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Review Article

Navel Nano Carriers for Targeted Delivery of Active Compounds of Medicinal Plants: Advances and Challenges

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Summary

Medicinal plants, owing to their richness in bioactive compounds like flavonoids, alkaloids, and polyphenols, have become very crucial in the fight against diseases and also in health maintenance. Nonetheless, the mentioned drawbacks, such as instability, low solubility, and inefficient targeting of these active substances, have resulted in a huge decline in their therapeutic effectiveness. On the other hand, nanotechnology is said to enhance the optimal utilization of active principles from medicinal plants by providing advanced nanocarriers. The paper discusses the challenges of using medicinal plants and, simultaneously, the need for nanocarriers to overcome these limitations, particularly the introduction of lipid nanocarriers containing resveratrol and methyl gallate for dermatological infections. Moreover, the green synthesis of nanoparticles using medicinal plants offers a method that is both biocompatible and cost-effective for nanoparticle production, thereby improving their efficiency and safety. The application of these nanoparticles has been very successful in the management of inflammatory diseases, cancer, and other chronic disorders. Today, the use of nanocarrier systems (liposomes, polymeric nanoparticles, and protein-based) in conjunction with herbal medicine has become practicable as they enhance the medicinal properties of plant compounds. The developments achieved in this area have not only increased the opportunities of application of herbal remedies in modern medicine but also reduced drug reactions and improved the quality of care. This article has provided the avenues to the answers to the questions of how nanocarriers can be used in the future to enhance the efficacy of herbal extracts, presented the state-of-the-art application of nanocarriers in enhancing the efficacy of herbal extracts, and offered practical solutions to the predicaments that the application presented, thus providing new avenues to future research and application of herbal nanocarriers.

Keywords: Medicinal plants, Nanocarriers, Bioactive compounds

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Introduction

Medicinal plants have long played a part in maintaining human health and treating diseases.[1] By looking at the plant characteristics through observation and testing, humans have been treating diseases with the plants and making their health better for at least thousands of years, according to the historical evidence.[2] The medical texts of ancient times, such as the Greek medical works of Hippocrates, the ayurvedic practice in India, and the Iranian system of healing, are very knowledgeable about the plants that possess many therapeutic properties and thus are very valuable.[3,4] This understanding has been inherited through the centuries and is still a significant aspect of both the modern and the traditional ways of healing in different parts of the globe.[5] The diverse spectrum of diseases that can be prevented and cured using medicinal plants is attributed to their bioactive compounds, which include alkaloids, flavonoids, glycosides, terpenes, phenols, and saponins, etc.[6] For instance, the natural substance called curcumin present in turmeric is a potent anti-inflammatory and antioxidant agent, while aloe vera is proven for its anesthetic action in wounds and anti-inflammatory in skin conditions. The above-mentioned compounds, mostly obtained from the secondary metabolites of plants, produce their therapeutic effects through multifaceted mechanisms like free radical scavenging, immune system boosting, and anti-inflammatory activity.[7] Though medicinal plants provide unmatched value, their use is troubled by a number of issues like biodiversity loss, the use of inefficient methods for extracting the active ingredients, and the environmental limitations imposed on their mass production.[8] Moreover, the quality and effectiveness of the phytochemical compounds are influenced by the growing conditions, soil quality, and climate change. Therefore, these hurdles have drawn attention to the fact that new technologies should be employed to increase the quality,

volume, and eco-friendliness of medicinal plants.[9]

The employment of herbal remedies for the treatment of ailments, as well as for the good maintenance of human health, has been prevalent in the past. The natural products have several roadblocks to their effective utilization.[8] The low stability of the active compounds of medicinal plants is one of the most critical challenges. A lot of these compounds, like flavonoids, alkaloids, and terpenes, are highly responsive to the environmental factors and perish easily in light, oxygen, heat, and pH. The very same sensitivity limits the medicinal potential of these compounds in storage, processing, or even after administration.[10] An illustration is curcumin, which is the active ingredient in turmeric, and is unstable with light and oxygen; due to that, it is quickly degraded, thus, its potency is limited.[9] The low solubility of most active ingredients in water is one of the major drawbacks of using medicinal plants. Since water constitutes the main component of the human biological system, the poorly soluble compounds can't be absorbed effectively, thereby leading to insufficient therapeutic levels not being reached in the body as a result.[11] To illustrate, resveratrol and curcumin, while possessing many biological properties such as antioxidant and anticancer activities, suffer from poor absorption resulting from their low water solubility, which in turn diminishes their effectiveness in curing diseases.[12] Another significant drawback to the usage of medicinal plants is insufficient targeting. A lot of medicinal plant active ingredients, after being absorbed into the body, are disseminated in a non-specific manner all over the body.[13] Such a non-specific distribution can result in reduced therapeutic efficacy, necessitating higher doses and causing undesirable side effects. As an illustration, in the case of cancer therapy, numerous active natural substances like epigallocatechin gallate (EGCG) and Taxol are non-selectively dispersed among healthy and tumorous cells, which in turn diminishes the effectiveness of the treatment and escalates the harm to normal tissues.[7]

The quick metabolism of these compounds in the human body is yet another hurdle in the use of medicinal plants. Active compounds derived from plants are often quickly metabolized and then removed through liver enzymes, which results in their limited effective presence in the body. As an instance, curcumin and catechins undergo fast metabolism and have brief half-lives, which means their application as drugs is limited. Furthermore, poor absorption of most active plant compounds is a further hindrance to the complete utilization of these natural resources.[14] Inasmuch as many plant compounds cannot penetrate the bloodstream and reach the target tissues effectively, this is primarily due to their restricted absorption in the gastrointestinal tract. The issue, in turn, imposes the need for high doses of herbal medicines, as a result of which, simultaneously, there can be an aggravation of side effects. As a matter of fact, the mentioned challenges demand technology, as well as new ways of addressing the shortcomings of medicinal plants. New technologies such as nanocarriers involving modification of the chemical structure of active compounds and the utilization of a ;0otargeted system of drug delivery have the potential to significantly improve the stability, solubility, and accuracy of herbal compounds and, accordingly, expand their application in the treatment of disorders with medicines.[15]

The necessity of using nanocarriers to improve the delivery of active compounds

The necessity of using nanocarriers to improve the delivery of active compounds of medicinal plants stems from the inherent challenges of these compounds. Many active compounds of medicinal plants, despite their remarkable biological properties, have limitations such as low bioavailability, low stability, poor solubility, and lack of effective targeting. The inadequacies mentioned above are the main reasons why the compounds are unable to completely show their healing properties. Nanocarriers, being modern techniques, are the leading innovators that will help in getting rid of these hurdles. One of the most important reasons for using nanocarriers is to improve the bioavailability of active compounds of medicinal

Table 1. A comparison between the advantages, disadvantages, and applications of nanocarriers

Nanocarrier type	Advantage	Disadvantage	Application
Liposomes	Biocompatible and non-toxic- can carry both hydrophilic and lipophilic drugs, surface modification possible for targeting	Physical and chemical instability_ high production cost, risk of rapid drug release	Chemotherapy, vaccines, and drug delivery to the brain and specific tissues
Polymeric nanoparticle	Precise- control of drug release- can load diverse drugs- smart design possible (pH or temperature-sensitive)	Potential- toxicity from synthetic polymers- difficulty in uniform production	Cancer therapy, long – term drug delivery, gene therapy
Solid lipid nanoparticles (SLN)	High –stability, relatively low- cost production, biocompatible	Limited drug loading capacity and potential drug crystallization	Oral and topical drug delivery, cosmetics and personal care, antiviral drugs
Protein-based carriers	Enable theranostics (therapy + diagnostics, high chemical stability, surface modification possible)	Risk of aggregation and cytotoxicity, clearance challenges from the body	Medic: imaging-magnetic hyperthermia, targeted drug delivery to tumors
Inorganic nanoparticles (gold, silica, magnetic, etc.)	Natural and biocompatible- lower toxicity compared to synthetic materials – biodegradable	Lower stability under physiological conditions, industrial-scale production challenges	Protein therapies targeted delivery for chronic diseases

plants.[16] The body lacks the capacity to absorb most of these substances due to poor solubility in water or other body fluids. Nanocarriers that include lipid nanoparticles, biodegradable polymers, and nanoemulsions offer solutions to these substances to make them more soluble as well as to their delivery. The use of this technology increases the absorption and, therefore, the uptake of active substances within the bloodstream. Additionally, nanocarriers can provide the herbal extracts with a higher resistance to degrading environmental factors. As an illustration, nanoparticles can act as a shield for heat, light, or oxygen-sensitive compounds against their breakdown.[9]

This function contributes to the prolongation and effectiveness of these substances, making them more apt for pharmaceutical formulations. Another major benefit of nanocarriers is facilitating the release of active compounds, directly targeting them.[17] Nanocarriers are capable of being engineered to target and transport drug compounds only to predetermined cells or tissues. Such a trait not only amplifies treatment efficiency but also minimizes the possibility of adverse effects in the rest of the body's tissues.[15] The application of nanoparticles harbored with biomolecular ligands can allow selective attachment to the receptors of the target cells. Among the biomolecular ligands utilized in the targeted delivery of nanocarriers are Trastuzumab, used for delivering nanocarriers to the HER2 receptor in breast cancer, RGD peptide, which targets αvβ3 integrin receptors, AS1411 aptamer (the aptamer can attach to the nucleolin receptor found on the surface of tumor cells), hyaluronic acid (HA), which targets CD44 receptors present on the majority of cancer cells and cancer stem cells, and folate that binds to the folate receptors that are upregulated in various cancer cells, especially in ovarian and colorectal cancers.[18]

The capability of nanocarriers to release active agents in a controlled way is one of their major features. This quality allows for control of the total amount and the speed of a drug release in the body, so that at the target point, a certain level of the medicine is present for a longer time. Such a property is very crucial in the case of chronic disorders that need considerable time for drug administration. Last but not least, is that by using nanocarriers, one can also minimize the toxicity and chemical interaction issues of herbal compounds.[15,19] Wrapping active substances in nanocarriers prevents side effects and reactions with other body compounds from taking place. Owing to these characteristics, nanocarriers are considered a necessary instrument for the improvement of the efficacy, stability, and safety of active compounds sourced from medicinal plants and are thus positioned to facilitate new drug development, which is natural resource-based.[15]

Lipid Nanocarriers for Drug Delivery

Lipid nanoparticles are known as one of the most widely used drug delivery systems in various fields of medicine and pharmacy, and play a special role in the delivery of active compounds of herbal medicines.[20] These nanoparticles include diverse lipid structures such as liposomes, solid lipid nanoparticles (SLNs), and emerging lipid nanocarriers (NLCs), which have a high potential to improve the efficacy of herbal medicines due to their unique properties.[16] Active compounds of medicinal plants, such as alkaloids, flavonoids, terpenes, and polyphenols, require advanced systems to improve their delivery and release in the body due to limitations such as low stability, poor solubility, and insufficient targeting. Lipid nanoparticles provide an effective solution to this requirement. The lipid nanoparticles known as liposomes comprise one or several lipid bilayers that can simultaneously contain hydrophilic and hydrophobic compounds. This exceptional architecture not only supports the entrapment of a wide range of medicinal plant compounds but also permits the controlled and targeted delivery of drugs. To illustrate, liposomes with curcumin extract (the active ingredient of turmeric) have been reported to boost the anticancer effect of this compound in laboratory trials with animals.[9]

Solid lipid nanoparticles (SLNs), yet another advanced system, are for the delivery of herbal medicines. The nanoparticles consist of solid lipids, thereby giving the benefits of being physically very stable, controlling the drug release precisely, and having a larger capacity for the drug to be loaded. SLNs have also improved the solubility of some of the poorly water-soluble medicinal plant compounds, like flavonoids and terpenes, and thus, their therapeutic effects are enhanced. For example, the use of SLNs to deliver resveratrol (an active compound in grapes) has shown that its antioxidant and anti-inflammatory properties can be significantly enhanced.[15] Moreover, lipid nanoparticles could be administered through different ways, such as oral, injectable, topical, and inhaled. This characteristic of having several administration routes made it possible for lipid nanoparticles to be used in a wider range of applications, treating various diseases. Lipid nanoparticles with plant essential oils like eugenol (from cloves) have been applied topically for the treatment of skin infections and joint diseases.[21]

Resveratrol is a natural polyphenolic compound found mainly in grapes and other plants. It has attracted attention for its antioxidant, anti-inflammatory, and antimicrobial properties and has great potential for the treatment of skin infections.[15] In a study, a gel containing solid lipid nanoparticles loaded with resveratrol was used to treat chemical-induced irritant contact dermatitis. The developed formulation was designed to improve the penetration of resveratrol into the skin and increase its stability. The results showed that this delivery system helps reduce inflammation, heal wounds, and improve dermatitis symptoms, and can be used as an effective and safe method for the treatment of infections and skin disorders caused by inflammation.[22]

Inflammatory arthritis is a type of joint disease

characterized by inflammation in the joints and can lead to pain, swelling, warmth, stiffness, and decreased joint function. Unlike osteoarthritis, which is more likely to be caused by wear-and-tear damage to the joints, this type of arthritis is caused by abnormal immune system responses or the presence of inflammatory factors in the body.[10] Methyl gallate has been identified as a natural substance coming from plants that demonstrate antioxidant and anti-inflammatory effects. The compound's poor solubility, along with its very low bioavailability, were the main factors preventing effective use of the compound for patients' treatment. By employing nanomicelles as vehicles, scientists have carried out a study to determine the efficiency and enhanced qualities of methyl gallate in suppressing inflammation

Recent Developments and New Technologies

New Wound Dressings: The Synergistic Role of Nanoparticles and Medicinal Plants in Infection Control and Tissue Regeneration

Wound dressings containing antibacterial herbal medicines and silver nanoparticles are an innovative combination for wound healing and prevention of microbial infections. This technology creates a sterile environment suitable for wound healing by utilizing the strong antibacterial properties of silver nanoparticles and active compounds present in herbal medicines. Silver nanoparticles show a strong antimicrobial effect by destroying the bacterial cell membrane, producing reactive oxygen species (ROS), and inhibiting vital microbial enzymes. On the other hand, herbal medicines with their anti-inflammatory, antioxidant, and tissue-repairing properties play an important role in reducing inflammation and wound healing.[23] Wound dressings based on this technology are usually designed as films, hydrogels, or nanocomposites that allow for the controlled release of active ingredients. This feature allows the appropriate concentration of antimicrobial agents to be maintained at the wound site, while also reducing the risk of microbial resistance. The combination of silver nanoparticles and herbal medicines can have a synergistic effect; so that the antibacterial properties of silver nanoparticles are enhanced by the restorative effects of herbal medicines.[24] The use of these wound dressings is very effective in the treatment of chronic wounds such as diabetic ulcers, pressure ulcers, and infected burns. The properties of this technology are particularly specific against antibiotic-resistant strains, such as Staphylococcus and Methicillin-resistant Staphylococcus aureus (MRSA). In addition, these dressings improve the quality of life of patients by reducing pain, accelerating wound closure, and preventing scar formation. The production of these dressings usually involves loading silver nanoparticles and plant extracts into a polymer matrix. The selection of the appropriate polymer (natural or synthetic) improves the mechanical properties, adhesion, and biocompatibility of the dressing. Laboratory and clinical studies of these products show that in addition to reducing microbial counts, they also help reduce healing time. Given the increasing need for basic and safe treatments in the field of wound management, this technology is considered an advanced and efficient option.[25]

Nanocarriers for the Delivery of CRISPR/Cas Complex Components: Application in Genetic Modification of Medicinal Plants

The CRISPR/Cas complex is known as an effective and precise tool for genome editing. This system is able to purposefully cut DNA and make specific changes to it using the cell's repair mechanisms. The main components of the CRISPR complex include gRNA (guide RNA) and the Cas enzyme (such as Cas9), which require effective and safe delivery into plant cells. This is where nanocarriers come in; by providing a safe and efficient method for delivering these components, they can increase the efficiency and accuracy of gene editing. One of the major benefits of genome editing in medicinal plants is the increase in the production of active pharmaceutical ingredients.[26] By editing the genes that control the metabolic pathways for the production of medicinal compounds, the production of these compounds can be increased, and the quality of plants can be improved. For example, in plants such as turmeric, which contains curcumin, genome editing can increase the production of this effective substance and enhance its anti-inflammatory and anticancer effects.[27]

In addition to increasing the production of medicinal compounds, genome editing can improve the resistance of medicinal plants to diseases and harsh environmental conditions.[26] By modifying genes responsible for resistance to pests, drought, soil salinity, or temperature changes, plants can be optimized for growth in adverse environments. This not only increases agricultural yields, but also helps reduce the use of pesticides and chemical fertilizers, which is more environmentally friendly.[28] In recent years, nanocarriers have received much attention for the delivery of CRISPR/Cas9 system components to cells due to their unique properties. These nanoparticles can efficiently and safely deliver sensitive molecules such as Cas9 protein and guide RNAs (gRNAs) to target cells.[29] The main goal of using nanocarriers in the CRISPR/Cas9 system is to overcome the limitations of traditional gene delivery methods, such as particle bombardment or the use of viral vectors, which can have side effects such as toxicity or stimulation of the immune response. Nanoparticles are ideal vehicles for the delivery of CRISPR components due to their small size, tunable surface area, and diverse functional capabilities.[30]

Nanocarriers may consist of several different materials, such as lipid nanoparticles, polymers, carbon nanotubes, silica nanoparticles, and metal nanoparticles, among others. As an illustration, the lipid nanoparticles, including liposomes and solid lipid nanoparticles, are capable of

transferring CRISPR elements to the intended cells very efficiently [31]. Due to their lipid layers, these nanoparticles can interact with cell membranes and facilitate entry into the cell. Polymer nanoparticles such as polyethyleneimine (PEI) can form stable complexes with RNA or DNA due to their positive charge, and protect the molecules from degradation.[32] Another important feature of nanoparticles is the possibility of functionalizing their surface.[30] By modifying the surface of nanoparticles, properties such as specific targeting to specific cells or controlled release can be added to them. For example, the attachment of specific ligands to the surface of nanoparticles can lead to the precise identification of target cells. The use of nanoparticles can also solve the problems associated with entry into difficult cells, such as plant cells or bacteria. The nanoparticles, owing to their minuscule size, can penetrate even the toughest natural barriers, such as the cell wall, and get inside the cell. Furthermore, the use of nanocarriers for transporting CRISPR/Cas9 components not only boosts efficiency and safety but also makes it possible to deliver different molecules at the same time, for example, Cas9 and sgRNA. These characteristics render nanoparticles a formidable weapon in the war of genetic engineering, particularly in the delicate areas of plant genome editing and medical treatments.[33]

Conclusion and Future Outlook

In this study, the role of novel nanocarriers in improving the targeted delivery of active medicinal plant compounds was investigated as an effective strategy to overcome the inherent limitations of these compounds. The findings demonstrate that nanotechnology has managed to use advanced systems like liposomes, polymer nanoparticles, lipid nanoparticles, and micelles to tackle poor solubility, low stability, and inadequate targeting of herbal compounds to a large extent. Moreover, the incorporation of biological ligands, including peptides, aptamers, and antibodies, in these nanocarriers has contributed to better therapeutic efficacy, lower side effects, and higher drug levels in the affected tissues. Furthermore, green synthesis of nanoparticles using medicinal plants offers a biocompatible and economical approach that not only helps to reduce environmental impacts but also shows significant potential in the treatment of various diseases, including cancer, inflammation, and chronic diseases, by combining the therapeutic properties of plants with the unique properties of nanoparticles. Nonetheless, obstacles still exist, such as accurate governance of the dimensions, contours, and steadiness of the nanoparticles, the enhancement of the targeting techniques on a molecular level, and the lengthy safety evaluation. The researchers in the future should be directed towards the nanocarriers that not only enhance the pharmacological properties but also have a low cost and can be produced in large quantities. All in all, new nanocarriers present a potential means for bettering the effect of herbal medicine, and the combination of nanotech with herbal practice can create new possibilities for superior treatments in the realm of medicine.

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