

The Role of Phytoconstituents in the development of coating material: A Systematic Review

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ABSTRACT

Phytoconstituents, bioactive compounds derived from plants, are extensively used as coating materials in drug formulations. They play multifaceted roles in Nano formulations, enhancing drug delivery through synthesis, stabilization, and bioactivity. Polysaccharides, proteins, and lipids, are all used to create functional films and coatings with desirable properties. Adding bioactive compounds and antimicrobial agents and employing nanotechnological approaches has improved the functional properties of plant-based materials, extending their shelf life and preserving food quality. Novel strategies have been developed to implement natural biopolymers as drug coating materials. Natural biopolymers have inherent properties such as biodegradability, biocompatibility, and low immunogenicity, and are sensitive to a wide range of physicochemical and biological stimuli. Phytoconstituent-phospholipid complexes (phytosomes) improve bioavailability in drug delivery and enable transdermal penetration of poorly soluble compounds, overcoming skin barrier limitations.

These coating materials provide an excellent film-forming mechanism, act as barriers to oxygen and moisture, while inheriting bioactivities like antimicrobial and antioxidant effects. Plant-based polymers that have “Generally Recognized As Safe” (GRAS) status, particularly those that are pH-responsive (pKa~3.5), provide gastroprotection for nutraceuticals without synthetic additives.

In recent years, significant research has been done into their application as biocompatible smart coatings. This systematic review summarizes the challenges faced while using synthetic polymers and the importance of plant-derived phytoconstituents to overcome the problems of accumulation, low bioavailability, targeted drug delivery, biodegradability, and biocompatibility.

Keywords: Phytoconstituents, targeted drug delivery, coatings, bioactivity.

1. INTRODUCTION

Nanotechnology encompasses the scientific and engineering processes involved in the Drug delivery systems (DDS) are the subject of widespread research and development, aiming to enhance the effectiveness and administration of active pharmaceutical agents, including drugs, vaccines, antibodies, enzymes, peptides, and proteins.¹ These nanoparticles are

designed to specifically target diseased cells, enabling direct treatment of these cells. Nevertheless, this targeted approach enhances treatment effectiveness, minimizes side effects, and improves overall human health. By focusing on the affected cells, this method reduces the adverse effects typically associated with medications. Despite the potential of nanomedicine for treating various diseases, there are several drawbacks related to the use of these Nano drug delivery systems that must be considered.^{1,2} Drugs administered through nanoscale carriers can exhibit distinct behaviours compared to those delivered in traditional forms. For example, when using carriers like poly lactic-co-glycolic acid (PLGA) nanoparticles, the pharmacokinetics and biodistribution of the drugs may change significantly due to cellular uptake and interactions with immune cells. This can lead to improved efficacy and reduced side effects, which depend on the specific delivery system employed. A study has validated this by comparing free drugs and those that are intravenously injected. Poly lactic-co-glycolic acid (PLGA) nanoparticles delivery in rats showed that the uptake of intravenously administered PLGA was significantly lower due to the action of liver Kupffer cells.²

Manipulation of matter at the atomic and molecular scales, generally within dimensions of 1 to 100 nanometers.³ At this nanoscale, materials display unique physical, chemical, and biological properties that are markedly different from those of their larger-scale equivalents. The exceptional traits of nanoscale carriers stem from their higher surface area-to-volume ratio and quantum effects, which can enhance various properties. For instance, these characteristics can improve reactivity, strength, electrical conductivity, and optical properties, ultimately influencing how drugs behave in the body when delivered through these advanced systems. This enhancement not only boosts the effectiveness of the drugs but also minimizes side effects, providing a more targeted therapeutic approach. Physicist Richard Feynman (1959) delivered a lecture titled “There's Plenty of Room at the Bottom”, which was linked to the roots of nanotechnology to propose the concept of manipulating individual atoms and molecules. In 1974, Norio Taniguchi introduced the phrase “nanotechnology” to specify precision machining at the Nanometre scale.⁴

The need for developing a more advanced drug delivery system (DDS) is driven by the limitations of traditional methods, such as emulsions, suspensions, and solutions. These conventional systems face several challenges, including the first-pass effect, instability, intolerance, and fluctuations in plasma drug concentrations. Additionally, they often lack sustained effects and selectivity, while also exhibiting poor bioavailability and necessitating high doses to achieve desired therapeutic outcomes. This highlights the importance of innovating new delivery mechanisms to enhance the effectiveness and safety of drug therapy.⁵ To facilitate targeted delivery and prevent the rapid degradation of drugs or their clearance, a wide range of controlled drug delivery systems has been developed. The significance of utilizing nanoparticles (NPs) as effective drug delivery systems (DDS) for the enhanced bioavailability, controlled and sustained release of medications, a high capacity for drug loading, extended circulation time, improved penetration into cells, and targeted delivery to specific organs or sites. Additionally, NPs offer protection for active ingredients against physiological pH, enzymes, and moisture, and they can be administered through multiple routes, such as parenteral, oral, nasal, and intraocular methods, among others. Green nanotechnology involves the utilization of the twelve principles of green chemistry to create innovative nanomaterials aimed at delivering economic, social, health, and environmental advantages.^{5,6}

The global interest in the study, design, and production of functional bioactive ingredients and pharmaceuticals has reached unprecedented heights. As consumers grow increasingly aware of the vital connection between food, health, and disease prevention, the demand for plant-based bioactive ingredients has soared. Both ancient and modern medicines draw upon the wealth of medicinal plants, which serve as the cornerstone for developing pharmaceuticals, dietary supplements, and essential chemical components found in manufactured medicines. A wealth of clinical and animal studies highlights that regularly incorporating whole grains, fruits, and vegetables into our diets can significantly reduce the risk of diseases linked to oxidative damage. Furthermore, leveraging natural plant compounds in coating materials enhances their functional properties, which highlights the phytochemicals-food industry connection. Plants are essential in promoting human health, enriched in bioactive compounds with proven antioxidant and microbial properties. By integrating these compounds into innovative coating materials, manufacturers can craft packaging solutions that effectively preserve the quality and safety of pharmaceuticals, ensuring they remain effective over extended storage periods.⁸

The primary applications of nanomaterials in medicine and pharmacy encompass diagnostics, regenerative medicine, and therapeutic interventions. In diagnostics, nanomaterials can be utilized as quantum dots for enhanced tissue analysis, extending to the development of multi-modal imaging systems and nanorobots designed for tissue capture. Within regenerative medicine, a focus will be placed on nanotechnologies aimed at skin and motor neuron applications.⁶ In the therapeutic domain, the emphasis will be on the creation of magnetic and paramagnetic nanoparticles, along with nanocarriers that deliver active pharmaceutical ingredients.⁷

This text highlights the diverse range of phytoconstituents and their innovative applications in developing advanced coating materials. This document provides an in-depth analysis of the function of phytoconstituents in nanomedicine as coating materials. It discusses their significance in enhancing bioactivity and bioavailability, besides their applications in targeted, sustained, and controlled drug delivery systems. Phytoconstituents, or compounds derived from plants, show potential for application in pharmaceutical coatings. They provide advantages such as improved stability, regulated release, and serve as natural substitutes for synthetic coatings. Additionally, this review highlights crucial factors, perspectives, and patents

relevant to this field.

2. MATERIAL AND METHODS

The primary review source of our article was a different mode of online database. Keywords “phytoconstituents, ‘drug delivery’, ‘targeted drug delivery’, ‘coating’, and ‘bioactivity’ were utilized in the literature search. Publications are restricted to the last 10 years. The Literature published in the previous five years is reviewed to ensure that the most up-to-date information is included. Most of the literature was scrutinized for the original articles, systematic reviews, meta-analyses, etc. The article was chosen following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.²³

A total of 46 articles were yielded from the different modes of online search engines and were further screened for elimination of duplicates. Screening was rigorously conducted based on topics and abstracts, leading to the information retrieval of 23 eligible articles in full text. Twenty-three articles relevant to the research objective were included after further evaluation.

Ethical Approval

This review article does not contain any studies involving human participants or animals conducted by any of the authors in this review article.

Polymeric Nanoparticles

The adaptability of nanotechnology offers a novel approach to drug delivery, enabling targeted administration of medications to specific sites. Nanoparticles are colloidal entities with sizes ranging from 10 to 1000 nanometers.⁹ Nanospheres feature a matrix structure that encapsulates the active pharmaceutical ingredient (API), while Nano capsules consist of a polymeric membrane that houses the API within its core.^{8,9} These nanoparticles serve as efficient carriers for a diverse array of drugs, encompassing both small molecular weight compounds and larger molecules. There has been a recent heightened focus on the application of nanoparticles in the formulation of herbal drugs. The release mechanisms of drugs from nanoparticles may occur through either bulk erosion of the matrix or surface erosion of the polymer, contingent upon the specific characteristics of the drug and the employed preparation method.¹⁰

Role of Phytoconstituents used as coating materials

Synthesis and Stabilization: Phytoconstituents, such as polysaccharides, flavonoids, and terpenoids, play a pivotal role in reducing metal ions and regulating the growth of nanoparticles (NPs), thereby ensuring a uniform size distribution.

When formulating, the stability of phytoconstituents is a concern as most of them are pH and photosensitive, including polyphenols, terpenoids, flavonoids, proteins, polysaccharides, and vitamins. Thus, considering these inconveniences, it is crucial to address these issues for optimal use of these plant-derived constituents. The compounds that can enhance their efficacy to serve as natural reducing agents, enhancing their stability vital for optimal performance.

The process of transforming metal ions into nanoparticles is achieved through the donation of electrons, enabling production methods that are both environmentally sustainable and energy-efficient, which are non-toxic. This new methodology significantly departs from traditional chemical techniques, making it a better choice for environmentally conscious practices.

For instance, extracts from Aloe-Vera stabilize silver and gold nanoparticles by creating a protective coating that inhibits aggregation. They improve the stability of colloids in biological fluids by repelling proteins and reducing opsonization, which is essential for extended circulation in drug delivery systems.²

Biocompatibility and Bioactivity

Plant-derived coatings, such as cellulose, hemicelluloses, gallic acid, alginate (from algae), chitosan (from fungi), and catechin, can enhance biocompatibility and bioactivity. These biopolymers improve the cytocompatibility of nanoparticles and reduce immunogenicity by mimicking components of the extracellular matrix, which enhances cellular uptake.

Phytoconstituents, including polysaccharides like chitosan and alginate, proteins such as soy protein isolate, and polyphenols like curcumin and phloretin, stand out for their exceptional biocompatibility due to their natural origins and low toxicity levels. These compounds engage beneficially with biological tissues, significantly lowering the risk of adverse immune responses or cytotoxic effects. Notably, coatings featuring chitosan adeptly optimize hydrophilicity to ideal levels (contact angles between 60 and 80 degrees), promoting enhanced cell attachment and proliferation while preserving vital antimicrobial properties. Furthermore, boron nitride coatings infused with phytochemicals showcase outstanding biocompatibility and superior mechanical strength, making them highly suitable for biomedical implants. Choose these innovative materials for safer and more effective medical applications.¹¹

Enhancing Bioavailability

Plant-derived coatings significantly improve the absorption rates of poorly soluble medications. A prime example is

nanophytosomes, which are phospholipid complexes infused with phytoconstituents designed to boost the bioavailability of polyphenols, enabling more effective transdermal and oral delivery. This innovative approach can transform how we enhance drug effectiveness and patient outcomes.^{11,12}

Revolutionizing Drug Delivery

Coatings developed with phytoconstituent ligands, such as lectins, enable targeted therapy, significantly improving drug efficacy while minimizing undesirable side effects that commonly occur from the distribution of drugs in non-target regions.¹³

These innovative coatings actively respond to pH levels and various enzymatic triggers within the body, ensuring a sustained and precise release of encapsulated medications for optimal therapeutic effects.

Table 1: List of Nanoformulations encapsulated with phytoconstituents as coating material.

Nanoformulations	Key Phytoconstituents	Role of phytoconstituents	Reference
Phytosomes	Flavonoids	Chemical conjugation with phospholipids	Alharbi WS <i>et.al.</i> , Phytosomes as an Emerging Nanotechnology Platform for the Topical Delivery of Bioactive Phytochemicals. <i>Pharmaceutics</i> . 2021 Sep 15;13(9):14 ⁷⁵ . doi: 10.3390/pharmaceutics130914 ⁷⁵ . PMID: 345 ⁷⁵⁵⁵¹ ; PMCID: PMC8465302.
Ethosomes	Cellulose	Enhanced permeation via ethanol	
Solid Lipid Nanoparticles	Terpenoid	Encapsulation in lipid matrix	Han HS, Koo SY, Choi KY. Emerging nanoformulation strategies for phytocompounds and applications from drug delivery to phototherapy to imaging. <i>Bioact Mater</i> . 2021 Dec 20;14:182-205. doi: 10.1016/j.bioactmat.2021.11.02 ⁷ . PMID: 35310344; PMCID: PMC8892098.
Mesoporous silica nanoparticles	Quercetin	Biodegradable coating to enhance stability	Dumontel B, Conejo-Rodríguez V, Vallet-Regí M, Manzano M. Natural Biopolymers as Smart Coating Materials of Mesoporous Silica Nanoparticles for Drug Delivery. <i>Pharmaceutics</i> . 2023 Jan 29;15(2):44 ⁷ . doi: 10.3390/pharmaceutics1502044 ⁷ . PMID: 36839 ⁷⁷¹ ; PMCID: PMC9965229.

Colloidal nanoparticles	Trans-resveratrol	Nanoencapsulation of resveratrol, curcumin and quercetin	Goktas Z, Zu Y, Abbasi M, Galyean S, Wu D, Fan Z, Wang S. Recent Advances in Nanoencapsulation of Phytochemicals to Combat Obesity and Its Comorbidities. J Agric Food Chem. 2020 Aug 5;68(31):8119-8131. doi: 10.1021/acs.jafc.0c00131. Epub 2020 Jul 27. PMID: 32633507; PMCID: PMC8507418.
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Advantages and disadvantages of Phytosome technology

Advantages

Enhanced Bioavailability and Absorption

Phytoconstituent-based carriers, such as phytosomes, enhance the solubility and absorption of hydrophobic drugs by forming lipid-compatible complexes, leading to improved bioavailability. For instance, phytosomes promote the transdermal delivery of polyphenols like curcumin, which enhances their therapeutic efficacy.

Improved Stability

Phytosomes are natural polymers that provide exemplary stability for sensitive compounds by protecting them from degradation during storage and within the digestive system. This ensures that consumers receive the maximum potential benefits from the compounds.¹⁵

Biocompatibility and Reduced Toxicity

Biocompatibility denotes the capacity of a material to interact harmoniously with living tissues, avoiding adverse effects such as inflammation, cytotoxicity, or immune rejection. Plant-derived coatings typically exhibit superior biocompatibility compared to synthetic polymers, thereby reducing immunogenicity and the likelihood of adverse reactions. For instance, nanoparticles stabilized with Aloe vera demonstrate considerable reductions in cytotoxicity. Furthermore, coatings derived from apple polyphenols have been found to enhance the biocompatibility of titanium implants by improving cell adhesion and mitigating inflammatory responses.^{15,16}

Natural compounds derived from plants, such as polyphenols, flavonoids, polysaccharides, and proteins, exhibit a high level of biocompatibility due to their biological origins and structural similarities to natural biomolecules.

Coatings based on these phytoconstituents help reduce toxicity, as they circumvent the use of harsh synthetic chemicals and heavy metals that are typically found in conventional coatings. Additionally, many natural phytochemicals demonstrate antioxidant and anti-inflammatory properties, which can alleviate oxidative stress and minimize tissue damage surrounding implants or drug delivery systems. For example, coatings made from choline phosphate have been shown to decrease the degradation rates of zinc alloys, effectively reducing cytotoxicity linked to the excessive release of zinc ions.

Multi-Target Therapeutic Effects

Phytoconstituents such as alkaloids, flavonoids, and terpenoids demonstrate pleiotropic effects by targeting multiple biological pathways. They may contribute to combating multidrug resistance while enhancing the effects of co-administered pharmaceuticals. This synergy can lead to decreased required dosages and reduced toxicity. Additionally, phytochemicals have been observed to work in conjunction with antibiotics to improve efficacy against *Mycobacterium tuberculosis*, potentially lowering drug resistance and associated side effects.¹⁰

Targeted and controlled delivery

Phytoconstituents that enhance drug stability are complexed with phospholipids and allow for sustained, controlled release, which acts as a boost to bioavailability. Additionally, hyaluronic acid derived from plant sources serves as a ligand, facilitating tissue-specific targeting, particularly in cancer cells that overexpress CD44.¹⁷

Coatings like chitosan, known for their high pH sensitivity, facilitate targeted drug release exactly where it's needed in the gastrointestinal tract.¹⁶

Biodegradable and Sustainable

Utilizing phytoconstituents in green synthesis minimizes our dependence on harmful solvents, promoting a more sustainable approach in the pharmaceutical industry.¹²

Reduced toxicity

Phytoconstituent-based coatings effectively minimize toxicity by eliminating the need for harsh synthetic chemicals, which can cause tissue damage around implants or drug delivery systems. Research has demonstrated that choline phosphate coatings are beneficial in this context. For example, these coatings have been shown to decrease the degradation rates of zinc alloys, which helps to reduce cytotoxicity that can arise from excessive release of zinc ions.

3. DISADVANTAGES OF PHYTOCONSTITUENT COATINGS

Standardization challenges

As a pioneering advancement in nutritional science, phytosomes represent a novel approach to enhancing the bioavailability and efficacy of herbal compounds. However, due to their innovative nature, they may encounter significant regulatory challenges and protracted approval processes. These hurdles could lead to delays in their entry into the market, particularly when compared to traditional herbal solutions, which often possess established pathways for approval and commercialization.¹⁸

The uniformity and efficacy of the coating are negatively impacted, making it extremely difficult to achieve consistent results during large-scale industrial production.

Stability issues

Phytoconstituents, including polyphenols and flavonoids, are highly susceptible to oxidative degradation when exposed to heat, light, or moisture, compromising their coating efficacy over time. Degradation of phytoconstituent coatings can occur due to exposure to UV light and other environmental conditions. For instance, research has demonstrated that liposomes coated with polysaccharides may experience a degradation rate of 36% under UV irradiation. Moreover, high-temperature extraction methods, such as decoction, can denature compounds sensitive to heat, further impacting the stability and effectiveness of these phytoconstituents.¹⁰

Complex production and scalability

The presence of phytochemicals in coatings may compromise drug stability and bioavailability. Techniques such as supercritical fluid extraction (SFE) require sophisticated instrumentation and a high-pressure environment, which increases production costs. Furthermore, natural polymer coatings lead to the formation of viscous systems, such as those derived from gums, thereby complicating the manufacturing process.²⁰

Allergic potential

While phytosome formulations offer numerous benefits, it is important to note that some individuals may experience allergic reactions to phospholipids. This emphasizes the necessity for thorough consideration and consultation before use, to ensure its safety and effectiveness.

Limitations of the study

The potential of phytosome technology is truly significant; however, research in this field remains in its developmental stages. It is imperative that more comprehensive studies be conducted to thoroughly validate the safety and efficacy of this technology.

By examining the significant advantages and potential limitations of phytosome technology, stakeholders can gain a deeper understanding of its transformative impact within the pharmaceutical and nutraceutical sectors. This innovative technology enhances the bioavailability and efficacy of active compounds, thereby positioning itself as a critical area of focus for ongoing research and development in these fields.

Future Innovations

Development of multifunctional phytoconstituent coatings with properties like self-healing, antibacterial activity, or UV protection.¹⁹ Integration of recycled content alongside phytoconstituents to enhance sustainability while reducing costs.²¹

Exploration of non-isocyanate routes and energy-curing methods to minimize environmental impact during protection.^{19,22}

4. CONCLUSION

Phytoconstituents as coating materials hold significant promise as sustainable and effective solutions across various industries, owing to their natural origin, biocompatibility, and multifunctional properties. Their ability to improve drug solubility, stability, and targeted delivery addresses key challenges in pharmaceutical and cosmetic formulations, while their

eco-friendly nature aligns with increasing environmental and regulatory demands. Advances in nanotechnology, such as phytosome-based delivery systems, have further enhanced the bioavailability and therapeutic efficacy of phytochemicals by facilitating better penetration through biological barriers and protecting active compounds from degradation. Additionally, phytoconstituents are important from a dermatological perspective. To completely comprehend phytoconstituents' beneficial properties for real-world use, more research is required, as there haven't been many studies done on them yet.

Looking ahead, continued innovation in formulation techniques will be essential to optimize the performance and stability of phytoconstituent coatings. Overcoming challenges related to standardization and scalability will enable broader commercial adoption, while regulatory frameworks are evolving to support the integration of these natural materials into mainstream applications. Moreover, expanding their use beyond pharmaceuticals into food packaging, agriculture, and industrial coatings can leverage their biodegradability and functional versatility, contributing to a more sustainable future.

In essence, the convergence of green chemistry, nanotechnology, and plant-based materials positions phytoconstituents as a transformative platform for next-generation coatings. Their full potential will be realized through interdisciplinary research, technological advancements, and supportive policies that together foster sustainable innovation and improved health outcomes.

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