. Wasiak *et al.*, "Dextran Nanoparticle Synthesis and Properties," *PLoS One*, vol. 11, no. 1, p. e0146237, Jan. 2016, doi: 10.1371/journal.pone.0146237.
- [55] A. V. Samrot *et al.*, "The Synthesis, Characterization and Applications of Polyhydroxyalkanoates (PHAs) and PHA-Based Nanoparticles," *Polymers (Basel)*, vol. 13, no. 19, p. 3302, Sep. 2021, doi: 10.3390/polym13193302.
- [56] A. F. Albuquerque, J. S. Ribeiro, F. Kummrow, A. J. A. Nogueira, C. C. Montagner, and G. A. Umbuzeiro, "Pesticides in Brazilian freshwaters: a critical review," *Environ. Sci. Process. Impacts*, vol. 18, no. 7, pp. 779–787, 2016, doi: 10.1039/C6EM00268D.
- [57] J. L. de Oliveira *et al.*, "Zein Nanoparticles as Eco-Friendly Carrier Systems for Botanical Repellents Aiming Sustainable Agriculture," *J. Agric. Food Chem.*, vol. 66, no. 6, pp. 1330–1340, Feb. 2018, doi: 10.1021/acs.jafc.7b05552.
- [58] R. Grillo, N. Z. P. dos Santos, C. R. Maruyama, A. H. Rosa, R. de Lima, and L. F. Fraceto, "Poly(ϵ -caprolactone)nanocapsules as carrier systems for herbicides: Physico-chemical characterization and genotoxicity evaluation," *J. Hazard. Mater.*, vol. 231–232, pp. 1–9, Sep. 2012, doi: 10.1016/j.jhazmat.2012.06.019.
- [59] V. Takeshita *et al.*, "Development of a Preemergent Nanoherbicide: From Efficiency Evaluation to the Assessment of Environmental Fate and Risks to Soil Microorganisms," *ACS Nanosci. Au*, vol. 2, no. 4, pp. 307–323, Aug. 2022, doi: 10.1021/acsnanoscienceau.1c00055.

- [60] P. Mondal, R. Kumar, and R. Gogoi, "Azomethine based nano-chemicals: Development, in vitro and in vivo fungicidal evaluation against *Sclerotium rolfsii*, *Rhizoctonia bataticola* and *Rhizoctonia solani*," *Bioorg. Chem.*, vol. 70, pp. 153–162, Feb. 2017, doi: 10.1016/j.bioorg.2016.12.006.
- [61] M. Pascoli, P. J. Lopes-Oliveira, L. F. Fraceto, A. B. Seabra, and H. C. Oliveira, "State of the art of polymeric nanoparticles as carrier systems with agricultural applications: a minireview," *Energy, Ecol. Environ.*, vol. 3, no. 3, pp. 137–148, Jun. 2018, doi: 10.1007/s40974-018-0090-2.
- [62] R. Gogoi, "Suitability of Nano-sulphur for Biorational Management of Powdery mildew of Okra (*Abelmoschus esculentus* Moench) caused by *Erysiphe cichoracearum*," *J. Plant Pathol. Microbiol.*, vol. 04, no. 04, 2013, doi: 10.4172/2157-7471.1000171.
- [63] B. Perlatti, P. L. de Souza Bergo, M. F. das G. Fernandes da Silva, J. Batista, and M. Rossi, "Polymeric Nanoparticle-Based Insecticides: A Controlled Release Purpose for Agrochemicals," in *Insecticides - Development of Safer and More Effective Technologies*, InTech, 2013.
- [64] S. Chaudhary, "Progress on *Azadirachta indica* Based Biopesticides in Replacing Synthetic Toxic Pesticides," *Front. Plant Sci.*, vol. 8, 2017, doi: 10.3389/fpls.2017.00610.
- [65] M. Menossi, R. P. Ollier, C. A. Casalongué, and V. A. Alvarez, "Essential oil-loaded bio-nanomaterials for sustainable agricultural applications," *J. Chem. Technol. Biotechnol.*, vol. 96, no. 8, pp. 2109–2122, Aug. 2021, doi: 10.1002/jctb.6705.
- [66] Imran, S. Fahad, Amanullah, S. Khalid, M. Arif, and A. R. Al-Tawaha, "Climate Change and Climate Smart Plants Production Technology," in *Climate Change and Plants*, CRC Press, 2021, pp. 19–36.
- [67] O. S. Olanrewaju, A. S. Ayangbenro, B. R. Glick, and O. O. Babalola, "Plant health: feedback effect of root exudates-rhizobiome interactions," *Appl. Microbiol. Biotechnol.*, vol. 103, no. 3, pp. 1155–1166, Feb. 2019, doi: 10.1007/s00253-018-9556-6.
- [68] E. V. R. Campos, J. L. de Oliveira, and L. F. Fraceto, "Applications of Controlled Release Systems for Fungicides, Herbicides, Acaricides, Nutrients, and Plant Growth Hormones: A Review," *Adv. Sci. Eng. Med.*, vol. 6, no. 4, pp. 373–387, Apr. 2014, doi: 10.1166/ asem.2014.1538.
- [69] A. E. S. Pereira, P. M. Silva, J. L. Oliveira, H. C. Oliveira, and L. F. Fraceto, "Chitosan nanoparticles as carrier systems for the plant growth hormone gibberellic acid," *Colloids Surfaces B Biointerfaces*, vol. 150, pp. 141–152, Feb. 2017, doi: 10.1016/j.colsurfb.2016.11.027.
- [70] R. Yang, C.-F. Xiao, Y.-F. Guo, M. Ye, and J. Lin, "Inclusion complexes of GA3 and the plant growth regulation activities," *Mater. Sci. Eng. C*, vol. 91, pp. 475–485, Oct. 2018, doi: 10.1016/j.msec.2018.05.043.
- [71] R. AKÇAN, H. C. AYDOĞAN, M. Ş. YILDIRIM, B. TAŞTEKİN, and N. SAĞLAM, "Nanotoxicity: a challenge for future medicine," *TURKISH J. Med. Sci.*, vol. 50, no. 4, pp. 1180–1196, Jun. 2020, doi: 10.3906/sag-1912-209.
- [72] K.-I. Inoue and H. Takano, "Aggravating Impact of Nanoparticles on Immune-Mediated Pulmonary Inflammation," *Sci. World J.*, vol. 11, pp. 382–390, 2011, doi: 10.1100/tsw.2011.44.
- [73] K. W. Powers, M. Palazuelos, B. M. Moudgil, and S. M. Roberts, "Characterization of the size, shape, and state of dispersion of nanoparticles for toxicological studies," *Nanotoxicology*, vol. 1, no. 1, pp. 42–51, Jan. 2007, doi: 10.1080/17435390701314902.
- [74] H. Huang, L. Shen, J. Ford, Y. H. Wang, and Y. R. Xu, "Computational Issues in Biomedical Nanometrics and Nano-Materials," *J. Nano Res.*, vol. 1, pp. 50–58, Jan. 2008, doi: 10.4028/www.scientific.net/JNanoR.1.50.
- [75] A. D. Maynard *et al.*, "Safe handling of nanotechnology," *Nature*, vol. 444, no. 7117, pp. 267–269, Nov. 2006, doi: 10.1038/444267a.
- [76] A. Barhoum, M. L. García-Betancourt, H. Rahier, and G. Van Assche, "Physicochemical characterization of nanomaterials: polymorph, composition, wettability, and thermal stability," in *Emerging Applications of Nanoparticles and Architecture Nanostructures*, Elsevier, 2018, pp. 255–278.
- [77] S. Shin, I. Song, and S. Um, "Role of Physicochemical Properties in Nanoparticle Toxicity," *Nanomaterials*, vol. 5, no. 3, pp. 1351–1365, Aug. 2015, doi: 10.3390/nano5031351.
- [78] S. Sharma, R. Parveen, and B. P. Chatterji, "Toxicology of Nanoparticles in Drug Delivery," *Curr. Pathobiol. Rep.*, vol. 9, no. 4, pp. 133–144, Dec. 2021, doi: 10.1007/s40139-021-00227-z.
- [79] A. M. Alkilany and C. J. Murphy, "Toxicity and cellular uptake of gold nanoparticles: what we have learned so far?," *J. Nanoparticle Res.*, vol. 12, no. 7, pp. 2313–2333, Sep. 2010, doi: 10.1007/s11051-010-9911-8.
- [80] Y. Yang *et al.*, "Toxicity assessment of nanoparticles in various systems and organs," *Nanotechnol. Rev.*, vol. 6, no. 3, pp. 279–289, Jun. 2017, doi: 10.1515/ntrev-2016-0047.
- [81] D. T. Savage, J. Z. Hilt, and T. D. Dziubla, "In Vitro Methods for Assessing Nanoparticle Toxicity,"

- 2019, pp. 1–29.
- [82] H.-J. Huang, Y.-H. Lee, Y.-H. Hsu, C.-T. Liao, Y.-F. Lin, and H.-W. Chiu, “Current Strategies in Assessment of Nanotoxicity: Alternatives to In Vivo Animal Testing,” *Int. J. Mol. Sci.*, vol. 22, no. 8, p. 4216, Apr. 2021, doi: 10.3390/ijms22084216.
- [83] M. A. Dobrovolskaia, “Pre-clinical immunotoxicity studies of nanotechnology-formulated drugs: Challenges, considerations and strategy,” *J. Control. Release*, vol. 220, pp. 571–583, Dec. 2015, doi: 10.1016/j.jconrel.2015.08.056.
- [84] A. B. More, M. D. Patel, V. C. Malshe, P. V. Devarajan, and G. R. Vanage, “Genotoxicity and Mutagenicity Evaluation of Polyethylene Sebacate Nanoparticles,” *J. Nanopharmaceutics Drug Deliv.*, vol. 1, no. 3, pp. 301–310, Sep. 2013, doi: 10.1166/jnd.2013.1023.
- [85] S. Ravindran, A. J. Tambe, J. K. Suthar, D. S. Chahar, J. M. Fernandes, and V. Desai, “Nanomedicine: Bioavailability, Biotransformation and Biokinetics,” *Curr. Drug Metab.*, vol. 20, no. 7, pp. 542–555, Aug. 2019, doi: 10.2174/1389200220666190614150708.
- [86] J. Shanu-Wilson, L. Evans, S. Wrigley, J. Steele, J. Atherton, and J. Boer, “Biotransformation: Impact and Application of Metabolism in Drug Discovery,” *ACS Med. Chem. Lett.*, vol. 11, no. 11, pp. 2087–2107, Nov. 2020, doi: 10.1021/acsmchemlett.0c00202.
- [87] S. C. Carroccio, P. Scarfato, E. Bruno, P. Aprea, N. T. Dintcheva, and G. Filippone, “Impact of nanoparticles on the environmental sustainability of polymer nanocomposites based on bioplastics or recycled plastics – A review of life-cycle assessment studies,” *J. Clean. Prod.*, vol. 335, p. 130322, Feb. 2022, doi: 10.1016/j.jclepro.2021.130322.
- [88] G. Martínez *et al.*, “Environmental Impact of Nanoparticles’ Application as an Emerging Technology: A Review,” *Materials (Basel)*, vol. 14, no. 1, p. 166, Dec. 2020, doi: 10.3390/ma14010166.
- [89] A. do E. S. Pereira, H. C. Oliveira, and L. F. Fraceto, “Polymeric nanoparticles as an alternative for application of gibberellic acid in sustainable agriculture: a field study,” *Sci. Rep.*, vol. 9, no. 1, p. 7135, May 2019, doi: 10.1038/s41598-019-43494-y.
- [90] Y. Vasseghian *et al.*, “Metal-organic framework-enabled pesticides are an emerging tool for sustainable cleaner production and environmental hazard reduction,” *J. Clean. Prod.*, vol. 373, p. 133966, Nov. 2022, doi: 10.1016/j.jclepro.2022.133966.
- [91] M. Monirul Hasan Tipu *et al.*, “Potential Applications of Nanotechnology in Agriculture: A Smart Tool for Sustainable Agriculture,” in *Agricultural Development in Asia - Potential Use of Nano-Materials and Nano-Technology*, IntechOpen, 2022.
- [92] S. Kumar, M. Nehra, N. Dilbaghi, G. Marrazza, A. A. Hassan, and K.-H. Kim, “Nano-based smart pesticide formulations: Emerging opportunities for agriculture,” *J. Control. Release*, vol. 294, pp. 131–153, Jan. 2019, doi: 10.1016/j.jconrel.2018.12.012.
- [93] B. Sharma, U. Lakra, R. Sharma, and S. R. Sharma, “A comprehensive review on nanopesticides and nanofertilizers—A boon for agriculture,” in *Nano-enabled Agrochemicals in Agriculture*, Elsevier, 2022, pp. 273–290.
- [94] S. K. Patra *et al.*, “Prospects of Hydrogels in Agriculture for Enhancing Crop and Water Productivity under Water Deficit Condition,” *Int. J. Polym. Sci.*, vol. 2022, pp. 1–15, Jun. 2022, doi: 10.1155/2022/4914836.
- [95] I. Iavicoli, V. Leso, D. H. Beezhold, and A. A. Shvedova, “Nanotechnology in agriculture: Opportunities, toxicological implications, and occupational risks,” *Toxicol. Appl. Pharmacol.*, vol. 329, pp. 96–111, Aug. 2017, doi: 10.1016/j.taap.2017.05.025.
- [96] T. C. Madzokere, L. T. Murombo, and H. Chiririwa, “Nano-based slow releasing fertilizers for enhanced agricultural productivity,” *Mater. Today Proc.*, vol. 45, pp. 3709–3715, 2021, doi: 10.1016/j.matpr.2020.12.674.
- [97] A. Yadav, K. Yadav, and K. A. Abd-Elsalam, “Nanofertilizers: Types, Delivery and Advantages in Agricultural Sustainability,” *Agrochemicals*, vol. 2, no. 2, pp. 296–336, Jun. 2023, doi: 10.3390/agrochemicals2020019.
- [98] Y. Shang, M. K. Hasan, G. J. Ahammed, M. Li, H. Yin, and J. Zhou, “Applications of Nanotechnology in Plant Growth and Crop Protection: A Review,” *Molecules*, vol. 24, no. 14, p. 2558, Jul. 2019, doi: 10.3390/molecules24142558.
- [99] R. Von Schomberg, “Prospects for Technology Assessment in a Framework of Responsible Research and Innovation,” *SSRN Electron. J.*, 2011, doi: 10.2139/ssrn.2439112.
- [100] G. E. Schaumann *et al.*, “Understanding the fate and biological effects of Ag- and TiO₂-nanoparticles in the environment: The quest for advanced analytics and interdisciplinary concepts,” *Sci. Total Environ.*, vol. 535, pp. 3–19, Dec. 2015, doi: 10.1016/j.scitotenv.2014.10.035.

- [101] M. Kannan *et al.*, “Nanopesticides in agricultural pest management and their environmental risks: a review,” *Int. J. Environ. Sci. Technol.*, Feb. 2023, doi: 10.1007/s13762-023-04795-y.
- [102] S. Kumar *et al.*, “Hazardous heavy metals contamination of vegetables and food chain: Role of sustainable remediation approaches - A review,” *Environ. Res.*, vol. 179, p. 108792, Dec. 2019, doi: 10.1016/j.envres.2019.108792.
- [103] V. Agrahari and V. Agrahari, “Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities,” *Drug Discov. Today*, vol. 23, no. 5, pp. 974–991, May 2018, doi: 10.1016/j.drudis.2018.01.047.
- [104] J. Kuzma, J. Romanchek, and A. Kokotovich, “Upstream Oversight Assessment for Agrifood Nanotechnology: A Case Studies Approach,” *Risk Anal.*, p. ???-???, Jun. 2008, doi: 10.1111/j.1539-6924.2008.01071.x.
- [105] J. S. Van Dyk and B. Pletschke, “Review on the use of enzymes for the detection of organochlorine, organophosphate and carbamate pesticides in the environment,” *Chemosphere*, vol. 82, no. 3, pp. 291–307, Jan. 2011, doi: 10.1016/j.chemosphere.2010.10.033.
- [106] J. Allan *et al.*, “Regulatory landscape of nanotechnology and nanoplastics from a global perspective,” *Regul. Toxicol. Pharmacol.*, vol. 122, p. 104885, Jun. 2021, doi: 10.1016/j.yrtph.2021.104885.
- [107] I. Linkov and F. K. Satterstrom, “Nanomaterial Risk Assessment and Risk Management,” pp. 129–157.
- [108] Z. Yu, X. Shen, H. Yu, H. Tu, C. Chittasupho, and Y. Zhao, “Smart Polymeric Nanoparticles in Cancer Immunotherapy,” *Pharmaceutics*, vol. 15, no. 3, p. 775, Feb. 2023, doi: 10.3390/pharmaceutics15030775.
- [109] S. Raman, S. Mahmood, A. R. Hilles, M. N. Javed, M. Azmana, and K. A. S. Al-Japairai, “Polymeric Nanoparticles for Brain Drug Delivery - A Review,” *Curr. Drug Metab.*, vol. 21, no. 9, pp. 649–660, Dec. 2020, doi: 10.2174/1389200221666200508074348.
- [110] L. La Barbera, E. Mauri, M. D’Amelio, and M. Gori, “Functionalization strategies of polymeric nanoparticles for drug delivery in Alzheimer’s disease: Current trends and future perspectives,” *Front. Neurosci.*, vol. 16, Aug. 2022, doi: 10.3389/fnins.2022.939855.
- [111] T. M. D. Le, A.-R. Yoon, T. Thambi, and C.-O. Yun, “Polymeric Systems for Cancer Immunotherapy: A Review,” *Front. Immunol.*, vol. 13, Feb. 2022, doi: 10.3389/fimmu.2022.826876.
- [112] M. Ashfaq, N. Talreja, D. Chuahan, and W. Srituravanich, “Polymeric Nanocomposite-Based Agriculture Delivery System: Emerging Technology for Agriculture,” in *Genetic Engineering - A Glimpse of Techniques and Applications*, IntechOpen, 2020.