

Lipid And Polymer Based Nano-Phytotherapeutics

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Abstract: The development of efficient drug delivery systems is pivotal in modern pharmacotherapy, aiming to enhance biological efficacy while minimizing the adverse effects of pharmaceutical agents. Recent focus has shifted towards lipid as well as polymer-containing nano-phytotherapeutics, amalgamating the benefits of natural and synthetic materials. Lipid-containing nano-carriers, like liposomes and lipid nanoparticles, are particularly suited for encapsulating hydrophobic phytochemicals, thereby augmenting their bioavailability and stability. Incorporating biodegradable polymers like chitosan and polyethylene glycol facilitates controlled release and target-specific delivery. Furthermore, the utilization of plant-derived phytochemicals offers reduced toxicity compared to synthetic drugs. This chapter outlines current research in this domain, emphasizing the synergistic potential of lipid-based nanocarriers and biocompatible polymers for phytochemical delivery. Strategies encompass formulation techniques, surface modifications, and targeted drug release mechanisms. The potential applications of these systems in treating diverse diseases, including cancer, cardiovascular disorders, and infectious diseases, are also discussed. Overall, lipid and polymer-based Nano-phytotherapeutics exhibit promise as adaptable and biocompatible drug delivery platforms, heralding benefits for efficient and targeted phytochemical delivery, potentially revolutionizing modern medicine. Further advancement in this field is anticipated to yield novel therapeutic solutions with enhanced clinical outcomes and reduced side effects.

Keywords: Bioavailability; Controlled release; Lipid nanoparticles; Nano-phytotherapeutics; Phytochemicals.

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1. INTRODUCTION

Over the past few years, nanotechnology has experienced significant progress, resulting in the creation of cutting-edge drug delivery systems that offer improved effectiveness and minimize adverse effects. One of the most hopeful and fast-evolving areas in this domain is the design and application of lipid and polymer-based Nano-phytotherapeutics. These Nano-phytotherapeutics represent a convergence of two key elements: nanotechnology and phytotherapy, which harness the therapeutic potential of plant-derived compounds. This emerging field holds immense promise for addressing some of the most challenging issues in modern medicine, such as drug bioavailability, targeted delivery, and minimizing the toxicity of therapeutic agents. Phytotherapeutics, derived from natural sources such as plants, have been utilized for centuries for their medicinal properties. However, the widespread application of phytochemicals is often hindered by issues like low bioavailability, limited stability, and rapid metabolism. The advent of

nanotechnology has revolutionized the field by enabling the fabrication and development of nano-sized drug distribution systems, which can encapsulate and protect phytochemicals, enhancing their therapeutic potential. The integration of nanotechnology and phytotherapy is poised to perform a fundamental role in the growth of safer, more effective, and patient-centric therapeutic strategies, ultimately advancing the frontiers of modern healthcare.

Lipid and polymer-based Nano-phytotherapeutics leverage the rich pharmacological arsenal found in plants, which has been employed for centuries in traditional remedies to treat an extensive range of ailments. Plant-derived compounds, also known as phytochemicals, have been shown to possess diverse and potent therapeutic traits, encompassing antimicrobial, antioxidant, anticancer and anti-inflammatory activities, among others. However, the clinical application of phytochemicals has been limited by challenges related to their poor solubility, low bioavailability, and off-target effects. To overcome these limitations, researchers have turned to nanotechnology as a solution. Phytochemicals are increasingly being transported by versatile carriers, including lipid-containing nanoparticles (like solid lipid nanoparticles and liposomes) and polymer-containing nanoparticles (like micelles based on polymer and nanocapsules). These nanoparticles provide a protective shell that encapsulates and shields the phytochemicals from degradation, allowing for controlled release and targeted delivery to specific tissues or cells. This approach enhances the therapeutic efficacy of phytochemicals while minimizing their systemic exposure, thereby reducing the risk of adverse effects. Lipid-based Nano-phytotherapeutics employ lipids or lipid-based carriers to encapsulate phytochemicals, creating lipid nanoparticles, liposomes, or nanoemulsions. These lipid-based formulations provide an ideal platform for solubilizing and delivering hydrophobic phytochemicals, allowing for improved bioavailability and controlled release. Furthermore, the lipid-based systems can offer protection against degradation, ensuring the stability of the encapsulated phytotherapeutic agents during storage and transportation.

Polymer-based Nano-phytotherapeutics, on the other hand, utilize biocompatible and biodegradable polymers to create nanoparticles or nanocarriers for phytochemicals. These polymer-based systems can protect phytochemicals from environmental factors and enzymatic degradation, ensuring their sustained

release and therapeutic efficacy. Additionally, these nanosystems can be tailored to have specific drug release kinetics and targeting properties, enabling site-specific delivery and reducing side effects.

The combination of lipids and polymers in Nano-phytotherapeutics has the potential to address many challenges associated with traditional phytotherapy, offering several advantages, such as improved solubility, enhanced stability, controlled release, and targeted delivery. This synergy has led to the development of innovative formulations that hold great promise for the management of various disorders and diseases.

The union of lipid and polymer-based nanocarriers with phytotherapy not only offers improved drug delivery but also opens up new possibilities for personalized medicine. By selecting and designing nanoparticles with tailored properties, researchers can optimize the release kinetics and target the delivery of phytochemicals to particular disease sites, maximizing their therapeutic impact. Moreover, this synergy facilitates the development of combination therapies, where multiple phytochemicals can be loaded into a single nanocarrier, potentially offering enhanced therapeutic effects and synergistic benefits [Heng *et al.*, 2020].

This appraisal explores the principles of lipid and polymer-based Nano-phytotherapeutics, their preparation methods and their applications in the field of modern medicine also spotlights the advantages and challenges associated with these systems, highlighting their potential in revolutionizing the delivery of phytochemicals for enhanced therapeutic outcomes. This review goals to explore the key parameters of lipid as well as polymer containing Nano-phytotherapeutics, including their formulation, characterization, mechanisms of action, and their applications in various disease conditions. Moreover, it explores current research trends and prospects for lipid and polymer-based Nano-phytotherapeutics, emphasizing their role in advancing the arena of delivery of drugs and personalized medicine. [Ceramella *et al.*, 2021].

The key aspects of lipid and polymer-based Nano-phytotherapeutics [Deng *et al.*, 2022; Bagade *et al.*, 2020; Colombo *et al.*, 2018; Panapisal *et al.*, 2012; Yang *et al.*, 2015]:

1. Nanotechnology in Drug Delivery:

- Nanotechnology involves manipulating materials at the nanoscale, typically ranging from 1 to 100 nanometers. In drug delivery, nanocarriers

are used to encapsulate and transport therapeutic agents to specific targets in the body.

- Nano-phytotherapeutics utilize nanoparticles made of lipids and/or polymers as carriers for phytochemicals. These nanoparticles offer several advantages:
 - Increased solubility: Poor solubility is a common issue with many phytochemicals. Nano-phytotherapeutics enhance solubility, ensuring better absorption and bioavailability.
 - Controlled release: Nanoparticles can provide sustained or controlled release of phytochemicals, leading to prolonged therapeutic effects and reduced dosing frequency.
 - Targeted delivery: Functionalization of nanoparticles allows for targeted drug delivery to specific tissues, cells, or organs, minimizing off-target effects.

- Protection: Nano-phytotherapeutics can protect phytochemicals from degradation, oxidation, and enzymatic breakdown, enhancing their stability.

2. Lipid-Based Nano-phytotherapeutics :

- It includes “nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), and liposomes”, and these transporters encompass lipids, which are biocompatible and mimic the body’s natural membranes.
- Lipid-based Nano-phytotherapeutics can encapsulate hydrophobic phytochemicals within their lipid bilayers or cores.
- Lipid-based carriers can also be surface-modified with ligands or antibodies to achieve active targeting of specific cells or tissues. Different lipid-based nanotherapeutics are mentioned in Table 1.

Aspect	Description
Definition	Nanotherapeutics based on lipid nanoparticles.
Types	Liposomes, lipid nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and lipid-polymer hybrid nanoparticles.
Composition	Composed of lipids, such as phospholipids, cholesterol, and lipid-like molecules.
Size	Typically ranges from 10 to 200 nanometers in diameter.
Drug Loading Capacity	High drug loading capacity, both hydrophobic and hydrophilic drugs can be encapsulated.
Drug Release	Controlled and sustained drug release.
Targeted Delivery	Can be designed for targeted drug delivery to specific tissues or cells.
Stability	Good physical and chemical stability.
Biocompatibility	Generally considered biocompatible and less immunogenic.
Advantages	Improved drug solubility, bioavailability, reduced side effects and prolonged drug circulation time.
Challenges	Batch-to-batch variability, potential leakage, and drug stability issues.
Applications	Cancer therapy, gene therapy, vaccines, treatment of infectious diseases, and more.
Notable Examples	Doxil (liposomal doxorubicin), Lipitor (atorvastatin solid lipid nanoparticles), mRNA COVID-19 vaccines (lipid nanoparticles for delivery).

Table 1. Lipid-based nanotherapeutics.

3. Polymer-Based Nano-phytotherapeutics:

- Polymer-based nanoparticles are typically formulated from biocompatible and biodegradable polymers such as polyethylene glycol (PEG), “poly(lactic-co-glycolic acid) (PLGA), and chitosan”.
- This encapsulates both hydrophobic and hydrophilic phytochemicals within their polymeric matrix.
- Polymer-based carriers offer tunable properties, allowing control over drug release rates, particle size, and surface characteristics which are mentioned in Table 2.

Aspect	Description
Definition	Polymer-based nanotherapeutics refer to drug delivery systems where polymers are used to encapsulate, target, or release therapeutic agents at the nanoscale (typically 1-100 nm). These systems aim to improve drug efficacy, reduce side effects, and enhance patient outcomes.
Types of Polymers	Various polymers are employed in nanotherapeutics, including natural (e.g., chitosan, albumin) and synthetic (e.g., polyethylene glycol, poly(lactic-co-glycolic acid)) polymers. These polymers can be tailored for specific applications.
Drug Encapsulation	Polymers can encapsulate drugs within nanoparticles, protecting them from degradation and enabling controlled release. This improves drug bioavailability and reduces frequent dosing.
Passive Targeting	Polymer nanoparticles can exploit the enhanced permeability and retention (EPR) effect, accumulating in tumour tissues due to leaky vasculature. This is a common approach in cancer therapy.
Active Targeting	Surface modification with ligands or antibodies allows polymer nanoparticles to actively target specific cells or tissues, enhancing drug delivery precision.
Controlled Release	Polymers can be engineered to provide sustained, controlled drug release over an extended period. This minimizes side effects and maintains therapeutic levels.
Biocompatibility	The choice of biocompatible polymers minimizes immunogenicity and toxicity, making these nanotherapeutics safer for use in the body.
Reduced Side Effects	By targeting specific tissues and controlling drug release, polymer-based nanotherapeutics can reduce systemic side effects typically associated with conventional drug delivery.
Challenges	Challenges include optimizing drug loading, ensuring stability, and the potential for immunogenicity with synthetic polymers. Regulatory approval is also a complex process.
Applications	Polymer-based nanotherapeutics find applications in various medical fields, including oncology, infectious diseases, neurology, and regenerative medicine.

Table 2. Polymer-based nanotherapeutics.

Even poles apart traits of combined lipid-polymer-based nanotherapeutics have been massively mentioned in Table 3.

Key Aspect	Description
Definition	Nanotherapeutics that combine lipids and polymers to form nanoparticles for targeted drug delivery.
Structure	Core-shell structure with a lipid-based outer shell and a polymer-based inner core.
Composition	Lipids (such as phospholipids) and polymers (e.g., PLGA, PCL, PEG) are commonly used components.
Synthesis methods	Emulsion/solvent evaporation, nanoprecipitation, and self-assembly are commonly employed techniques.
Drug encapsulation efficiency	High encapsulation efficiency due to the versatility of both lipids and polymers in accommodating drugs.
Stability	Improved stability due to the protective lipid layer shielding the core from degradation.
Biocompatibility	Generally high biocompatibility due to the biodegradable nature of many of the components used.
Targeting ability	Enhanced targeting ability via surface modification with ligands or antibodies for specific receptors.
Controlled release	Controlled release of drugs is achievable through the manipulation of the lipid and polymer properties.
Applications	Used in the treatment of various diseases including cancer, cardiovascular diseases, and infections.
Current challenges	Scale-up challenges, regulatory hurdles, and potential toxicity concerns are current hurdles.

Table 3. Lipid-polymer-based nanotherapeutics.

4. Applications:

- Nano-phytotherapeutics find applications in various therapeutic areas, including cancer therapy, cardiovascular diseases, neurodegenerative disorders, and inflammatory conditions.
- They can improve the therapeutic index of phytochemicals by reducing side effects and enhancing the therapeutic effect.

Nano-phytotherapeutics have the potential for personalized remedy; Treatment can be customized based on an individual’s genetic and physiological traits.

5. Challenges and Future Directions:

- Despite their promise, Nano-phytotherapeutics face challenges related to scale-up, manufacturing, and regulatory approval.
- Ensuring the long-term safety and biocompatibility of these nanoparticles is critical.

- Continued research is needed to optimize formulation, drug loading, and targeting strategies for specific diseases.

In the ever-evolving landscape of modern medicine, the pursuit of innovative therapeutic solutions has led to groundbreaking developments in nanotechnology and the integration of natural plant-based compounds, giving rise to a fascinating field known as Nano-phytotherapeutics. This interdisciplinary domain marries the principles of nanoscience with the therapeutic potential of phytochemicals, promising revolutionary advances in drug delivery, disease treatment, and patient care. Specifically, lipid and polymer-based approaches have emerged as crucial components in harnessing the full potential of Nano-phytotherapeutics, offering precise control over drug delivery and enhancing the therapeutic efficacy of phytochemicals.

Phytotherapeutics, rooted in traditional herbal remedies, have long been valued for their therapeutic properties. However, their practical application in modern medicine has often been hampered by challenges related to poor bioavailability, stability, and controlled release of bioactive compounds. Nano-phytotherapeutics addresses these limitations by capitalizing on nanoscale platforms that enable the encapsulation, protection, and targeted delivery of phytochemicals. In this context, lipids and polymers play pivotal roles in designing carrier systems that optimize the pharmacokinetics and pharmacodynamics of these natural compounds [Tang *et al.*, 2020].

Lipid-based approaches have gained prominence due to their biocompatibility and the ability to mimic biological membranes. Lipid nanoparticles, liposomes, and solid lipid nanoparticles serve as versatile carriers for phytochemicals, enhancing their solubility and stability, and facilitating their passage across biological barriers. Additionally, lipid-based systems enable controlled release profiles, minimizing side effects and maximizing therapeutic benefits.

On the other hand, polymer-based approaches offer a diverse range of materials and structures tailored to the specific needs of Nano-phytotherapeutics. Polymeric nanoparticles, micelles, and nanofibers offer advantages such as tunable drug release kinetics, prolonged circulation times, and targeted delivery to disease sites. Moreover, polymer-drug conjugates and nanogels enable the efficient integration of phytochemicals into the polymer matrix, ensuring their sustained release and enhanced therapeutic effects [Zhang *et al.*, 2012].

The amalgamation of lipid and polymer-based approaches with phytotherapeutics is poised to revolutionize modern medicine across various domains. In cancer therapy, Nano-phytotherapeutics can improve the selectivity and efficacy of chemotherapeutic agents, reducing off-target effects and refining the excellence of life for patients. In infectious diseases, the targeted delivery of phytochemicals can combat drug-resistant pathogens, offering new hope in the battle against evolving microbial threats. Furthermore, neurodegenerative disorders, cardiovascular diseases, and chronic inflammatory conditions stand to benefit from the precision and enhanced bioavailability that Nano-phytotherapeutics can provide.

As delve deeper into the intricate world of Nano-phytotherapeutics, this multifaceted approach

promises to redefine the landscape of modern medicine. The journey ahead involves not only the synthesis of innovative lipid and polymer-based carriers but also a comprehensive understanding of the biological interactions and regulatory considerations that underpin the translation of these novel therapies into clinical practice. This review explores the recent advancements, challenges, and transformative potential of Nano-phytotherapeutics, shedding light on how this emerging field holds the promise of a brighter and more efficacious future for modern medicine [Khan *et al.*, 2015].

2. NANO-PHYTOTHERAPEUTICS: AN OVERVIEW

2.1. Nanotechnology in Phytotherapeutics

- **Definition and significance of Nano-phytotherapeutics:**

Nano-phytotherapeutics refers to a cutting-edge field of science and medicine that combines nanotechnology with the principles of phytotherapy, which involves the use of plant-derived compounds for therapeutic purposes. This emerging field focuses on designing and developing nanoscale drug delivery systems and formulations using bioactive compounds extracted from plants or botanical sources. These Nano-phytotherapeutics aim to boost the bio-availability, target specificity, and overall healing efficacy of phytochemicals, ultimately leading to improved health outcomes [Jing *et al.*, 2022].

Definition:

Nano-phytotherapeutics is the interdisciplinary integration of nanotechnology and phytotherapy. Nanotechnology involves manipulating materials at the nanoscale (typically below 100 nanometers) to create nanoparticles, nanocarriers, and nanostructured materials. Phytotherapy, on the other hand, utilizes bioactive compounds found in plants, such as polyphenols, alkaloids, flavonoids, and essential oils, for therapeutic purposes. In Nano-phytotherapeutics, these phytochemicals are encapsulated, modified, or combined with nanomaterials to enhance their pharmacokinetic and pharmacodynamic properties, resulting in more effective and targeted therapeutic interventions which are highlighted in Fig. 1.

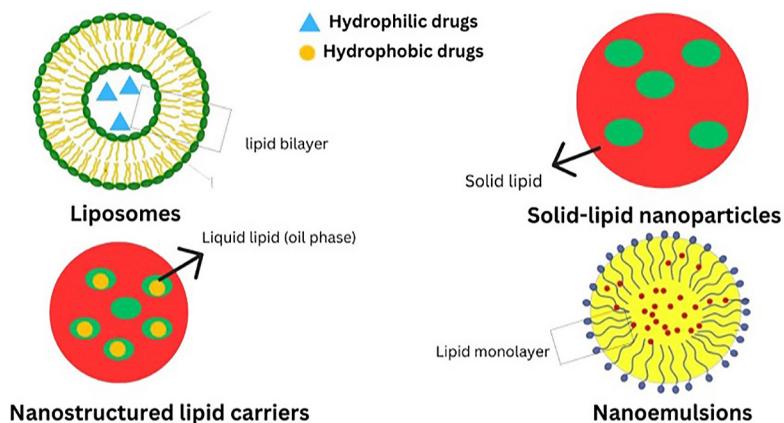


Figure 1. Classifying nanocarriers based on lipids or phospholipids [Herault *et al.*, 2020].

Potential Significance of nanoscale drug delivery systems [Alexander *et al.*, 2016; Bagade *et al.*, 2014; Sharma *et al.*, 2022; Agarawal *et al.*, 2023; Smith *et al.*, 2020]:

Enhanced Bioavailability: Many plant-derived bioactive compounds have low bioavailability, which means they are poorly absorbed by the body when taken orally. Nano-phytotherapeutics can encapsulate these compounds within nanoparticles or liposomes, protecting them from degradation in the gastrointestinal system and improving their absorption. This leads to higher concentrations of the therapeutic agents in the bloodstream, enhancing their effectiveness.

Targeted Drug Delivery: Nano-phytotherapeutics can be engineered to deliver phytochemicals specifically to the affected tissues or cells in the body. This targeted drug delivery minimizes side effects by reducing exposure to healthy tissues while maximizing the therapeutic impact on diseased areas, such as tumors or inflamed tissues.

Controlled Release: Nanoscale drug delivery systems can be designed to release phytochemicals gradually over time. This sustained release ensures a prolonged therapeutic effect, reducing the frequency of administration and improving patient compliance.

Overcoming Solubility Issues: Many phytochemicals have limited solubility in water, which hinders their formulation into conventional medicines. Nanotechnology allows these compounds to be solubilized and incorporated into various dosage forms, such as nanoparticles, micelles,

or nanocrystals, making it easier to prepare pharmaceutical products.

Synergy and Combination Therapies: Nano-phytotherapeutics enable the combination of multiple plant-derived compounds or the incorporation of phytochemicals with conventional drugs. This approach can result in synergistic effects, enhancing therapeutic outcomes and reducing the risk of drug resistance.

Reduced Toxicity: By improving drug targeting and reducing the required dosage, Nano-phytotherapeutics can help mitigate the toxicity associated with some phytochemicals, making them safer for long-term use.

Potential for Personalized Medicine: Nano-phytotherapeutics can be tailored to individual patient needs, allowing for personalized treatment strategies based on genetic and physiological differences.

Improved Patient Compliance: The reduced dosing frequency and improved tolerability associated with Nano-phytotherapeutics can enhance patient compliance, as individuals are more likely to adhere to treatment regimens that are convenient and have fewer side effects.

Minimized Herb-Drug Interactions: Nano-phytotherapeutics can help mitigate potential interactions between herbal medicines and conventional pharmaceutical drugs by controlling the release and distribution of active compounds, reducing the likelihood of adverse drug interactions.

Enhanced Imaging and Diagnosis: Nanoparticles used in phytotherapeutics can serve as contrast agents for imaging techniques, facilitating the early detection and monitoring of diseases. They

can also enable more accurate diagnosis and disease staging.

Reduced Environmental Impact: Nano-phytotherapeutics often require smaller quantities of herbal extracts, contributing to the conservation of medicinal plant resources and reducing the environmental footprint associated with the production of herbal medicines.

Cost-Effective Manufacturing: Advances in nanotechnology have made the production of Nano-phytotherapeutics more cost-effective over time. As the technology matures, it is likely that the cost barrier for these treatments will decrease, making them more accessible to a broader population.

Nano-phytotherapeutics represents a promising frontier in healthcare, where the fusion of nanotechnology and phytotherapy offers innovative solutions to overcome the boundaries of traditional delivery systems of drug and harnesses the full therapeutic potential of plant-derived compounds. This field has the impending to modernize the management of various diseases and conditions, offering more effective and patient-friendly therapies.

Challenges in traditional phytotherapeutic formulations [Srivastava et al., 2021; Tian et al., 2021; Mehnert et al., 2012; Has et al., 2020].

Traditional phytotherapeutic formulations, which involve the use of plant-based remedies for the treatment of several disorders, have been practiced for centuries in different cultures around the world. While these remedies have often proven effective, they also come with a set of challenges that need to be considered to ensure their safety, efficacy, and proper integration into modern healthcare systems. Some of the challenges associated with traditional phytotherapeutic formulations:

1. **Lack of Standardization:** Traditional herbal remedies often lack standardized formulations, making it difficult to ensure consistent quality and efficacy. Plants can vary significantly in their chemical composition based on factors like growing conditions, harvesting times, and processing methods. Without standardization, it becomes challenging to determine the appropriate dosage and predict the therapeutic effects accurately.
2. **Safety Concerns:** Many traditional phytotherapeutic formulations may not undergo rigorous

safety testing or quality control measures. This can lead to potential risks, including contamination with toxic substances, allergens, or the presence of harmful microorganisms. Improper use or dosage can also result in adverse effects or interactions with other medications.

3. **Limited Scientific Evidence:** Traditional herbal remedies are often based on anecdotal evidence and traditional knowledge passed down through generations. While this knowledge can be valuable, it may not always align with modern scientific understanding. The lack of rigorous clinical trials and scientific validation can make it difficult to establish the safety and efficacy of these formulations.
4. **Variability in Plant Potency:** Natural variability in plant potency can affect the therapeutic outcomes of herbal treatments. Even when using the same plant species, variations in factors such as soil composition, climate, and genetic differences can lead to differences in the concentration of active compounds. This makes it challenging to ensure consistent results with herbal remedies.
5. **Lack of Regulation:** In many regions, traditional phytotherapeutic formulations are not subject to the same regulatory oversight as pharmaceutical drugs. This can result in a lack of quality control, inaccurate labeling, and potential misbranding of products. Without adequate regulation, consumers may be at risk of purchasing ineffective or unsafe remedies.
6. **Cultural and Ethical Considerations:** Traditional herbal knowledge is often closely tied to specific cultural practices and traditions. When integrating these remedies into modern healthcare systems, it's essential to respect cultural beliefs and ethical considerations. Balancing traditional knowledge with scientific rigor and ethical standards can be a complex challenge.
7. **Sustainability and Conservation:** The increasing demand for certain medicinal plants has led to overharvesting and habitat destruction, threatening the sustainability of some plant species. Conservation efforts are desirable to ensure the lasting availability of these plants for traditional herbal medicine and to protect biodiversity.
8. **Lack of Interactions Data:** Herbal remedies may interact with pharmaceutical drugs or other treatments, potentially affecting their efficacy or safety. However, there is often limited data on herb-drug interactions, making it challenging for healthcare providers to make informed

decisions when patients use both traditional herbal remedies and conventional medications.

9. Education and Training: Proper knowledge and training are essential for the safe and effective use of traditional phytotherapeutic formulations. Both healthcare practitioners and consumers may lack the necessary education to make informed decisions regarding herbal remedies, dosages, and potential risks.

While traditional phytotherapeutic formulations have a rich history and offer potential benefits, addressing the challenges associated with their use is crucial for ensuring their safety, efficacy, and integration into modern healthcare systems. This requires a multidisciplinary approach involving traditional knowledge, scientific research, regulation, and education to harness the potential of herbal remedies while minimizing risks.

2.2. Lipid-Based Nano-phytotherapeutics

Lipid-based Nano-phytotherapeutics represent a hopeful methodology for the delivery of bioactive complexes derived from plant sources, also known as phytochemicals or phytotherapeutics. These nanoformulations aim to enhance the solubility, stability, bioavailability, and targeted delivery of phytochemicals, which can have various pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial, anticancer, and more. The methodology for developing lipid-based Nano-phytotherapeutics involves several key steps, each of which contributes to the successful formulation and therapeutic efficacy of these nanoparticles which is mentioned in Fig. 2. [Gonzalez *et al.*, 2018; Brown *et al.*, 2019; Li *et al.*, 2021; He *et al.*, 2007; Li *et al.*, 2022].

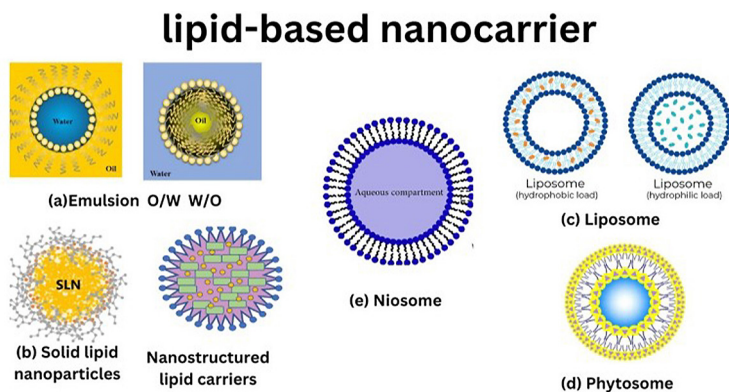


Figure 2. "Lipid-based systems for the release of hydrophobic and hydrophilic actives".

1. Selection of Phytochemicals:

The first step in developing lipid-based Nano-phytotherapeutics is the careful selection of phytochemicals or bioactive compounds from plant sources based on their therapeutic potential and relevance to the intended application. These compounds can include flavonoids, terpenoids, alkaloids, polyphenols, and more.

2. Lipid Material Selection:

Lipid-based Nano-phytotherapeutics rely on the use of lipids as the primary material for nanoparticle formation. Common lipids include phospholipids, triglycerides, and cholesterol. The choice of lipid will impact the physicochemical properties of the nanoparticles, such as size, stability, and drug loading capacity.

3. Nanoparticle Formulation:

The selected lipids are then used to formulate nanoparticles using various techniques, such as

solvent evaporation, emulsification, and lipid hydration. The optimal formulation technique depends on the specific properties of the phytochemical and lipid combination.

4. Characterization of Nanoparticles:

The resulting lipid-based nanoparticles need to be thoroughly characterized to ensure their quality and performance. Characterization techniques include Quantifying the size of particles, assessing polydispersity index, examining zeta potential, analyzing morphology, evaluating encapsulation efficiency, and studying drug release kinetics.

5. Drug Loading:

Phytochemicals are incorporated into the lipid nanoparticles through methods such as co-solvent evaporation or emulsification, where the phytochemicals are dissolved or dispersed in the lipid phase. Optimizing the drug loading capacity is crucial to ensure the therapeutic dose is delivered.

6. Stabilization and Surface Modification:

To enhance the stability of lipid-based Nano-phytotherapeutics, surface modifications can be employed. This may involve the addition of stabilizers, such as surfactants or polymers, which can prevent aggregation and improve colloidal stability.

7. *In vitro* Testing:

The prepared nanoparticles are subjected to *in vitro* testing to evaluate their drug release profile, cytotoxicity, and cellular uptake. These tests help determine the nanoparticles' potential efficacy and safety.

8. *In vivo* Testing:

Promising formulations are then evaluated in animal models to assess their pharmacokinetics, biodistribution, and therapeutic efficacy. This step provides critical data on the nanoparticles' performance in a biological system.

9. Targeted Delivery Strategies:

Depending on the therapeutic application, researchers may explore targeted delivery strategies. This can involve Enhancing the surface through the addition of ligands that possess a high specificity for binding to receptors located on target cells. or tissues, enhancing the nanoparticles' ability to reach and accumulate at the desired site of action.

10. Scale-Up and Optimization:

Once a promising formulation is identified, efforts are made to scale up the production process while maintaining product quality and consistency. Process optimization ensures reproducibility and cost-effectiveness.

11. Safety and Toxicity Assessment:

Comprehensive safety and toxicity assessments, including acute and chronic toxicity studies, are conducted to evaluate the safety profile of lipid-based Nano-phytotherapeutics.

12. Clinical Trials:

If the preclinical studies demonstrate positive results and safety, lipid-based Nano-phytotherapeutics can advance to clinical trials involving human subjects. These trials assess the formulation's efficacy and safety in a clinical setting.

13. Regulatory Approval:

Following successful clinical trials, regulatory approval from relevant health authorities is sought, allowing the lipid-based Nano-phytotherapeutics to be marketed and prescribed for therapeutic use.

The methodology for developing lipid-based Nano-phytotherapeutics involves a systematic approach encompassing phytochemical selection, lipid formulation, rigorous characterization, *in vitro* and *in vivo* testing, targeted delivery strategies, scale-up, safety evaluation, and clinical trials. This multi-step process aims to harness the potential of phytochemicals for therapeutic applications while overcoming the challenges associated with their poor solubility and bioavailability.

2.3. Polymer-Based Nano-phytotherapeutics [Kumar *et al.*, 2013; McClements *et al.*, 2012; Md *et al.*, 2018; Ochi *et al.*, 2016; Shaker *et al.*, 2019; Talarico *et al* 2021]

Polymer-based Nano-phytotherapeutics is an emerging field in pharmaceutical and medical research that combines the benefits of nanotechnology and phytotherapy to improve innovative drug transport systems. These systems aim to enhance the therapeutic efficacy of phytochemicals (compounds derived from plants) by improving their bioavailability, stability, and targeted delivery. This methodology involves several key steps, from the selection of suitable polymers and phytochemicals to the fabrication of nanoparticles and their evaluation for pharmaceutical applications which is depicted in Fig. 3.

- 1. Phytochemical Selection:** The first step in developing polymer-based Nano-phytotherapeutics is the careful selection of phytochemicals. Researchers must identify plant-derived compounds with known therapeutic properties and low toxicity. Common phytochemicals used include flavonoids, alkaloids, polyphenols, and terpenoids, which have demonstrated various health benefits.
- 2. Polymer Selection:** Choosing the right polymer is crucial for the success of this methodology. Polymers serve as carriers to encapsulate phytochemicals and control their release. Biodegradable and biocompatible polymers such as "poly(lactic-co-glycolic acid) (PLGA)", chitosan, alginate, and polymeric micelles are often preferred due to their safety profiles and controlled release properties.
- 3. Nanoparticle Fabrication:** The fabrication of nanoparticles involves various techniques, and the choice of method depends on the polymer and phytochemical combination. Common methods include:

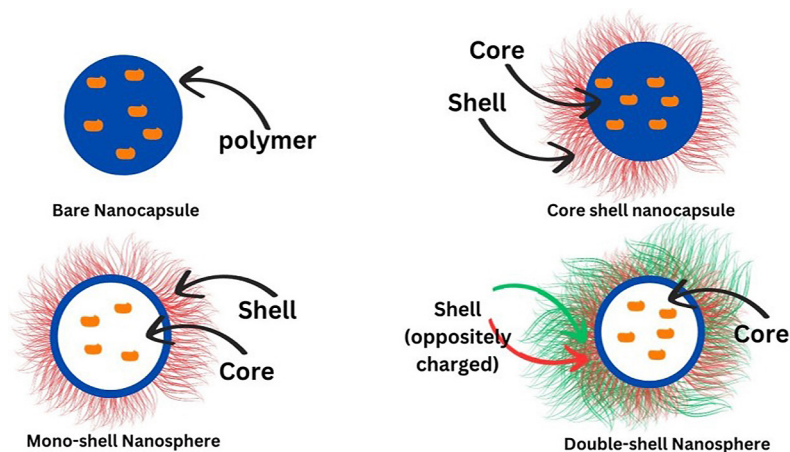


Figure 3. a) Core-shell nanocapsules b) Double shape nanospheres.

- a. Emulsion Solvent Evaporation:** In this method, a polymer solution that includes the phytochemical is mixed with an aqueous phase to create an emulsion, and then nanoparticles are produced through solvent evaporation.
- b. Nanoprecipitation:** This method involves mixing a polymer solution and a non-solvent to induce nanoparticle formation by rapid precipitation.
- c. Electrospaying:** Electrostatic forces are used to disintegrate a polymer-phytochemical solution into droplets, which then solidify into nanoparticles.
- 4. Characterization:** Characterization of the polymer-based nanoparticles is essential to ensure their quality and suitability for therapeutic use. Common characterization techniques include [Singh *et al.*, 2022; Wu *et al.*, 2007; Vijayakumar *et al.*, 2017; Shangguan *et al.*, 2015; Patel *et al.*, 2014]:
- a. Particle Size Analysis:** Assessing nanoparticle size distribution through methods such as “dynamic light scattering (DLS) or scanning electron microscopy (SEM)”.
 - b. Surface Charge (Zeta Potential):** Determining the surface charge of nanoparticles to assess their stability and potential for aggregation.
 - c. Encapsulation Efficiency:** Quantifying how efficiently the nanoparticles encapsulate the phytochemical of interest.
 - d. Drug Release Kinetics:** Studying the release profile of the phytochemical from the nanoparticles over time.
 - e. Morphological Analysis:** Examining the shape and morphology of nanoparticles using imaging techniques like transmission electron microscopy (TEM).
- 5. Drug Loading:** After fabrication and characterization, the phytochemicals are loaded into the nanoparticles. This step ensures that the nanoparticles carry a sufficient amount of the active compound for therapeutic effectiveness.
 - 6. In vitro and In vivo Evaluation:** The next phase involves testing the polymer-based Nano-phytotherapeutics in controlled laboratory settings (*in vitro study*) and animal models (*in vivo study*) to assess their safety and efficacy. These evaluations include cell viability assays, pharmacokinetics, and pharmacodynamics studies.
 - 7. Targeted Delivery and Bioavailability Enhancement:** One of the primary objectives of polymer-based Nano-phytotherapeutics is to improve targeted delivery to specific tissues or cells while enhancing bioavailability. Surface modifications and ligand conjugations can be employed to achieve this goal, allowing the nanoparticles to accumulate at the target site.
 - 8. Toxicity Assessment:** Safety assessment is an acute stage in the expansion of nano-phytotherapeutics. researchers must conduct comprehensive toxicity studies to ensure that the nanoparticles do not induce adverse effects.
 - 9. Scale-Up and Formulation Optimization:** Once the initial studies are promising, the methodology can be scaled up for large-scale production. Formulation optimization may be necessary to fine-tune the nanoparticles for commercial production.
 - 10. Clinical Trials:** After extensive preclinical evaluation, polymer-based Nano-phytotherapeutics

can enter clinical trials to assess their safety and efficacy in humans. These trials typically involve phases I, II, and III to determine dosing, safety, and efficacy profiles.

11. Regulatory Approval and Commercialization: Successful completion of clinical trials may lead to regulatory approval for pharmaceutical use. Once approved, these Nano-phytotherapeutics can be commercialized and made available to patients.

The methodology for developing polymer-based Nano-phytotherapeutics is a multi-step process that combines expertise in phytochemistry, polymer science, nanotechnology, and pharmacology. Through careful selection of phytochemicals, polymers, and fabrication techniques, researchers can create innovative and active transport systems that have the possibility to revolutionize the field of herbal medicine and traditional therapies. However, it is essential to prioritize safety and efficacy throughout the development process to ensure the effective conversion of these novel treatments into clinical exercise [Mady et al 2016; Marques et al 2021; Li et al., 2020; Kaplan et al., 2019; Azizi et al., 2019; Mohanty et al., 2020; Patel et al., 2014].

- Polymer NPs (micelles based on polymer, nanospheres, dendrimers).
- Drug-polymer conjugates for targeted delivery.
- Sustained release of phytochemicals using polymeric carriers.

3. FORMULATION STRATEGIES

Formulation strategies for the development of polymer-based Nano-phytotherapeutics signify an escalating arena at the connection of pharmaceuticals, nanotechnology, and natural medicine. These strategies aim to enhance the therapeutic potential of phytochemicals, compounds derived from plants, by incorporating them into nanoscale polymer-based delivery systems. This approach offers several advantages, such as improved bioavailability, controlled release, and targeted delivery, making it a promising avenue for drug development. Here, the formulation strategies for polymer-based Nano-phytotherapeutics in detail are as follows [Pavoni et al., 2020; Bagade et al., 2020; AhmadiOskooei et al., 2021; Cengiz et al., 2015].

Selection of Phytochemicals: The process begins with the selection of suitable chemical constituents,

that are bioactive mixtures extracted from plants. These compounds could include polyphenols, flavonoids, alkaloids, terpenoids, and more. The choice of phytochemical depends on the therapeutic application and the desired bioactivity.

Polymer Selection: The choice of polymer is critical in formulating Nano-phytotherapeutics. Bio-degradable and biocompatible polymers like “poly(lactic-co-glycolic acid) (PLGA)”, chitosan, alginate, and polymeric micelles are commonly used. The polymer should provide stability to the nano-phytotherapeutic system, protect the phytochemical from degradation, and control its release.

Nanoencapsulation Techniques: Several techniques can be employed for encapsulating phytochemicals within polymer nanoparticles:

- a. Nanoprecipitation:** This technique involves the precipitation of polymer and phytochemicals in a solvent-non-solvent system. It is suitable for hydrophobic compounds and is relatively simple.
- b. Emulsification-Solvent Evaporation:** Here, an emulsion of the polymer and phytochemical is prepared, followed by the evaporation of the solvent. It's effective for both hydrophobic and hydrophilic compounds.
- c. Coacervation:** This method involves the phase separation of polymers, leading to the formation of polymer-rich droplets containing the phytochemical. It's useful for encapsulating both hydrophobic and hydrophilic compounds.
- d. Electrospinning:** Electrospinning generates ultrafine fibers from a polymer solution containing the phytochemical. It's suitable for creating nanofiber-based systems.

Surface Modification: The surface of the polymer nanoparticles can be modified to enhance their stability, drug loading capacity, and targeting ability. Surface modifications may include the attachment of ligands, such as antibodies or peptides, to facilitate targeted drug delivery.

Characterization: Comprehensive characterization of the nano-phytotherapeutic system is crucial. Techniques like “dynamic light scattering (DLS), transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FTIR)” can be employed to assess particle size, morphology, encapsulation efficiency, and stability.

Incorporation of Targeting Ligands: To achieve targeted therapy, ligands that bind explicitly to receptors on the marked cells or tissues can be added to the nanoparticle surface. This helps improve the precision of drug delivery while reducing off-target effects.

Controlled Release: Polymer-based Nano-phytotherapeutics can be designed to provide sustained and controlled drug release. Factors like polymer degradation rate, particle size, and composition can be adjusted to achieve the desired release kinetics.

Bioavailability Enhancement: Nanoformulations can significantly improve the bioavailability of phytochemicals by protecting them from enzymatic degradation and promoting their GI absorption.

Biocompatibility and Safety: Extensive preclinical examinations are essential to assess the safety and biocompatibility of polymer-based Nano-phytotherapeutics. Toxicity assessments, including *in vitro* and *in vivo* determinations, are performed to ensure the formulation’s safety profile.

Scale-Up and Manufacturing: The successful formulation must be scalable for commercial production. Transitioning from lab-scale to large-scale manufacturing involves optimizing processes and ensuring consistency in product quality.

Regulatory Considerations: Complying with regulatory requirements is critical for the approval and commercialization of polymer-based Nano-phytotherapeutics. This includes conducting clinical trials, submitting regulatory documents, and meeting quality control standards.

The formulation strategies for polymer-based Nano-phytotherapeutics combine the principles of nanotechnology with the therapeutic potential of phytochemicals. These strategies are multifaceted, involving careful selection of polymers, encapsulation techniques, surface modifications, and targeted delivery to maximize the therapeutic benefits while ensuring safety and efficacy. The advancement of such an innovative active delivery method holds promise for the advancement of phytotherapy and personalized medicine depicted in Table 4.

Sr. No.	Nanoformulations	Herbal Drugs	Significant Outcome	Uses
1	Casein micelles	Berberine	Prolonged release	HCC therapy
2	Solid Lipid Nanoparticles (SLNs)	Berberine	Prolonged release	NSCLC therapy
3	Phytosomes	Celastrol	Improved solubility	HCC therapy
4	Magnetic nanoparticles	Curcumin	Enhanced MRI imaging and therapeutic efficacy	Theranostics
5	Gliadin nanospheres	Diosmin	Enhanced solubility	HCC therapy
6	Solid lipid nanoparticles	EGCG	Increased stability	Anticancer, antioxidant
7	Chitosan nanoparticles	EGCG	Increased stability	Anticancer, antioxidant
8	Lactoferrin-chondroitin DPI nanocomposites	Ellagic acid	Improved pulmonary delivery and enhanced lung deposition	Lung cancer therapy
9	Liposomes	Ginsenosides	Improved synergistic anticancer efficacy	Gastric cancer therapy
10	Lactoferrin-chondroitin LbL QD-nanocapsules	Honokiol	Enhanced fluorescence imaging and therapeutic efficacy	Breast cancer theranostics
11	Nebulized PLGA nanoparticles	Naringin	Improved pulmonary delivery and enhanced lung deposition	Lung cancer therapy

Sr. No.	Nanoformulations	Herbal Drugs	Significant Outcome	Uses
12	Phytosomes	Quercetin	Improved pharmacokinetics	Anticancer, antioxidant
13	Lactoferrin nanocapsules	Quercetin	Enhanced tumor targeting	HCC therapy
14	Phospholipid bilayer-enveloped casein micelles	Resveratrol	Improved solubility and enhanced tumor targeting	Breast cancer therapy
15	Zeinnanocapsules	Resveratrol	Prolonged half-life	Breast cancer therapy
16	Nanosuspension tablet	Silymarin	Improved dissolution rate	Hepatoprotective
17	Chitosan nanoparticles	Triptolide	Enhanced tumor targeting	HCC therapy
18	Lactoferrin-zein micelles	Wogonin	Improved synergistic anticancer efficacy	Breast cancer therapy

Table 4. Some phytotherapeutics based nanoformulations [Liu *et al.*, 2015; Halevas *et al.*, 2022; Bulbake *et al.*, 2017; Li *et al.*, 2009; Nagi *et al.*, 2017; Rostami *et al.*, 2014; Souto *et al.*, 2014]

3.1. Selection of Phytochemicals

- **Criteria for choosing bioactive compounds** [Son *et al.*, 2019; Xu *et al.*, 2013; Shtay *et al.*, 2019; Müller *et al.*, 2000; Magura *et al.*, 2021; Komath *et al.*, 2018].

Criteria for Choosing Bioactive Compounds for Advancement of Lipid and Polymer containing Nano-phytotherapeutics

The expansion of lipid as well as polymer-containing nano-phytotherapeutics involves the selection of appropriate bioactive compounds from natural sources, such as plants, for therapeutic purposes. These Nano-phytotherapeutics hold promise in the field of medicine due to their potential for enhanced drug delivery, improved bioavailability, and reduced side effects. Choosing the right bioactive compounds is crucial for the success of such formulations. Here, it investigates the criteria for selecting bioactive compounds for the advancement of lipid as well as polymer-containing nano-phytotherapeutics:

Pharmacological Activity and Therapeutic Potential:

The bioactive compounds should possess well-documented pharmacological activities that align with the intended therapeutic purpose. Extensive

research on the compound's biological effects, such as anti-inflammatory, antioxidant, anticancer, or antimicrobial properties, is essential.

The potential of the bioactive compound to address a specific medical condition or disease should be evident through preclinical and clinical studies.

Safety Profile:

Safety is paramount in pharmaceutical development. The selected bioactive compounds should have a favorable safety profile with minimal toxicity or adverse effects.

Comprehensive toxicological studies should be conducted to evaluate the compound's safety, including acute and chronic toxicity, mutagenicity, and genotoxicity assessments.

Bioavailability Enhancement:

The compounds chosen should have poor aqueous solubility or bioavailability issues, making them suitable candidates for nanoformulation. Lipid-based and polymer-based Nano-phytotherapeutics are particularly effective in improving the solubility and absorption of poorly water-soluble compounds.

Stability and Compatibility:

Bioactive compounds must remain stable within the nanoformulation throughout storage and administration. They should not degrade or interact adversely with the lipid or polymer matrices. Compatibility studies should be conducted to

ensure that the selected compound does not compromise the stability of the nanocarrier.

Controlled Release:

Depending on the therapeutic need, the compound should exhibit the potential for controlled and sustained release. This is particularly important for chronic conditions where prolonged drug action is required.

Biodegradability and Biocompatibility:

Both the bioactive compound and the nanocarrier should be biodegradable and biocompatible to minimize the risk of toxicity and immune responses.

Compatibility with the body's natural processes, including metabolism and elimination, is essential.

Targeting and Specificity:

If the therapeutic strategy involves targeting specific cells, tissues, or organs, the selected compound should facilitate active or passive targeting.

Surface modifications of the nanocarrier with ligands or antibodies may be necessary to enhance targeting and reduce off-target effects.

Ease of Formulation:

The practicality of formulating the bioactive compound into lipid-based or polymer-based Nano-phytotherapeutics is crucial. It should be feasible to encapsulate or load the compound into the chosen nanocarrier without significant challenges.

Scalability and Cost-Effectiveness:

The availability of the bioactive compound in sufficient quantities and at a reasonable cost is essential for commercial viability.

The scalability of the production process should be considered to meet market demand.

Intellectual Property**and Regulatory Considerations:**

Intellectual property rights should be clear for the selected compound, allowing for the development and commercialization of the nano-phytotherapeutic.

Regulatory requirements and compliance, including obtaining necessary approvals from regulatory authorities, should be considered from the early stages of development.

The selection of bioactive compounds for the advancement of lipid as well as polymer-containing nano-phytotherapeutics involves a comprehensive evaluation process that takes into account pharmacological activity, safety,

compatibility, biodegradability, and other critical factors. The ultimate goal is to create effective, safe, and commercially viable formulations that can improve the treatment of various medical conditions.

- **Examples of phytochemicals with therapeutic potential** [Huang et al., 2022; Gill et al., 2014; Calligaris et al., 2015; Bagade et al., 2018; Liu et al., 2012; Mishra et al., 2018; Renault-Mahieux et al., 2021; Wu et al., 2006].

Phytochemicals are natural compounds present in plants that have been investigated for their potential healing properties. These compounds are not considered essential nutrients, but they can provide various health benefits when consumed as part of a balanced diet. Here are some examples of phytochemicals with therapeutic potential:

Flavonoids:

Quercetin: Found in apples, onions, and tea, quercetin is known for its antioxidant and anti-inflammatory properties. It has potential benefits for cardiovascular health and may help reduce the risk of chronic diseases.

Epigallocatechingallate (EGCG): Predominantly found in green tea, EGCG has antioxidant and anti-cancer properties. It is believed to play a role in reducing the risk of certain cancers and supporting weight management.

Anthocyanins: These pigments give fruits like berries and cherries their vibrant colors. Anthocyanins have anti-inflammatory and antioxidant properties and may contribute to improved cognitive function and reduced risk of chronic diseases.

Carotenoids:

Beta-carotene: Present in carrots, sweet potatoes, and spinach, beta-carotene is converted into vitamin A in the body, supporting healthy vision and immune function. It also acts as an antioxidant, helping to reduce oxidative stress.

Lycopene: Found in tomatoes and watermelon, lycopene is known for its potential to reduce the risk of prostate cancer. It also has antioxidant properties and may contribute to heart health.

Glucosinolates:

Sulforaphane: Found in cruciferous vegetables like broccoli, cauliflower, and Brussels sprouts, sulforaphane is a powerful antioxidant and has

been studied for its “potential” in cancer prevention and as an anti-inflammatory agent.

Resveratrol:

Found in grapes, red wine, and peanuts, resveratrol has gained attention for its potential cardiovascular benefits. It may help improve heart health by reducing inflammation and supporting healthy blood vessels.

Curcumin:

Derived from turmeric, curcumin is a powerful anti-inflammatory and antioxidant compound. It has been studied for its potential in managing conditions such as arthritis and Alzheimer’s disease.

Allicin:

Present in garlic, allicin has antimicrobial properties and may help lower blood pressure and cholesterol levels. It is also being explored for its potential in preventing cardiovascular disease.

Isoflavones:

Found in soy products like tofu and soybeans, isoflavones have estrogen-like effects on the body. They are studied for their potential in alleviating menopausal symptoms and reducing the risk of hormone-related cancers.

Catechins:

Commonly found in tea, particularly green tea, catechins have antioxidant properties and may contribute to weight management and reduced risk of chronic diseases.

Capsaicin:

Present in chili peppers, capsaicin is known for its spicy heat. It may have potential benefits for weight loss, pain relief, and even reducing the risk of some cancers.

Phytosterols:

These plant compounds, found in nuts, seeds, and vegetable oils, have a structure similar to cholesterol and may benefit by “lower LDL (bad) cholesterol levels”, dropping the risk of heart disease.

These examples highlight the diverse range of phytochemicals found in various plant foods and their potential therapeutic benefits. However, it’s essential to consume a balanced nutrition rich in a variety of fruits, vegetables, and whole grains to maximize the health benefits of phytochemicals. Additionally, further research is ongoing to better understand their specific mechanisms of action and possible uses in preventing and managing various health conditions.

3.2. Lipid-Based Formulations

[Yang *et al.*, 2015; Xiao *et al.*, 2005; Rishitha *et al.*, 2018]

• Lipid selection and compatibility.

Lipid selection and compatibility play a crucial role in enhancing the bioavailability and therapeutic potential of phytochemicals as bioactive substances resulting from plants. Phytochemicals have gained significant attention for their possible health benefits, including “antioxidant, anti-inflammatory, and anticancer properties”. However, their poor solubility and bioavailability can limit their efficacy. Lipid-based formulations offer a promising solution to overcome these challenges and optimize the delivery of phytochemicals. The considerations for lipid selection and compatibility in designing phytochemical-based therapeutic formulations.

1. Lipid Types [Rogerio *et al.*, 2010; Ahmad *et al.*, 2016]:

- **Triglycerides:** Triglycerides are commonly used lipids in phytochemical formulations. They are natural fats and oils derived from sources like plant seeds (e.g., sunflower oil, olive oil), which makes them compatible with plant-based phytochemicals. Triglycerides can improve the solubility of lipophilic phytochemicals and facilitate their absorption.
- **Phospholipids:** Phospholipids, such as lecithin, are essential components of cell membranes and are known for their amphiphilic nature. They are often used in liposomal formulations to encapsulate hydrophobic phytochemicals, improving their stability and bioavailability.
- **Fatty Acids:** Fatty acids like oleic acid and linoleic acid can be used as co-solvents or carriers for lipophilic phytochemicals. They enhance the solubility of the compounds and can be incorporated into emulsions or self-emulsifying drug delivery systems (SEDDS).
- **Solid Lipids:** Solid lipids, including stearic acid and glycerylmonostearate, are used in lipid nanoparticles and solid lipid nanoparticles (SLNs). These solid lipid carriers can protect phytochemicals from degradation and provide sustained release.

2. Phytochemical Properties:

- **Lipophilicity:** The lipid choice should match the lipophilicity of the phytochemical. Highly lipophilic phytochemicals may require oils

with a higher hydrophobic character, while less lipophilic compounds may benefit from phospholipid-based systems.

- **Chemical Compatibility:** Ensure that the selected lipid is chemically compatible with the phytochemicals to avoid interactions or degradation. Analytical techniques such as Fourier-transform infrared spectroscopy (FTIR) can assess compatibility.

3. Formulation Strategies [Wei et al., 2012]:

- **Microemulsions:** Microemulsions are thermodynamically stable, transparent systems that can encapsulate both hydrophilic and lipophilic phytochemicals. They consist of oil, water, surfactant, and co-surfactant, providing improved solubility and absorption.
- **Liposomes:** Liposomes are lipid vesicles that can encapsulate phytochemicals within their aqueous or lipid bilayer compartments. They are versatile carriers suitable for various phytochemicals, enhancing their stability and cellular uptake.
- **Nanoparticles:** Lipid nanoparticles, including nanoemulsions, SLNs, and nanostructured lipid carriers (NLCs), offer controlled release and protection for phytochemicals. These formulations are particularly effective for poorly water-soluble compounds.

4. Stability and Shelf Life:

- **Oxidative Stability:** Lipid-based formulations can be susceptible to oxidation. To prevent phytochemical degradation, antioxidants such as tocopherols or ascorbic acid may be added to the formulation.
- **Storage Conditions:** Proper storage conditions, such as refrigeration or inert gas packaging, can extend the shelf life of lipid-based phytochemical formulations.

5. Bioavailability Enhancement:

- **Digestibility:** Lipid-based formulations can improve the digestibility of phytochemicals by promoting their incorporation into micelles during digestion, facilitating absorption through the intestinal epithelium.
- **Lymphatic Transport:** Lipid-based formulations can bypass the hepatic first-pass metabolism, leading to lymphatic transport and enhanced bioavailability of phytochemicals.

6. Targeted Delivery:

- **Functionalization:** Lipid carriers can be functionalized with ligands or peptides for targeted delivery to specific tissues or cells, increasing the therapeutic potential of phytochemicals.

Lipid selection and compatibility are critical considerations in designing effective phytochemical-based therapeutic formulations. Proper selection of lipids and formulation strategies can enhance the solubility, stability, and bioavailability of phytochemicals, ultimately improving their therapeutic potential and promoting their use in healthcare and pharmaceutical applications. However, it is essential to conduct thorough research, including compatibility testing and stability studies, to tailor lipid-based formulations to the specific phytochemical and therapeutic goals.

• Techniques for phytochemical encapsulation [Xu et al., 2005; Zanchetta et al., 2015].

Phytochemical encapsulation is a process used to protect and deliver bioactive compounds derived from plants, known as phytochemicals, in a controlled and targeted manner. These compounds can have various health benefits, but they often face challenges related to stability, bioavailability, and controlled release. Encapsulation techniques are employed to address these issues. Below is the in-depth overview of some common techniques for phytochemical encapsulation:

Microencapsulation:

Definition: Microencapsulation involves enclosing phytochemicals within microscopic particles or capsules made from various materials such as proteins, carbohydrates, or lipids.

Techniques:

Spray Drying: This method involves spraying a solution containing the phytochemical onto a heated surface. The solvent evaporates, leaving behind microcapsules.

Coacervation: It utilizes the phase separation of colloidal substances to form capsules around the phytochemical.

Fluid Bed Coating: Phytochemicals are sprayed onto particles (often sugar or starch) in a fluidized bed, creating a coating.

Advantages: Enhances stability, controls release, masks taste and odour, and improves bioavailability.

Nanoencapsulation:

Definition: Nanoencapsulation reduces the size of capsules to the nanometer scale, which can improve bioavailability and provide sustained release. Which is mentioned in Fig. 4.

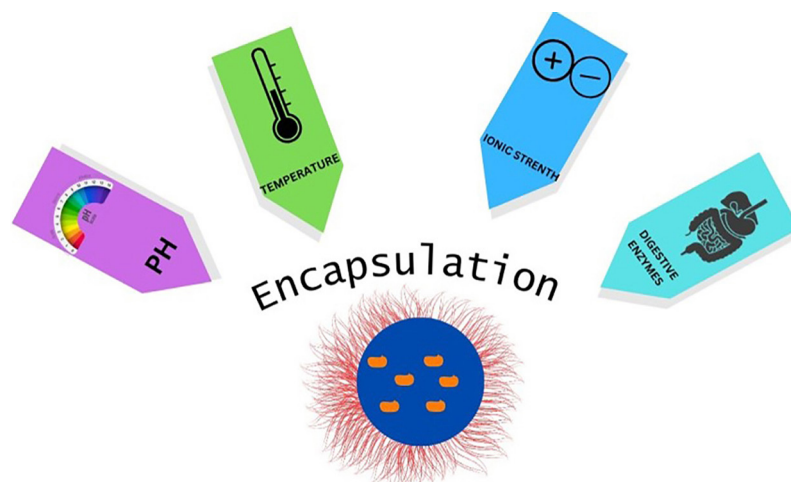


Figure 4. Stimuli from the environment that influence the stability of encapsulation.

Techniques:

Nanoprecipitation: Phytochemicals are dissolved in a solvent and then added to an antisolvent, leading to the formation of nanoparticles.

Emulsification-Solvent Evaporation: An emulsion is formed by mixing the phytochemical in an organic phase with an aqueous phase. The solvent is then evaporated.

Advantages: Enhanced bioavailability, prolonged release, and improved solubility.

Liposome Encapsulation:

Definition: Liposomes are spherical vesicles composed of lipid bilayers. They can encapsulate both hydrophobic and hydrophilic phytochemicals.

Techniques:

Thin-Film Hydration: Lipids are dissolved in an organic solvent, and then the phytochemical is added. The solvent is evaporated, and the resulting film is hydrated to form liposomes.

Reverse Phase Evaporation: This method is used for encapsulating hydrophobic compounds. It involves forming a water-in-oil emulsion followed by solvent removal.

Advantages: Improves solubility of lipophilic phytochemicals, enhances stability, and provides controlled release.

Polymeric Nanoparticles:

Definition: Polymeric nanoparticles are formed by encapsulating phytochemicals within biocompatible and biodegradable polymers.

Techniques:

Nanoprecipitation: Similar to nanoencapsulation, polymers are used instead of lipids.

Solvent Evaporation: Phytochemicals are dissolved in a polymer solution, and a nonsolvent is added to induce nanoparticle formation.

Advantages: Controlled release, improved stability, and protection against degradation.

Electrospinning:

Definition: Electrospinning creates nanofibers by applying an electric field to a polymer solution containing phytochemicals.

Advantages: High surface area for efficient release, suitable for wound healing and tissue engineering applications.

Coating Techniques:

Definition: In this approach, phytochemicals are coated onto carrier particles, such as microcrystals or nanoparticles.

Techniques: Layer-by-Layer Assembly, Fluid Bed Coating, Spray Layering.

Advantages: Improved stability, taste masking, and controlled release.

Extrusion-based Techniques:

Definition: Phytochemicals are mixed with polymers and processed through extrusion techniques to form controlled-release matrices.

Advantages: Sustained release, enhanced stability.

Each of these techniques offers distinct advantages and is chosen based on the specific phytochemical, its properties, the desired release profile, and the intended application. Phytochemical encapsulation is a promising approach to harness the health benefits of plant compounds while overcoming challenges related to their delivery and stability. Researchers continue to explore innovative

encapsulation methods to optimize the bioavailability and therapeutic potential of phytochemicals.

- **Stability and shelf-life considerations [Zhang et al., 2022; Sakat et al., 2022].**

Stability and shelf-life considerations are crucial when it comes to the encapsulation of phytochemicals, which are bioactive compounds derived from plants. Phytochemical encapsulation involves the process of enclosing these compounds within a protective matrix or carrier system to enhance their stability, bioavailability, and controlled release. Properly addressing stability and shelf-life concerns is essential to ensure that the encapsulated phytochemicals retain their efficacy over time. Here's an in-depth look at these considerations:

1. Oxidation and Degradation:

- **Oxidation:** Many phytochemicals are highly susceptible to oxidation when exposed to oxygen and light. This can result in the loss of their bioactivity. Encapsulation materials should provide a barrier against oxygen to prevent oxidation.
- **Degradation:** Some phytochemicals are sensitive to heat, pH changes, and enzymatic degradation. Encapsulation can protect them from these factors, extending their shelf life.

2. Encapsulation Materials:

- **Selection of Carrier Systems:** The choice of encapsulation materials is crucial. It can be natural or synthetic, depending on the desired application. Common natural carriers include proteins (e.g., whey, casein), lipids (e.g., liposomes), and carbohydrates (e.g., starch, cellulose).
- **Compatibility:** Ensure that the selected encapsulation material is compatible with the phytochemical to prevent chemical interactions that may compromise stability.

3. Processing Methods:

- **Emulsification and Spray Drying:** Techniques like emulsification and spray drying can be used to encapsulate phytochemicals. The process parameters, such as temperature and pressure, should be optimized to minimize degradation during encapsulation.
- **Microencapsulation:** This method involves coating individual particles of the phytochemical with a protective material. It can provide enhanced stability by preventing direct contact with external factors.

4. Packaging:

- **Light-Blocking Packaging:** Use opaque or UV-resistant packaging materials to protect encapsulated phytochemicals from light exposure, which can trigger degradation.
- **Airtight Sealing:** Ensure that the packaging is airtight to prevent oxygen ingress, which can lead to oxidation.

5. Storage Conditions:

- **Temperature and Humidity:** Store encapsulated phytochemicals at appropriate temperatures and humidity levels. Refrigeration or freezer storage may be necessary for some sensitive compounds.
- **Avoidance of Moisture:** Moisture can cause clumping and deterioration of the encapsulated product. Use desiccants or moisture-absorbing packets in the packaging if necessary.

6. Quality Control:

- **Regular Testing:** Perform regular stability testing, including assays for phytochemical content, encapsulation efficiency, and degradation products. This helps in monitoring shelf life and ensuring product quality.
- **Accelerated Stability Studies:** Conduct accelerated stability studies under controlled conditions to estimate the shelf life of the product over a shorter time frame.

7. Regulatory Compliance:

- **Labeling and Claims:** Ensure that any claims regarding the stability and shelf life of the encapsulated phytochemicals comply with regulatory guidelines and are supported by scientific evidence.

8. Packaging Size:

- **Consider Packaging Sizes:** Offering encapsulated phytochemicals in various packaging sizes can help consumers use the product within its recommended shelf life, reducing waste and ensuring freshness.

In conclusion, stability and shelf-life considerations are critical for phytochemical encapsulation to maintain the efficacy and quality of these bioactive compounds. Proper selection of encapsulation materials, processing methods, packaging, storage conditions, and quality control measures are all vital to achieving long-lasting and effective encapsulated phytochemical products. Meeting these considerations can result in products that provide consistent benefits to consumers while minimizing waste and product degradation.

3.3. Polymer-Based Formulations (Ripoli *et al.*, 2016; Mishra *et al.*, 2018)

- **Polymer selection and biocompatibility.**

Polymer selection and biocompatibility play a crucial role in the encapsulation of phytochemicals for various applications in pharmaceuticals, food, and cosmetics. Encapsulation is a process in which bioactive compounds, such as phytochemicals derived from plants, are enclosed within a protective shell or matrix to improve stability, controlled release, and bioavailability. The choice of polymers for this purpose is a critical factor in ensuring the safety and effectiveness of the encapsulation process, especially when the ultimate goal is to use these encapsulated phytochemicals in human or animal applications.

The considerations for polymer selection and biocompatibility in phytochemical encapsulation [Mohsen *et al.*, 2017; Mehnert *et al.*, 2001; Mekjaruskul *et al.*, 2013; Hu *et al.*, 2016]:

1. Polymer Selection:

- Biodegradability:** Biodegradable polymers are preferred for encapsulation because they can be broken down into non-toxic byproducts, reducing environmental impact and potential harm when used in medical or food applications.
- Encapsulation Efficiency:** The selected polymer should have the ability to efficiently encapsulate phytochemicals while maintaining their stability and bioactivity. The polymer should form a protective barrier that prevents degradation of the encapsulated compounds.
- Controlled Release:** Some applications, like drug delivery, require controlled release of phytochemicals over time. Polymers with tunable release properties can be chosen to achieve this.
- Compatibility with Phytochemicals:** The polymer should be compatible with the specific phytochemicals being encapsulated. Some phytochemicals may interact with certain polymers, leading to degradation or loss of bioactivity. Compatibility testing is essential.
- Solubility:** The solubility of the polymer in the encapsulation medium (e.g., water, organic solvents) should be considered. Proper solubility ensures uniform distribution of the phytochemicals during the encapsulation process.
- Mechanical Strength:** Depending on the intended application, the polymer should have adequate mechanical strength to protect the phytochemicals during processing, storage, and release.

2. Biocompatibility:

- Cytotoxicity:** In medical applications, it's crucial to ensure that the selected polymer is non-cytotoxic. Cell culture tests can assess the impact of the polymer on cell viability and function.
- Immunogenicity:** Polymers should not trigger an immune response in the body, which can lead to adverse reactions. This is particularly important in drug delivery systems.
- Allergenicity:** Some polymers may contain allergenic components that could lead to allergic reactions in individuals. Allergenicity testing is essential, especially for food and pharmaceutical applications.
- Toxicological Assessment:** Comprehensive toxicological studies should be conducted to evaluate the safety of the polymer when it comes into contact with biological systems. This includes acute and chronic toxicity testing.
- Regulatory Compliance:** Depending on the application and region, there may be specific regulatory requirements for biocompatibility and safety assessments. Compliance with these regulations is critical.
- Long-term Effects:** For chronic or extended-release applications, long-term biocompatibility should be assessed to ensure that the encapsulated phytochemicals do not cause adverse effects over time.

Polymer selection and biocompatibility are vital considerations in the encapsulation of phytochemicals for various applications. The choice of a suitable polymer should be based on its biodegradability, compatibility with phytochemicals, controlled release properties, and mechanical strength. Biocompatibility testing is essential to ensure that the encapsulated phytochemicals can be safely used in pharmaceuticals, food products, or other applications where they come into contact with biological systems. Proper evaluation and adherence to regulatory requirements are essential to ensure the safety and efficacy of the encapsulated phytochemicals.

- **Conjugation strategies for phytochemicals** [Jain *et al.*, 2013; Ding *et al.*, 2015; Bagade *et al.*, 2014; Adhikari *et al.*, 2015].

Conjugation strategies for phytochemicals refer to the chemical modifications or transformations that naturally occurring plant compounds undergo within plants or during the extraction and processing of

plant materials. These strategies can significantly impact the biological activity, bioavailability, and stability of phytochemicals, which are secondary metabolites produced by plants for various ecological and physiological purposes. Understanding these conjugation strategies is crucial for pharmacologists, chemists, and researchers interested in harnessing the therapeutic potential of phytochemicals for human health.

Here is an in-depth exploration of some key conjugation strategies for phytochemicals:

1. Glycosylation:

Description: Glycosylation is one of the most common conjugation strategies in plants. It involves the attachment of one or more sugar molecules (e.g., glucose, rhamnose, or glucuronic acid) to the phytochemical molecule, forming glycosides.

Importance: Glycosylation enhances the water solubility of phytochemicals, making them more suitable for transport within the plant and potentially improving their bioavailability to humans. It can also serve as a storage form of phytochemicals.

Examples: Quercetin-3-glucoside, found in onions and apples, is a glycosylated form of the flavonoid quercetin.

2. Methylation:

Description: Methylation involves the addition of a methyl group (CH₃) to a phytochemical compound. This modification can occur in various functional groups, such as hydroxyl or amino groups.

Importance: Methylation can alter the bioactivity and pharmacokinetics of phytochemicals. It often results in increased stability and reduced reactivity, which may affect their interaction with enzymes and receptors.

Examples: Methylation can transform the phytochemical resveratrol into pterostilbene, which exhibits improved bioavailability and stability.

3. Acylation:

Description: Acylation involves the attachment of an acyl group (e.g., acetyl, malonyl) to a phytochemical molecule, typically through an ester linkage.

Importance: Acylation can affect the lipophilicity and bioactivity of phytochemicals. It may also contribute to the storage and transport of these compounds.

Examples: Curcumin, a well-known phytochemical from turmeric, can undergo acylation to form curcuminglucuronide, increasing its water solubility.

4. Sulfation:

Description: Sulfation entails the addition of a sulfate group (SO₄) to a phytochemical molecule, often through the action of sulfotransferase enzymes.

Importance: Sulfation can enhance the water solubility of phytochemicals and influence their interactions with enzymes and transport proteins in the body.

Examples: Sulforaphane, a sulfur-containing phytochemical found in broccoli, is formed from its precursor glucoraphanin through enzymatic sulfation.

5. Glutathionylation:

Description: Glutathionylation is the conjugation of a glutathione molecule to a phytochemical, often through a thioether linkage.

Importance: This conjugation strategy can modulate the antioxidant activity and detoxification potential of phytochemicals. It is particularly relevant in the context of phytochemicals' role in protecting plants from oxidative stress.

Examples: Glutathione can conjugate with quinones, such as those found in tea polyphenols, to form more stable and less reactive compounds.

These conjugation strategies are not mutually exclusive, and a single phytochemical can undergo multiple modifications simultaneously or sequentially. The resulting diversity of phytochemical forms contributes to the complex pharmacological and health-promoting effects associated with plant-based diets and herbal medicines. Researchers continue to investigate these strategies to optimize the bioactivity and bioavailability of phytochemicals for therapeutic applications in humans.

- **Tuning release kinetics for controlled delivery** [Altamimi et al., 2021; Deshmukh et al., 2021; Ferreira-Silva et al., 2022].

Controlled delivery of phytochemicals, which are bioactive compounds found in plants, is a critical aspect of pharmaceutical and biomedical research. These compounds have shown great potential in various therapeutic applications, such as treating chronic diseases, cancer, and inflammation. However, their effective utilization often depends on the

precise control of release kinetics to ensure optimal therapeutic outcomes. This article explores the strategies and methods for tuning release kinetics when delivering phytochemicals for therapeutic purposes.

1. Understanding Release Kinetics:

To effectively control the delivery of phytochemicals, it's essential to comprehend release kinetics. Release kinetics refers to the rate and pattern at which a substance is released from a delivery system, such as nanoparticles, microcapsules, or hydrogels, into the surrounding environment. Key parameters include release rate, release duration, and release profile (e.g., zero-order, first-order, or burst release).

2. Selection of Delivery Systems:

Choosing an appropriate delivery system is the first step in tuning release kinetics. Various systems are available, including nanoparticles, liposomes, microspheres, and hydrogels. The choice depends on the physicochemical properties of the phytochemicals, the desired release profile, and the target tissue or organ.

3. Encapsulation Techniques:

The encapsulation of phytochemicals within delivery systems can significantly impact release kinetics. Different encapsulation techniques like coacervation, solvent evaporation, or emulsification can be employed to control the loading capacity and release behavior.

4. Matrix Composition:

The composition of the delivery system matrix plays a crucial role in controlling release kinetics. Altering the matrix's polymer type, concentration, or crosslinking density can modulate the release rate. For example, increasing crosslinking in hydrogels can lead to slower release.

5. Size and Surface Properties:

The size and surface properties of the delivery system can influence release kinetics. Smaller particles generally exhibit faster release due to their larger surface area-to-volume ratio. Surface modifications, such as coating with polymers or lipid layers, can further control release rates.

6. pH and Temperature Sensitivity:

Some delivery systems are designed to be pH or temperature-sensitive. They release phytochemicals in response to changes in environmental conditions. For instance, pH-sensitive nanoparticles can release their payload selectively in acidic tumor microenvironments.

7. Drug Loading and Release Mechanisms:

Understanding the mechanisms of drug loading and release is crucial. Different phytochemicals may interact differently with the delivery system. Some phytochemicals may be encapsulated within the matrix, while others may adsorb or chemically bind to the system, affecting release kinetics.

8. Surface Modifications and Functionalization:

Surface modifications can be used to fine-tune release kinetics. Functional groups or ligands can be added to the delivery system's surface to influence interactions with the surrounding environment and control the release behavior.

9. In vitro and In vivo Testing:

Rigorous in vitro and in vivo testing is essential to evaluate and validate the tuned release kinetics. This test helps determine whether the delivery system effectively delivers phytochemicals to the target site and achieves the desired therapeutic outcomes.

10. Tailored Release Profiles:

The choice of release kinetics should be tailored to the specific therapeutic application. For instance, sustained release may be preferred for chronic conditions, while burst release may be necessary for immediate symptom relief.

The controlled delivery of phytochemicals is a multifaceted process that requires careful consideration of various factors to tune release kinetics effectively. The selection of appropriate delivery systems, encapsulation techniques, matrix composition, and surface modifications are all critical aspects of achieving the desired therapeutic effects while minimizing side effects. Continuous research in this field is essential to harness the full potential of phytochemicals in healthcare and medicine.

4. CHARACTERIZATION AND EVALUATION (Elena *et al.*, 2022; Hussein *et al.*, 2021; Li *et al.*, 2021; Mahadev *et al.*, 2022; Xu *et al.*, 2013)

4.1. Physicochemical Characterization

The physicochemical characterization of nano phytochemicals is a crucial aspect of nanotechnology-based research, particularly in the fields of pharmaceuticals, food science, and materials science. Nano phytochemicals refer to nanoparticles or nanoscale delivery systems that encapsulate or

incorporate phytochemical compounds derived from plants. These phytochemicals often have therapeutic or functional properties, and their nanoscale formulation can enhance their bioavailability, stability, and targeted delivery. To understand and harness the potential of these nano phytochemicals, a comprehensive physicochemical characterization is essential. This characterization involves a range of techniques and analyses to evaluate various aspects of the nanoparticles, including their size, shape, surface charge, stability, and drug release profiles. Here's an in-depth exploration of the physicochemical characterization methods for nano phytochemicals:

1. Particle Size Analysis:

- **Dynamic Light Scattering (DLS):** DLS measures the hydrodynamic size of nanoparticles in solution. It provides information about the size distribution and the presence of aggregates or agglomerates.
- **Scanning Electron Microscopy (SEM):** SEM is used to visualize the external morphology and size of nano phytochemicals. It offers high-resolution images of individual nanoparticles.
- **Transmission Electron Microscopy (TEM):** TEM provides detailed information about the internal structure and size of nanoparticles. It is especially useful for characterizing core-shell nanoparticles and assessing their crystallinity.

2. Surface Charge (Zeta Potential):

- **Zeta potential measurement:** This analysis determines the surface charge of nanoparticles. It is crucial for understanding the stability and colloidal behavior of nano phytochemicals. A higher absolute zeta potential indicates better stability due to electrostatic repulsion.

3. Structural Analysis:

- **X-ray Diffraction (XRD):** XRD is employed to study the crystalline structure of nanoparticles. It helps in identifying the crystalline phases present in the nano phytochemicals.
- **Fourier-Transform Infrared Spectroscopy (FTIR):** FTIR can identify chemical functional groups and assess the interaction between the phytochemicals and nanoparticle carriers.

4. Morphology and Surface Area:

- **BET Surface Area Analysis:** The Brunauer-Emmett-Teller (BET) method measures the specific surface area of nanoparticles, which is crucial for drug loading and release.

5. Stability Studies:

- **Stability Testing:** Stability studies involve monitoring the physical and chemical stability of nano phytochemicals over time, including factors like temperature, pH, and exposure to light.

6. Drug Release Profile:

- **In vitro Drug Release Studies:** These experiments assess how efficiently the nano phytochemicals release their cargo, such as phytochemicals, drugs, or bioactive compounds. It helps determine their potential as drug delivery systems.

7. Biocompatibility and Toxicity:

- **Cell Viability Assays:** Evaluating the cytotoxicity and biocompatibility of nano phytochemicals is essential for their safe use. Cell-based assays, such as MTT or AlamarBlue assays, can provide insights into their potential toxicity.

8. In Vivo Studies:

- **Animal Studies:** In vivo experiments are necessary to understand the pharmacokinetics, biodistribution, and therapeutic efficacy of nano phytochemicals. Techniques like in vivo imaging can track nanoparticle behavior in living organisms.

9. Surface Modification:

- **Surface Functionalization Analysis:** If surface modifications are employed to enhance targeting or drug release, their effectiveness and stability should be characterized using techniques like FTIR or XPS (X-ray photoelectron spectroscopy).

The physicochemical characterization of nano phytochemicals is a multidimensional process that encompasses various analytical techniques. This comprehensive approach is essential to designing and optimizing nano-delivery systems, ensuring their safety, efficacy, and successful application in pharmaceuticals, food science, and materials science. Researchers must adapt their characterization methods to the specific properties and objectives of the nano-phytochemical system under investigation.

4.2. *In vitro* Studies [Bagade et al., 2014; Ceramella et al., 2021; Halevas et al., 2022; Hussein et al., 2021; Marques et al., 2021; Nagi et al., 2017]

In vitro studies for nano phytochemicals involve the investigation of the potential health benefits, biological activities, and safety profiles of phytochemicals

when formulated into nanoparticles. Phytochemicals are bioactive compounds found in plants that have been studied extensively for their therapeutic properties, including antioxidant, anti-inflammatory, anticancer, and antimicrobial effects. Nanoformulation of these phytochemicals can enhance their bioavailability, stability, and efficacy, making them a promising area of research for various applications in medicine and nutrition.

Here is a detailed overview of *in vitro* studies for nano phytochemicals:

1. Phytochemical Selection:

- *In vitro* studies typically begin with the selection of specific phytochemicals based on their known bioactivity and potential applications.
- Common phytochemicals include polyphenols (e.g., curcumin, resveratrol, quercetin), alkaloids (e.g., berberine), terpenoids (e.g., carotenoids), and flavonoids (e.g., catechins).

2. Nanoformulation:

- Nanoformulation involves the encapsulation of phytochemicals within nanoparticles, which can be composed of various materials such as lipids, polymers, or metals.
- Techniques like nanoprecipitation, emulsification, and solvent evaporation are used to prepare these nanoparticles.
- Nanoformulation improves the solubility, stability, and bioavailability of phytochemicals.

3. Characterization of Nanoparticles:

- The physical and chemical properties of the nanoparticles are thoroughly characterized *in vitro*. This includes size distribution, surface charge, morphology, and drug loading capacity.
- Advanced techniques like dynamic light scattering (DLS), transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FTIR) are commonly employed.

4. Release Kinetics:

- *In vitro* studies assess the release kinetics of phytochemicals from nanoparticles over time. This helps in understanding the controlled release behavior of the nanoformulation.
- Different release profiles (e.g., burst release or sustained release) can be observed depending on the nanoparticle composition and design.

5. Bioactivity Assessment:

- *In vitro* bioactivity assays are conducted to evaluate the functional properties of nano phytochemicals. These assays can include:

- Antioxidant activity assays (e.g., DPPH scavenging, FRAP assay)
- Anti-inflammatory assays (e.g., inhibition of pro-inflammatory cytokines)
- Antimicrobial assays (e.g., MIC/MBC determination)
- Cytotoxicity assays on cancer cell lines

6. Cellular Uptake Studies:

- *In vitro* cell culture experiments are conducted to examine the cellular uptake and intracellular localization of nano phytochemicals using techniques like fluorescence microscopy and flow cytometry.
- Understanding cellular uptake is crucial for assessing the potential therapeutic effects of the nanoformulation.

7. Mechanistic Studies:

- Researchers investigate the underlying mechanisms of action of nano phytochemicals using various molecular and cellular biology techniques.
- This can include the analysis of gene expression, signaling pathways, and protein-protein interactions.

8. Toxicity Assessment:

- Safety evaluations are conducted to assess the cytotoxicity and genotoxicity of nano phytochemicals. This is essential for determining their safety profiles.
- Common assays include the MTT assay, LDH release assay, and comet assay.

9. Stability Studies:

- Nano phytochemical formulations are subjected to stability studies under different conditions (e.g., temperature, pH) to determine their shelf life and potential for degradation.

10. Future Applications:

– *In vitro* studies serve as a foundation for advancing nano phytochemical research towards *in vivo* studies and clinical trials. – Potential applications include drug delivery systems, functional foods, nutraceuticals, and cosmeceuticals.

In vitro studies for nano phytochemicals play a crucial role in bridging the gap between laboratory research and practical applications, providing valuable insights into their bioactivity, safety, and potential benefits for human health. These studies contribute to the development of innovative strategies for utilizing phytochemicals in a wide range of therapeutic and nutritional products illustrated in Fig. 5 [Ochi *et al.*, 2016; Renault-Mahieux *et al.*, 2021; Tian *et al.*, 2021].

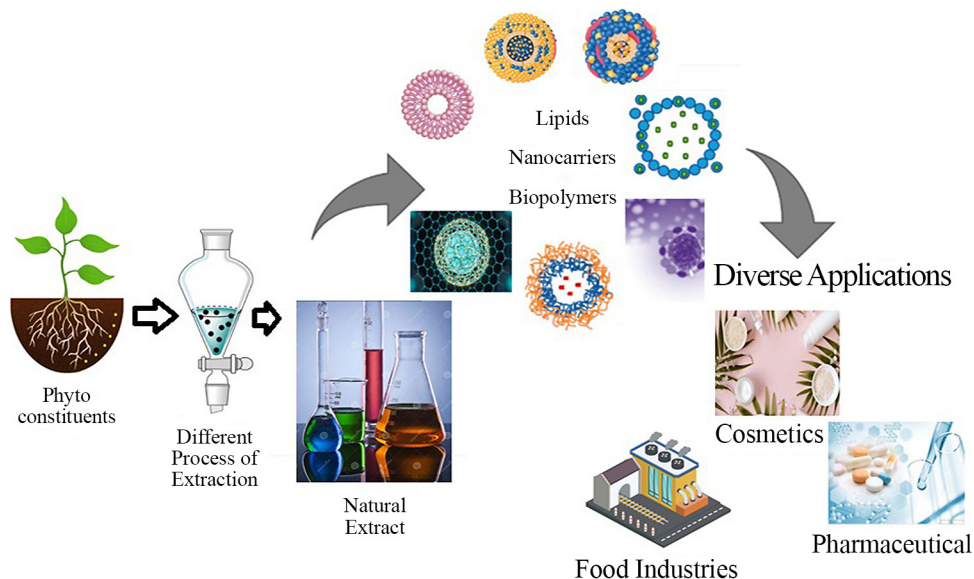


Figure 5. Various applications of phytotherapeutics through nanomedicines.

4.3. In vivo Studies [Wu et al., 2006; Sakat et al., 2022; Mishra et al., 2018; Li et al., 2021]

In vivo studies for nano phytochemicals involve the investigation of the biological effects, safety, and pharmacokinetics of phytochemicals that have been encapsulated or incorporated into nano-sized carriers. These studies are essential to understanding how these nanoparticles interact with living organisms, their biodistribution, and their potential therapeutic applications. The key aspects and methodologies involved in conducting *in vivo* studies for nano phytochemicals are Lipid and polymer-based Nano-phytotherapeutics are a promising category of drug delivery systems that combine the benefits of nanotechnology, lipids, and polymers to enhance the delivery and bioavailability of phytotherapeutic agents. Phytotherapeutics, also known as phytochemicals or natural compounds, are bioactive molecules derived from plants that have therapeutic properties. These compounds include flavonoids, alkaloids, terpenoids, and polyphenols, among others. Incorporating them into lipid and polymer-based nanocarriers can overcome many challenges associated with their poor solubility, stability, and bioavailability, thus improving their therapeutic potential.

1. Nanotechnology in Drug Delivery:

Nanotechnology involves manipulating materials at the nanoscale, typically ranging from 1 to 100

nanometers. In drug delivery, nanocarriers are used to encapsulate and transport therapeutic agents to specific targets in the body.

Nano-phytotherapeutics utilize nanoparticles made of lipids and/or polymers as carriers for phytochemicals.

These nanoparticles offer several advantages [29-34]:

- Increased solubility:** Poor solubility is a common issue with many phytochemicals. Nano-phytotherapeutics enhance solubility, ensuring better absorption and bioavailability.
- Controlled release:** Nanoparticles can provide sustained or controlled release of phytochemicals, leading to prolonged therapeutic effects and reduced dosing frequency.
- Targeted delivery:** Functionalization of nanoparticles allows for targeted drug delivery to specific tissues, cells, or organs, minimizing off-target effects.
- Protection:** Nano-phytotherapeutics can protect phytochemicals from degradation, oxidation, and enzymatic breakdown, enhancing their stability.

2. Lipid-Based Nano-phytotherapeutics :

It includes nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), and liposomes, and these transporters encompass lipids, which are biocompatible and mimic the body’s natural membranes. Lipid-based Nano-phytotherapeutics can encapsulate hydrophobic phytochemicals within their lipid bilayers or cores. Lipid-based carriers

can also be surface-modified with ligands or antibodies to achieve active targeting of specific cells or tissues.

3. Polymer-Based Nano-phytotherapeutics:

Polymer-based nanoparticles are typically made from biodegradable and biocompatible polymers such as polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), and chitosan. This encapsulates both hydrophobic and hydrophilic phytochemicals within their polymeric matrix. Polymer-based carriers offer tunable properties, allowing control over drug release rates, particle size, and surface characteristics.

4. Applications:

Nano-phytotherapeutics find applications in various therapeutic areas, including cancer therapy, cardiovascular diseases, neurodegenerative disorders, and inflammatory conditions. They can improve the therapeutic index of phytochemicals by reducing side effects and enhancing the therapeutic effect. Nano-phytotherapeutics have potential in personalized medicine, where treatments can be tailored to an individual's genetic and physiological characteristics.

5. Challenges and Future Directions:

Despite their promise, Nano-phytotherapeutics face challenges related to scale-up, manufacturing, and regulatory approval. Ensuring the long-term safety and biocompatibility of these nanoparticles is critical. Continued research is needed to optimize formulation, drug loading, and targeting strategies for specific diseases as follows [40-43].

1. Selection of Nano Carrier Systems:

- Researchers choose appropriate nanocarriers, such as liposomes, nanoparticles, micelles, or nanofibers, to encapsulate or deliver phytochemicals.
- The choice of nanocarrier depends on factors like the physicochemical properties of the phytochemical, its intended target, and the desired route of administration.

2. Dosing and Administration:

- Establishing the optimal dosage is crucial, as nano phytochemicals may exhibit different pharmacokinetics and bioavailability compared to free phytochemicals.
- Researchers administer the nano phytochemicals through various routes, including oral, intravenous, intraperitoneal, or topical, depending on the research objectives.

3. Biodistribution Studies:

- Determine how the nano phytochemicals are distributed in various tissues and organs within the body over time.
- Techniques like fluorescence imaging, radioisotope labeling, or mass spectrometry help track the nanoparticles' movement.

4. Pharmacokinetic Analysis:

- Measure the absorption, distribution, metabolism, and excretion (ADME) of the nano phytochemicals.
- Quantify plasma concentrations and calculate parameters like half-life, clearance, and area under the curve (AUC).

5. Toxicity Assessment:

- Evaluate the safety profile of nano phytochemicals by conducting acute and chronic toxicity studies.
- Assess potential adverse effects on vital organs and tissues.

6. Efficacy and Therapeutic Evaluation:

- Investigate the therapeutic effects of nano phytochemicals in animal models or, eventually, in human clinical trials.
- Determine the efficacy in terms of disease prevention, symptom relief, or other relevant endpoints.

7. Immunological and Inflammatory Responses:

- Assess the impact of nano phytochemicals on the immune system.
- Examine cytokine levels, immune cell profiles, and inflammatory markers to understand potential immunomodulatory effects.

8. Long-term Studies:

- Investigate the chronic effects and long-term safety of nano phytochemicals, especially when considering extended therapeutic use.

9. Nanoparticle Characterization:

- Continuously monitor the physicochemical properties of the nanoparticles to ensure stability and consistency during in vivo studies.

10. Data Analysis and Interpretation:

- Analyze the collected data using statistical methods to draw meaningful conclusions.
- Compare the results with appropriate controls and reference standards.

11. Ethical Considerations:

- Ensure that all in vivo studies involving animals or humans adhere to ethical guidelines and regulations, including obtaining informed consent and animal welfare protocols.

In vivo studies for nano phytochemicals play a vital role in bridging the gap between laboratory research and clinical applications. They provide valuable insights into the safety, efficacy, and mechanisms of action of these novel delivery systems, ultimately paving the way for the development of innovative therapeutic strategies and products.

5. APPLICATIONS IN MODERN MEDICINE

Lipid and polymer-based nano phytochemicals have gained significant attention in modern medicine due to their potential applications in drug delivery, diagnostics, and therapeutics. These nanosystems combine the unique properties of phytochemicals derived from plants with the benefits of nanotechnology to enhance the efficacy, bioavailability, and targeted delivery of drugs. Below are some detailed applications of lipid and polymer-based nano phytochemicals in modern medicine:

Drug Delivery Systems [Komath et al., 2018; Huang et al., 2022; Bagade et al., 2014]:

Enhanced Bioavailability: Lipid and polymer-based nanoparticles can encapsulate phytochemicals, protecting them from degradation in the gastrointestinal tract and improving their bioavailability. This is particularly beneficial for poorly soluble phytochemicals.

Sustained Release: Nano phytochemical delivery systems can provide sustained and controlled release of active compounds, ensuring a prolonged therapeutic effect and reduced dosing frequency.

Cancer Therapy:

Targeted Drug Delivery: Nanoparticles can be engineered to target cancer cells specifically, minimizing damage to healthy tissues. Phytochemicals like curcumin and resveratrol, when encapsulated in nanoparticles, have shown promising anticancer properties.

Combination Therapy: Lipid and polymer-based nanocarriers enable the co-delivery of multiple phytochemicals or drugs for a synergistic effect in cancer treatment.

Anti-Inflammatory Applications:

Reduced Side Effects: Nanophytochemicals can mitigate the side effects associated with chronic anti-inflammatory drug use by delivering active compounds directly to the affected tissues.

Improved Efficacy: Phytochemicals such as quercetin and catechins have anti-inflammatory properties and can be more effective when delivered via nanoparticles.

Neurological Disorders:

Blood-Brain Barrier Crossing: Lipid and polymer-based nanoparticles can facilitate the delivery of phytochemicals to the brain by crossing the blood-brain barrier. This is valuable in the treatment of neurodegenerative diseases like Alzheimer's and Parkinson's.

Antioxidant Protection: Phytochemicals with antioxidant properties, such as curcumin and EGCG, can be encapsulated in nanosystems to protect neurons from oxidative stress.

Cardiovascular Health:

Cholesterol Management: Nano phytochemicals can target lipid-lowering agents like phytosterols to reduce cholesterol levels, promoting cardiovascular health.

Antithrombotic Effects: Certain phytochemicals like resveratrol can be used in nanoparticles to prevent blood clot formation and reduce the risk of cardiovascular events.

Diabetes Management:

Blood Glucose Control: Nano phytochemicals containing compounds like berberine or bitter melon extract can help regulate blood sugar levels in diabetic patients.

Insulin Sensitization: Some phytochemicals can enhance insulin sensitivity when delivered in nanoparticle form.

Diagnostics:

Biosensors: Polymer-based nanoparticles can be functionalized with phytochemicals to create biosensors for the early detection of diseases. These nanoparticles can bind to specific biomarkers, facilitating the diagnosis of conditions like cancer or infectious diseases.

Wound Healing:

Topical Applications: Lipid and polymer-based nanoparticles loaded with phytochemicals like aloe vera or calendula can promote wound healing and tissue regeneration when applied topically.

Anti-Microbial Applications:

Infection Control: Nano phytochemicals can be used as antimicrobial agents against drug-resistant bacteria and fungi, offering an alternative to conventional antibiotics.

Nutraceuticals:

Enhanced Nutrient Absorption: Lipid-based nanosystems can be employed to encapsulate

phytochemicals and enhance their absorption in the gut, making them more effective as nutraceuticals.

The lipid and polymer-based nano phytochemicals have a wide range of applications in modern medicine, ranging from drug delivery systems and cancer therapy to neuroprotection and diagnostics. These advanced nanosystems have the potential to revolutionize the field of medicine by improving the efficacy and safety of phytochemical-based treatments while reducing side effects and increasing patient compliance. However, further research and clinical studies are necessary to fully unlock their potential and ensure their safety and efficacy in clinical practice.

6. FUTURE PERSPECTIVES AND CHALLENGES

Lipid and polymer-based nano phytochemicals represent a promising frontier in the field of drug delivery, nutraceuticals, and functional foods. These nanoscale systems offer several advantages, such as enhanced bioavailability, targeted delivery, and improved stability of phytochemicals. However, they also face various challenges that need to be addressed for their successful development and widespread application.

Future Perspectives [Ceramella et al., 2021; Altamimi et al., 2021; Huang et al., 2022]:

- 1. Enhanced Bioavailability:** One of the primary motivations for developing lipid and polymer-based nano phytochemicals is to improve the bioavailability of these compounds. These nanocarriers can protect phytochemicals from degradation in the gastrointestinal tract and facilitate their absorption in the body, potentially leading to increased therapeutic or nutritional benefits.
- 2. Targeted Delivery:** Nano phytochemicals can be designed to target specific tissues or cells, allowing for precision medicine and personalized nutrition. This is particularly relevant for phytochemicals with therapeutic potential in cancer, cardiovascular diseases, and other chronic conditions.
- 3. Combination Therapies:** Researchers are exploring the possibility of encapsulating multiple phytochemicals or combining them with other drugs within the same nanoformulation. This

could lead to synergistic effects and improved therapeutic outcomes.

- 4. Functional Foods:** Nanophytochemicals can be incorporated into functional foods and beverages to enhance their health-promoting properties. This could revolutionize the food industry, providing consumers with convenient and effective ways to improve their diet.
- 5. Biocompatibility and Safety:** The use of biocompatible lipids and polymers ensures the safety of these nanoformulations. Future research will focus on identifying and utilizing materials that are both safe and effective for encapsulating phytochemicals.
- 6. Scale-up and Commercialization:** As research progresses, efforts to scale up the production of lipid and polymer-based nano phytochemicals will be crucial. This involves developing cost-effective manufacturing processes that meet regulatory standards.

Challenges [Komath et al., 2018; Mady et al., 2016; Li et al., 2022; Müller et al., 2000]:

- 1. Formulation Complexity:** Designing nano phytochemicals with the right combination of lipids, polymers, and phytochemicals can be challenging. Achieving the desired physicochemical properties while maintaining stability is a complex task.
- 2. Stability and Shelf-life:** Nanoformulations can be susceptible to stability issues, including particle aggregation, drug leakage, and oxidation of lipids. Ensuring a sufficient shelf-life is essential for commercial viability.
- 3. Regulatory Hurdles:** The regulatory approval process for nano phytochemicals can be lengthy and rigorous. Developers must navigate a complex landscape of safety and efficacy assessments.
- 4. Quality Control:** Maintaining consistent quality and batch-to-batch reproducibility is challenging, especially when working with complex nanostructures.
- 5. Cost-effectiveness:** The production of lipid and polymer-based nano phytochemicals can be costlier than traditional formulations. Finding ways to reduce production costs while maintaining product quality is critical.
- 6. Biological Interactions:** The interactions of nano phytochemicals with the human body are not fully understood. Research into potential long-term effects, immunological responses, and organ-specific accumulation is ongoing.

7. Environmental Impact: The disposal of nano-formulations and their potential environmental impact need consideration. Sustainable production and disposal methods should be explored.

The future of lipid and polymer-based nano phytochemicals holds great promise in various fields, from healthcare to functional foods. However, addressing the challenges related to formulation complexity, stability, regulatory compliance, and cost-effectiveness is essential for realizing this potential. Collaborative efforts between researchers, industries, and regulatory bodies will play a crucial role in advancing these innovative nanoformulations while ensuring their safety and efficacy.

6.1. Emerging Trends [Li et al., 2021; Md et al., 2018; Pavoni et al., 2020; Tian et al., 2021]

A. Personalized Phytochemicals:

Personalized phytochemicals refer to a concept in nutrition and healthcare that involves tailoring the consumption of plant-based compounds, known as phytochemicals, to an individual's specific needs and genetic makeup. Phytochemicals are naturally occurring compounds found in plants that have been shown to have various health benefits, including antioxidant, anti-inflammatory, and anti-cancer properties. Personalizing the intake of these phytochemicals can optimize their therapeutic effects for an individual's unique health profile.

- 1. Understanding Phytochemicals:** Phytochemicals are diverse compounds found in fruits, vegetables, whole grains, nuts, seeds, and herbs. They include flavonoids, carotenoids, phenolic acids, terpenes, and glucosinolates, among others. These compounds contribute to the color, flavor, and disease-fighting properties of plant-based foods.
- 2. Genetic Variation:** Every individual has a unique genetic makeup, which can influence how their body metabolizes and responds to phytochemicals. Genetic variations can impact the absorption, metabolism, and utilization of these compounds.
- 3. Personalized Nutrition and Health:** The concept of personalized phytochemicals aligns with the broader field of personalized nutrition and health. It recognizes that one-size-fits-all dietary recommendations may not be optimal for everyone. Instead, it tailors dietary advice to an individual's genetics, lifestyle, and health goals.

4. Genetic Testing: To implement personalized phytochemical recommendations, individuals may undergo genetic testing. This involves analyzing specific genes related to phytochemical metabolism and response. Genetic testing can identify variations that affect how a person processes phytochemicals.

5. Tailored Dietary Recommendations: Once genetic information is available, healthcare professionals and nutritionists can create personalized dietary plans. These plans may include recommendations on which phytochemical-rich foods are most beneficial for the individual, as well as portion sizes and meal timing.

6. Examples of Personalized Phytochemical Recommendations:

- Sulforaphane:** Individuals with specific genetic variations may be advised to consume more cruciferous vegetables like broccoli and cauliflower, which are rich in sulforaphane, known for its potential anti-cancer properties.
 - Lycopene:** People with certain genetic variants might be encouraged to increase their intake of tomatoes and watermelon, as lycopene may help reduce the risk of certain cancers and cardiovascular diseases.
 - Quercetin:** Individuals with a genetic predisposition to inflammation may be advised to incorporate more onions, apples, and citrus fruits into their diet, as these contain quercetin, which has anti-inflammatory properties.
- 7. Monitoring and Adjustments:** Personalized phytochemical recommendations are not static. Regular monitoring and adjustments may be necessary based on an individual's health progress, changing genetic insights, and evolving dietary preferences.
- 8. Challenges and Considerations:**
- Data Privacy:** Genetic testing raises concerns about data privacy and security, as it involves sensitive information.
 - Cost:** Genetic testing can be expensive, and insurance coverage may vary.
 - Ethical and Cultural Factors:** Recommendations must consider individual preferences, cultural dietary habits, and ethical considerations.
- 9. Future Directions:** As our understanding of genetics and phytochemicals advances, personalized nutrition is likely to become more precise and widely adopted. Emerging technologies, such as AI-driven dietary planning, may play a significant role in making personalized phytochemical recommendations more accessible.

B. Drug Delivery: Lipid and polymer-based nano phytochemicals are being extensively explored for drug delivery systems. They can improve the solubility and targeted delivery of poorly water-soluble phytochemicals, enhancing their therapeutic efficacy.

C. Nutraceuticals and Functional Foods: The incorporation of nano phytochemicals into functional foods and nutraceuticals is on the rise. These products offer health benefits beyond basic nutrition and are gaining popularity among health-conscious consumers.

D. Cosmetics: Nanophytochemicals are being used in cosmetics to enhance the delivery of bioactive compounds into the skin. They can improve the efficacy of anti-aging and skin-care products.

E. Agriculture: Nano phytochemicals are being explored for use in agriculture to improve crop protection and enhance plant growth through targeted delivery of pesticides, nutrients, and plant growth regulators.

6.2. Regulatory Considerations [Zanchetta *et al.*, 2015; Xu *et al.*, 2013; Shtay *et al.*, 2019]

- 1. Safety Assessment:** Regulatory bodies like the FDA and EFSA require comprehensive safety assessments for nano-based products. Toxicological studies and risk assessments are crucial to ensure the safety of these products for human and environmental health.
- 2. Labeling and Claims:** Regulations regarding product labeling and health claims for nano-phytochemical-containing products must be clearly defined to prevent misleading marketing and ensure consumer safety.
- 3. Intellectual Property:** Protecting intellectual property rights is a significant challenge in the rapidly evolving field of nano-phytochemicals. Patents and regulatory exclusivity can play a crucial role in incentivizing innovation.

6.3. Sustainability and Ethical Concerns [Talarico *et al.*, 2021; Hussein *et al.*, 2021; Calligaris *et al.*, 2015]

- 1. Environmental Impact:** The production and disposal of nano phytochemicals may have environmental implications, including the potential release of nanoparticles into the environment.

Sustainable production processes and responsible waste management are essential.

- 2. Resource Usage:** The sourcing of raw materials for lipid and polymer-based nanocarriers should be done sustainably to avoid depleting natural resources and causing habitat destruction.

6.4. Ethical Concerns: [Altamimi *et al.*, 2021; Calligaris *et al.*, 2015; Huang *et al.*, 2022]

- 1. Informed Consent:** Ethical concerns may arise when nano phytochemicals are used in human trials or cosmetics. Informed consent and transparency about the use of nanomaterials in products are essential.
- 2. Equitable Access:** Ensuring equitable access to the benefits of nano phytochemicals is an ethical concern. Efforts should be made to prevent the exploitation of vulnerable populations.
- 3. Transparency and Accountability:** Ethical issues may arise concerning the transparency of research and potential conflicts of interest among researchers and industries. Ensuring accountability and disclosure of financial interests is important.

7. CONCLUSION

The lipid and polymer-based Nano-phytotherapeutics represent a promising frontier in the field of drug delivery and therapeutics. This innovative approach combines the unique properties of lipids and polymers with the therapeutic potential of phytochemicals, leading to a range of advantages that can significantly impact the pharmaceutical industry and healthcare as a whole. First and foremost, lipid and polymer-based Nano-phytotherapeutics offer enhanced solubility and bioavailability for phytochemical compounds. Many bioactive molecules derived from plants, such as curcumin, quercetin, and resveratrol; often suffer from poor water solubility, limiting their clinical utility. The use of lipids and polymers allows for the efficient encapsulation of these compounds, protecting them from degradation and increasing their absorption in the body. This improved solubility is crucial for the effective delivery of phytochemicals to target tissues and cells. Moreover, these Nano-phytotherapeutics can be designed to exhibit controlled and sustained release profiles. By tailoring the composition and structure of the lipid and polymer nanoparticles,

drug release kinetics can be finely tuned, resulting in prolonged therapeutic effects and reduced dosing frequencies. This not only enhances patient compliance but also minimizes side effects and maximizes the overall therapeutic benefit.

Another key advantage of lipid and polymer-based Nano-phytotherapeutics is their ability to provide targeted drug delivery. Functionalization of the nanoparticle surface with ligands or antibodies enables specific binding to disease-associated biomarkers, leading to the accumulation of the therapeutic payload at the site of action while sparing healthy tissues. This targeting strategy can enhance the efficacy of treatment and reduce off-target effects. Furthermore, the safety profile of these Nano-phytotherapeutics is often improved. The encapsulation of phytochemicals within lipid and polymer nanoparticles can shield them from interactions with biological components that may lead to toxicity or adverse reactions. This enhances the overall safety of phytochemical-based therapies, which can be a significant concern in conventional pharmaceutical formulations.

In addition to the therapeutic benefits, the development of lipid and polymer-based Nano-phytotherapeutics aligns well with the growing trend towards natural and plant-based medicine. Consumers and healthcare professionals are increasingly interested in alternative and complementary therapies that leverage the potential of phytochemicals while minimizing synthetic chemical interventions. Nano-phytotherapeutics bridges the gap between traditional herbal remedies and modern pharmaceuticals, offering a harmonious blend of the two approaches.

However, it is essential to acknowledge that challenges and considerations exist in the development and application of lipid and polymer-based Nano-phytotherapeutics. These include the need for rigorous characterization and quality control, potential issues related to long-term stability, and regulatory hurdles. Ongoing research and collaboration among scientists, clinicians, and regulatory agencies are crucial to address these challenges and ensure the safe and effective use of these innovative drug delivery systems.

In conclusion, lipid and polymer-based Nano-phytotherapeutics have immense potential to revolutionize drug delivery and therapeutic strategies. They offer solutions to long-standing issues in the pharmaceutical industry and contribute to the development of more efficient, targeted, and

safe therapies. As research in this field continues to advance, we can expect to see a growing range of Nano-phytotherapeutics entering clinical practice, offering new hope for the treatment of various diseases and conditions.

Conflicts of Interest

There are no competing interests associated with the publication of this review article. ♦

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