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Review Paper

Smart Nanocarriers for Herbal Drug Delivery: Overcoming Pharmacokinetic Barriers and Future Clinical Perspectives

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ABSTRACT

Present review explores the integration of traditional herbal medicine with modern nanotechnology, known as nano-phytomedicine, to overcome the pharmacokinetic limitations of plant-based therapies [4,6]. While herbal medicine has a long history of therapeutic use, clinical application is hindered by poor water solubility, rapid degradation, low oral absorption, and metabolic instability [1,2,3]. Smart nanocarriers-engineered at the nanoscale (1-100 nm)-address these barriers by protecting botanical compounds, controlling their release, and targeting specific tissues [5,7]. The gastrointestinal tract presents significant barriers to oral absorption, resulting in low bioavailability for most herbal compounds [8]. Nanocarriers, such as polymer-based and chitosan-coated nanoparticles, improve absorption by protecting compounds from enzymes and increasing retention time in the digestive system [10,12]. Furthermore, specialized nanocarriers can cross cellular barriers, including the blood-brain barrier (BBB), enhancing delivery to the central nervous system [18,19]. Various nanocarrier platforms are utilized, including polymeric nanoparticles (e.g., PLGA, chitosan) known for their adjustable properties and biocompatibility [7]. Lipid-based nanostructures (e.g., SLNs, liposomes) mimic biological membranes for natural cellular uptake [7,9]. Additionally, plant-derived and green-synthesized nanocarriers offer sustainable and highly biocompatible alternatives [25,27]. Crucially, these smart systems are designed to be stimuli-responsive, releasing therapeutics triggered by specific physiological conditions such as pH changes, glucose levels, or enzyme activity [7,29,31]. Active

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targeting using ligands further enhances precise delivery to diseased cells [7]. This nanotechnology approach represents a significant advancement, transforming herbal medicine from simple delivery methods into intelligent, body-mimicking therapeutic systems, ultimately paving the way for personalized and highly effective clinical applications [7].

INTRODUCTION

Herbal medicine has played a central role in healthcare systems across different cultures for more than 5,000 years, providing therapeutic benefits from natural plant components. Traditional healing systems, such as Ayurveda, Unani, and Traditional Chinese Medicine, have developed structured methods for using plant-based treatments. However, the rise of modern synthetic drugs in the 20th century led to a decline in interest in these traditional approaches. Recently, in the 21st century, there has been a renewed interest in herbal medicine due to the limitations and side effects of conventional treatments, with many healthcare professionals now acknowledging herbal therapies as balanced and less intense healing methods [1,2].

Despite their long history of use and proven therapeutic potential, herbal medicines face several challenges that have historically limited their widespread clinical use. These include poor solubility in bodily fluids, instability in the body, low absorption when taken by mouth, rapid breakdown in the liver, and quick removal from the body [3]. The use of nanotechnology with herbal medicine marks a major shift, leading to the development of smart nanocarriers that help overcome these drug delivery issues while maintaining or even enhancing the natural effectiveness of plant compounds [4].

Nanotechnology involves manipulating materials at the nanoscale (1-100 nm), and it has transformed the development of pharmaceuticals by allowing precise control over how drugs are delivered, where they go, and how well they work [5]. The combination of herbal medicine with nanotechnology has created a new field called nano-phytomedicine, which merges traditional herbal knowledge with modern biomedical research [6]. This integration goes beyond simply combining the two-it represents a synergistic transformation that can fully unlock the healing potential of botanical compounds.

Smart nanocarriers are advanced systems at the nanoscale that can respond to changes in the body's environment. Unlike conventional delivery systems, these smart carriers have multiple functions: they protect sensitive plant compounds from breaking down, control how and when the active ingredients are released, deliver them precisely to specific cells or tissues, and respond to changes in the body such as pH levels, enzyme activity, oxidative stress, or temperature [7].These systems represent a significant step away from simple drug delivery methods toward intelligent, body-mimicking therapeutic systems.

This review presents recent developments in smart nanocarrier systems used for delivering herbal medicines, with a focus on solving pharmacokinetic challenges, using responsive delivery methods, moving these treatments into real-world clinical applications, and exploring future possibilities for personalized herbal medicine.

2. Pharmacokinetic Challenges in Delivering Herbal Drugs

2.1 Gastrointestinal Barriers and Oral Absorption

The gastrointestinal tract presents multiple barriers that greatly limit the absorption of active ingredients from herbal medicines. These barriers include the acidic environment of the stomach, the mucus layer that covers the intestinal walls, tight junctions between cells in the intestinal lining, and the breakdown of compounds by digestive

enzymes and metabolic processes. Most herbal compounds have very low oral bioavailability (often less than 5%), making it difficult to use them effectively by mouth, even though many people prefer this non-invasive method [8]. Recent advancements in nanocarrier systems have successfully addressed these challenges through carefully designed approaches. Controlling the size, shape, and surface properties of nanoparticles greatly improves their ability to pass through the mucus layer and be taken up by cells [9].Studies using the Ussing chamber model showed that how long polymer-based nanoparticles stay in the mucous layer can vary greatly, from 18.5% to 97.3%, depending on their size and the material used to coat them, highlighting how important these factors are in absorption [10].Adding substances that improve absorption, such as borneol, can greatly increase the effectiveness of oral delivery. For example, one study showed that using borneol along with PLGA nanoparticles significantly increased retention in the gastrointestinal tract and the spread of the nanoparticles throughout the body, and toxicity tests confirmed safety at daily doses up to 270 mg/kg [11].

Chitosan-based nanoparticles are particularly promising for delivering herbal medicines through the mouth. They protect herbal compounds from digestive enzymes and stick to the intestinal walls, which helps them stay longer in the digestive system. A study showed that chitosan-coated nanoparticles containing exenatide had a 13.29% bioavailability, which helped regulate blood sugar and improve islet function over time [12]. Similarly, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) help preserve insulin-like herbal compounds by keeping them stable in the stomach and releasing them in response to changes in pH in the intestines [13].

2.2 Cellular Uptake and Blood-Brain Barrier Crossing

A major challenge in delivering herbal medicines is the intestinal epithelial barrier, which is one of the biggest obstacles to oral drug absorption. This barrier consists of several parts: tight connections between intestinal cells, a protective mucus layer, digestive enzymes throughout the digestive system, and transporter proteins (especially P-glycoprotein) that push hydrophobic drugs back into the intestinal lumen [14]. Phytochemicals such as curcumin, quercetin, and resveratrol are examples of plant-based compounds that are not easily absorbed by the body. These compounds often have limited ability to pass through cell membranes because they are water-loving, have a large size, or have other chemical features that make it difficult for them to move through the cells in the gut [15].

Moreover, many of these phytochemicals are recognized by the body's systems that remove substances from cells, which means they are actively pushed out before they can reach effective levels in the bloodstream [16]. The combined impact is that these compounds are typically absorbed in very small amounts, often less than 1-2%, which greatly hinders their use in treating diseases, even though they show promise in laboratory and early research tests [17]. Outside of the gut, herbal treatments must also get past several other obstacles, such as cell membranes and the blood-brain barrier (BBB) for treatments targeting the brain.

Nanocarriers that resemble viruses, designed with neutral surfaces and proteins that help them enter cells, show much better ability to pass through membranes. These systems achieve a transepithelial permeability rate of 14.61×10^{-5} cm/s, which is 2.4 times greater than that of positively charged nanoparticles, because they mimic viral properties and use a process called

caveolae-mediated endocytosis [18]. For herbal compounds aiming to affect the central nervous system, making these carriers have specific parts that can pass through the BBB greatly improves their ability to reach the brain. For example, curcumin-loaded nanoparticles that are modified with transferrin receptor antibodies and RVG29 peptides showed significant improvements in cognitive function in animal models of Alzheimer's disease. Their effects include stopping the clumping of a protein called amyloid-beta and affecting the activity of another protein called tau, often using much less of the compound than is needed for the pure drug [19].

2.3 Enzymatic Degradation and Metabolic Stability

Herbal compounds are quickly broken down and used up by the enzymes in the gut and liver, which greatly reduces how much of the compound gets into the bloodstream. Curcumin, the main active substance in turmeric, has very low absorption and is rapidly broken down, which limits its use in clinical settings despite its potential health benefits [20]. Using nanocarriers protects these compounds from being broken down and from being processed too quickly in the liver and gut. Formulations that include surfactants and lipid-based delivery systems help reduce the variability in absorption and improve the body's uptake by keeping the drug concentrated after it is mixed with stomach fluids [21].

For example, using a special technique called solid dispersion for poorly soluble plant compounds like icariin from Epimedium brevicornu improves their oral absorption significantly-up to 416% compared to using the raw extract [22]. These advances in formulation directly address the key problem that has kept many potent herbal compounds from being used in clinical medicine.

2.4 Solubility and Physicochemical Constraints

Many phytochemicals have poor solubility in water, which is a major issue for drug development. Compounds like curcumin, resveratrol, and quercetin are fat-loving molecules that do not dissolve well in water at the pH and salt levels found in the body. Based on the Biopharmaceutics Classification System, many herbal compounds fall into either Class II (low solubility, high permeability) or Class IV (low solubility, low permeability). Their low ability to dissolve in stomach fluids limits their absorption and results in very low and inconsistent absorption levels through the mouth [16].

3. Nanocarrier Platforms: Design, Mechanisms, and Classification

3.1 Polymeric Nanoparticles and Biodegradable Carriers

Polymeric nanoparticles are among the most widely studied and versatile types of nanocarriers for delivering herbal medicines due to their ability to be adjusted in terms of their physical and chemical properties, biocompatibility, and how they release the active compounds. Natural polymers such as chitosan and alginate, along with synthetic ones like poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), offer different benefits depending on their ability to break down, stability, and how they can be modified on their surface. PLGA nanoparticles provide a steady release of the active ingredients through bulk erosion, and since they have been approved for use by the FDA in multiple products, their safety is well established. PLGA nanoparticles can be adjusted to control how fast they break down by changing the ratio of lactide to glycolide, making them suitable for both quick and slow drug release. Nanostructures modified with phenylboronic acid (PBA) can release insulin in response to glucose levels, which has set the stage for the development of similar systems for herbal

compounds [7]. Chitosan-based nanoparticle formulations have shown excellent performance for delivering herbal drugs.

Encapsulating plant compounds in chitosan nanoparticles improves their solubility, stability, and absorption while allowing for controlled release at a specific site in the body. These chitosan nanoparticles have demonstrated a range of health benefits, including antioxidant, anti-inflammatory, antimicrobial, and liver-protecting effects. The ability of chitosan to break down in the body and stick to tissues makes it particularly useful for oral delivery. Additionally, chitosan has natural antiviral properties, adding to its therapeutic value [23].

3.2 Lipid-Based Nanostructures and Biomimetic Carriers

Lipid-based nanostructures represent another major type of smart nanocarriers and include structures like SLNs, NLCs, lipid-polymer hybrid nanoparticles (LPHNPs), and liposomes [7]. These systems use the dual nature of lipids to pack in both water-soluble and oil-soluble drugs. The similarity in structure between lipid-based carriers and biological membranes makes them highly compatible with the body and allows them to be taken up naturally by cells through endocytosis [9]. Phytosomes are a type of lipid-based delivery system developed for herbal active compounds. These compounds, which are derived from plants, are combined with phospholipids-most often phosphatidylcholine - to form unique molecular structures. This process increases the ability of the compounds to dissolve in fats and pass through cell membranes, thereby improving their stability, how well they are absorbed by the body, and their effectiveness [24]. Solid lipid nanoparticles are made from solid lipid materials such as triglycerides, waxes, or fatty alcohols and are stabilized using biocompatible surfactants. These nanoparticles protect the plant-based compounds they carry from being broken down by enzymes and from reacting with changes in pH. The solid form of the lipid at body temperature forms a structured lattice that allows for a slow and controlled release of the active ingredients, with the rate of release influenced by the type of lipid structure and how well the active ingredient can dissolve in the lipid [7]. Clinical use of liposomal formulations, like Doxil® which was approved in 1995, has set the stage for safely using lipid-based carriers in medical treatments. LPHNPs combine the best features of both liposomes and polymeric nanoparticles. They provide reliable protection and controlled release by using the stability and controlled release properties of polymers and the ability to be taken up by cells and their biocompatibility from lipids [7]. Glucose-modified PLGA-lipid hybrid nanoparticles have shown better results in delivering oral insulin by staying stable in the acidic stomach and releasing the insulin in the intestines at the right pH level [13].

3.3 Plant-Derived and Green-Synthesized Nanocarriers

Nanocarriers made from plant sources are becoming promising alternatives to synthetic ones due to their sustainability and biocompatibility. These include plant-derived extracellular vesicles, engineered phytosomes, bioinspired polymeric nanoparticles, and green-synthesized metal nanoparticles. These systems are highly biocompatible and can be made from natural sources, allowing for controlled drug loading. They are also less likely to cause immune responses or be toxic compared to synthetic alternatives [25]. Plant-derived exosome-like nanoparticles (PELNs) from edible plants and medicinal herbs offer a new, biocompatible alternative to mammalian exosomes. They are less likely to cause immune reactions and are safer, and they can be produced at scale [26]. Metal

nanoparticles created using plant extracts as natural reducing and capping agents provide an environmentally friendly alternative to traditional methods [27]. Silver nanoparticles made from plant extracts have good antibacterial, anti-inflammatory, antiviral, and anticancer properties and are better for the environment and biocompatible [28].

Although metallic nanoparticles (such as gold, silver, and iron oxide) and inorganic systems (like silica nanoparticles and mesoporous silica nanoparticles) are not often used as primary carriers for small plant-based compounds, they provide unique advantages in certain applications. For example, gold nanoparticles can be used for delivering drugs and for photothermal therapy, optical imaging, and biosensing. Silver nanoparticles have natural antimicrobial properties that can complement antibiotic or antimicrobial compounds from plants, creating synergistic effects [7].

4. Stimuli-Responsive Smart Nanocarrier Technologies

4.1 pH-Responsive Systems

pH-responsive nanocarriers use the differences in pH levels in different parts of the body to release drugs in a targeted way. Tumors and endolysosomal compartments have acidic conditions (pH 6.0-6.5 and 4-5 respectively), which can be used to trigger the release of drugs. These nanocarriers use special linkers and polymers that change when exposed to these acidic environments, allowing drugs to be released in specific conditions while staying stable in normal pH levels [29]. A pH-responsive system for oral insulin used insulin-silver sulfide quantum dot conjugates wrapped in a chitosan/glucose polymer matrix. This system protected the insulin in the stomach, improved its absorption in the duodenum, and showed effective glucose-lowering results in animal models without causing low blood sugar. Acid resistant, folate-functionalized metal-organic framework (MOF) nanoparticles kept the insulin intact during stomach passage and released it slowly in the intestines, allowing for better absorption [7].

4.2 Glucose-Responsive Delivery Systems

One of the most useful smart mechanisms for delivering herbal drugs involves systems that release medicine based on glucose levels. These systems use materials that change shape or dissolve when glucose binds to them, triggering drug release as needed. Another approach uses enzymes like glucose oxidase, which convert glucose into gluconic acid, creating a change in pH that activates release. A hydrogel modified with phenylboronic acid groups showed long and controlled release of various drugs and was also good at reducing harmful reactive oxygen species (ROS) inside cells. These systems are especially useful for herbal antidiabetic drugs, as they can release medication in line with changes in blood sugar levels. [7,30]

4.3 Enzyme-Responsive Systems

Enzyme-responsive nanocarriers take advantage of specific enzymes that are more active in certain disease areas. These enzymes help release drugs precisely where they are needed. [31] For example, nanocarriers with peptide links can be broken down by enzymes found in the colon or by proteins in tissues. Hyaluronic acid-based nanocarriers are useful because inflamed tissues and tumors often have higher levels of the enzyme hyaluronidase, making them suitable for targeted delivery. [7] Multienzyme systems respond to several enzymes at once, making them even more accurate in delivering drugs to the right place. [31]

4.4 Ligand-Directed Active Targeting

Passive targeting uses the natural ability of some nanocarriers to accumulate in diseased tissues due to increased permeability and retention. Active targeting, on the other hand, uses ligands like antibodies or peptides that bind to specific receptors on the surface of cells. This method improves the delivery of drugs to the right cells. For example, nanocarriers linked to transferrin can target cancer cells that need more iron. Folate-functionalized nanocarriers work well because some cancer cells have a lot of folate receptors. RGD peptides help target integrins that are common on cancer cell surfaces. [7] In herbal drug delivery, targeting tumors has been achieved by attaching antibodies that recognize cancer antigens or using aptamers that bind to specific biomarkers. Some herbal nanoformulations naturally include targeting ligands, like hyaluronic acid, which is found in many herbal extracts, adding to the targeting ability of these nanocarriers. [3]

4.5 Multi-Stimuli Responsive Systems

Advanced nanocarriers respond to multiple signals such as pH, redox changes, enzyme activity, and ROS. [29] These systems require several triggers to release drugs, making them more precise and reducing the chance of drugs being released too early. This multistimuli approach enhances therapeutic effectiveness and reduces unwanted side effects. [30]

5. Key Phytochemicals and Their Pharmacokinetic Enhancement through Nano Formulation

5.1 Curcumin: The Paradigmatic Example of Bioavailability Transformation

Curcumin is a yellow polyphenol found in turmeric (Curcuma longa) and has many health benefits like anti-inflammatory, antioxidant, anticancer, and neuroprotective properties. However, its poor oral bioavailability—only about 0.1-1%—has limited its use in clinical settings. This is due to low solubility in water, quick metabolism in the liver, and being pumped out by P-glycoprotein. Using nanoencapsulation has greatly improved curcumin's bioavailability. Chitosan-tripolyphosphate (CS-TPP) nanoparticles made through ionic gelation have a size of about 182 ± 9 nm and can encapsulate curcumin with 86.9 ± 2.1% efficiency. These nanoparticles show 3.9 times better absorption through intestinal cells and 5.7 times more effectiveness against colon cancer cells compared to regular curcumin [17]. PLGA-based nanoparticles have further increased curcumin's bioavailability by up to 15-29 times and provide a steady release of the drug, ensuring long-term therapeutic effects. [32] Combining curcumin with other plant-based compounds in nanoformulations also leads to better results. Curcumin, when combined with quercetin or resveratrol in polymeric nanoparticles, showed improved anticancer effects in colorectal cancer models. This was achieved by blocking multiple pathways, including Wnt/β-catenin, PI3K/Akt, and NF-κB-related inflammation. [33]

5.2 Quercetin and Flavonoid Bioavailability Enhancement

Quercetin, a flavonoid found in many plant-based foods like apples, onions, berries, and green tea, has strong antioxidant, anti-inflammatory, and anticancer properties. However, it has very low oral bioavailability, ranging from 0.8% to 2%, due to poor water solubility and quick metabolism through glucuronidation and sulfation processes. [34] Using solid lipid nanoparticles and nanostructured lipid carriers has increased quercetin's bioavailability by 8 to 15 times. Adding folic acid to the surface of these nanoparticles allows for better absorption through specific cell receptors. [35] Trimethylated chitosan-coated zein

nanoparticles (TMC-Zein-Q) can temporarily open the tight junctions between intestinal cells, allowing for better absorption via the paracellular pathway. This formulation significantly improves quercetin's bioavailability and shows better results in reducing obesity in mice fed a high-fat diet by activating the AMPK pathway. [34]

5.3 Resveratrol, EGCG, and Polyphenolic Compounds

Resveratrol, a compound found in grape skins and berries, and epigallocatechin gallate (EGCG), the main catechin in green tea, both have strong anti-cancer, neuroprotective, and metabolic benefits. However, their bioavailability is very low, with resveratrol having less than 0.5% and EGCG less than 0.3%. Nanoencapsulation using PLGA nanoparticles, solid lipid nanoparticles, and self-nanoemulsifying drug delivery systems (SNEDDS) has boosted resveratrol's bioavailability by 8 to 15 times. These formulations have shown greatly improved anticancer effects in colorectal cancer models. When combined with quercetin in nanoformulations, they also show synergistic effects in blocking cancer-related pathways. [36] EGCG-loaded nanostructured lipid carriers with folic acid on their surface showed 1.8 times better absorption and improved delivery to tissues that overexpress folate receptors. This highlights the benefits of using both nanoparticle delivery and targeted ligands [35]

5.4 Silymarin and Hepatoprotective Phytochemicals

Silymarin, derived from milk thistle (Silybum marianum), is mainly made up of silibinin, which has established benefits in protecting the liver. However, silibinin's use is limited due to its low solubility in water, poor ability to pass through intestinal cells, and fast metabolism in the liver, leading to low levels of the compound in the body. Phospholipid-based phytosomes (Siliphos®) have improved both the bioavailability and effectiveness of silibinin, resulting in better outcomes in models of liver fibrosis and cirrhosis. Nanostructured lipid carriers with modified surfaces have also shown similar improvements. These formulations may also be used in combination with other drugs for treating liver fibrosis [37].

6. Delivery Routes and Barrier Overcoming Strategies

6.1 Oral Delivery: The Preferred Route with Significant Challenges

The oral method is the most favoured way for medication administration from the patient's point of view because it is non-invasive, easy to use, leads to better adherence, and is cost-effective. Despite these benefits, delivering herbal nanoformulations through the mouth presents major difficulties like breakdown by digestive enzymes, instability depending on stomach acid levels, limited ability of the intestines to absorb the substances, removal by P-glycoprotein, and metabolism in the liver before reaching the bloodstream. [14]

New developments have tackled these issues using multiple strategies. Enteric-coated nanoparticles stay undamaged in the acidic stomach and release their contents in the less acidic environment of the small intestine, helping protect sensitive plant-based compounds.pH-sensitive liposomes that contain substances that break down in acidic conditions remain closed in the stomach but open up effectively in the intestine. Chitosan-PEG nanoparticles stick to the intestinal lining, increasing the time the drug stays in the gut and offering multiple chances for the body to absorb it. [7]

A new platform involves metal-organic frameworks (MOFs), which are porous, crystalline materials that can be adjusted in size and surface features. MOF nanoparticles that resist stomach acid and are modified with folate have shown the ability to keep insulin intact during digestion while releasing it steadily in the intestines, increasing bioavailability by two to three times. [6] These MOFs can hold a variety of plant-based compounds with high efficiency and controlled release.

6.2 Intranasal and Nose-to-Brain Delivery

The intranasal method has unique benefits since it allows the medication to travel directly from the nose to the brain, bypassing the blood-brain barrier via the olfactory and trigeminal nerves. [38] This method is especially useful for treating neurological disorders and delivering plant-based medicines to the brain. Nanoparticle systems used for intranasal delivery include lipid-based nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, polymeric nanoparticles, and in-situ gel systems. When curcumin is delivered through the nose in the form of polymeric nanoparticles, it shows better results in treating Alzheimer's disease compared to traditional methods, with increased accumulation in the brain and improved memory in certain mouse models. [19] Combining improved absorption through nanoparticles with direct delivery to the brain via the nose helps create a stronger therapeutic effect for conditions that involve the nervous system. [39]

6.3 Transdermal and Topical Delivery Systems

Transdermal delivery avoids the first breakdown of the medication in the liver and allows for a constant effect as the medicine slowly moves through the skin. However, the outer layer of the skin, called the stratum corneum, forms a strong barrier to most substances, making it hard for larger molecules or less lipophilic ones to pass through. Herbal nanoformulations such as nanoemulgels, solid lipid nanoparticles, and nanostructured lipid carriers have been developed to get around this barrier by reducing the size of the particles, modifying their surface with substances that help them pass through the skin, and using natural permeation enhancers, such as Nigella sativa oil, which also has anti-inflammatory properties. Nanoemulgels containing colchicine from herbal sources and Nigella sativa oil showed better effectiveness in reducing inflammation and penetrating the skin compared to traditional versions. [40] Formulations using phytsomes for topical delivery of herbal polyphenols have significantly improved penetration while maintaining their stability and activity. [41]

6.4 Injectable and Depot Delivery Systems

Injecting medicines bypasses the digestive system's challenges but involves the need for intravenous administration, which can be uncomfortable and lead to lower patient compliance. However, depot-based nanoparticle systems provide a steady release of medication over weeks or months from a single injection, greatly improving adherence in managing chronic diseases. Polymeric microparticles and nanoparticles, lipid-based carriers, and hydrogel depots loaded with herbal extracts have been effective in preclinical models of diabetes and inflammation. [7]

7. Clinical Perspectives and Translation Challenges

7.1 Current Clinical Status and Early-Phase Trials

Even though there are big successes in the lab, the use of smart nanocarriers for herbal medicine still has not moved very far in actual clinical use compared to synthetic medicines. Most nanocarrier-based herbal treatments are at intermediate development stages (TRL 3-5), with only a few advancing to the earliest stages of clinical trials. [42] One success example is using zein nanoparticles for delivering antidiabetic drugs: empty zein nanocapsules have gone through clinical trials, showing better blood sugar control in people with prediabetes. [7]

Another completed trial focused on nanostructured water, known as Magnalife®, for its ability to lower blood sugar in people with type 2 diabetes, showing growing interest in using nanotechnology for herbal treatments. Phase 1 trials have started for gold nanoparticles loaded with peptides, being used to deliver antigens through microneedles for type 1 diabetes treatment, and a tolerogenic dendritic cell vaccine, called PipepTolDC, has moved to Phase 1 as a way to modulate the immune system.[7] These early trials demonstrate the possibility of using nanocarriers for herbal medicines and provide key safety and immune response data.

7.2 Manufacturing Scalability and Quality Control

Producing smart nanomaterials on a large scale while keeping the size, surface qualities, drug content, and responsiveness to stimuli consistent is a major challenge when translating lab successes to real-world use. Many optimized processes developed in the lab, which involve multiple steps and surface modification techniques, often lose their consistency when moving to larger-scale manufacturing, leading to changes between batches that can hinder the translation of these innovations into clinical applications [7].

Standardized manufacturing techniques such as microfluidic fabrication, continuous-flow synthesis, and automated analytical nanometrology have become promising methods to enhance reproducibility, scalability, and cost efficiency. These advanced production methods allow for precise control over the properties of nanoparticles and support the transition from lab-based development to large-scale manufacturing. Nonetheless, the challenge of effectively encapsulating and preserving sensitive herbal bioactive compounds without losing their activity remains significant, necessitating continued innovation. [7]

7.3 Safety, Toxicity, and Regulatory Considerations

The physical and chemical traits of nanomaterials play a crucial role in how they spread in the body, break down, and may be harmful. Because of this, it is essential to assess the safety of these materials thoroughly before they can be used in medical treatments. Nanoparticles are often seen as foreign by the body's immune system, which can lead to harmful immune reactions. This happens when the immune system activates through the complement system or by recognizing certain patterns, causing the release of substances that trigger inflammation. [42]

The process of using nanomaterial-based systems in clinical settings is limited by challenges related to regulation and the lack of a single, agreed-upon set of rules for these complex materials. Regulatory bodies such as the FDA, EMA, CDSCO, and ISO are working to create guidelines that address how to classify nanomaterials, approve combinations of drugs and devices, and manage therapeutic systems that use digital technology. However, there are still important gaps, such as the absence of standard criteria for describing the physical and chemical properties of nanomaterials, the lack of unified methods to evaluate their toxicity and how they move through the body, and uncertainty about how to approve

systems that are fully integrated with digital technologies. [7]

To ensure long-term safety and the ability to use these materials in real-world medical applications, toxicological assessments should cover various effects, such as harm to the immune system, genetic damage, disruption of hormonal systems, and interactions between nanoparticles and proteins. Special attention should be given to the unpredictable absorption and spread of nanoparticles when taken by mouth, their quick removal by the body's natural defenses or through the kidneys, and immune reactions that may be more pronounced with certain types of nanoparticles, such as those made of metals. [7]

8. Clinical Trial Evidence and Market-Approved Products

Although nanotechnology has been studied for many years, the number of nanomedicine products that have been approved for use remains relatively low. As of 2025, it is estimated that between 50 and 80 nanomedicine products have received approval worldwide, including Doxil® (liposomal doxorubicin), which was approved in 1995, Abraxane® (albumin-bound paclitaxel), approved in 2005, and more recently approved nanoparticles used as checkpoint inhibitors. [43] For herbal compounds specifically, the translation of these into clinical use has been limited but is now speeding up.

Important clinical advancements include:

- **Zein nanoparticles for managing blood sugar levels:** Clinical trials using empty zein nanocapsules have shown improved blood sugar control in individuals with prediabetes, demonstrating that plant-based nanocarriers can be effective in medical treatments. [7]

- **Icaritin soft capsules for liver cancer**: Icaritin, a compound derived from Epimedium, was approved in 2022 by China's National Medical Products Administration for treating hepatocellular carcinoma. This marks a significant step forward in the clinical use of nanoformulated herbal compounds. [44]

- **Phase 1 trials for immune-related treatments**: Gold nanoparticles loaded with a specific peptide (C19-A3 antigen) for the treatment of Type 1 diabetes completed Phase 1 trials, showing safety and the ability to modulate the immune system. These trials represent the first major clinical assessment of nanotechnology-enhanced herbal immunotherapies. [6]

- **Ongoing clinical trials:** Several trials are currently evaluating nanoformulations of various plant-based compounds such as curcumin, resveratrol, and EGCG for treating cancer, inflammation, and neurodegenerative diseases. However, there is a limited number of published results from Phase 2 and Phase 3 trials, highlighting the challenges in translating nanomedicine into widespread clinical use. [43]

9. Future Clinical Perspectives and Emerging Technologies

9.1 Artificial Intelligence-Driven Design and Computational Design

The use of artificial intelligence in the development of smart nanocarriers is a major innovation, allowing for the systematic improvement of the physical and chemical properties of these materials as well as the prediction of how drugs interact with carriers.

AI methods support the creation of targeted delivery systems, controlled release mechanisms, and personalized treatment approaches tailored to individual patients. [45] Computational models can also be used to design nanocarriers that are customized for specific patient factors, such as

liver health, genetic makeup, and the presence of other medical conditions. [42] Machine learning algorithms can speed up the optimization process by predicting how drugs will interact with carriers and how stable or effective they will be, significantly reducing the need for extensive experimental testing. [42]

These computational tools have great potential for the rational design of herbal nanocarriers, taking into account the complex nature of plant-based compounds and the varying ways the body responds to them. Machine learning models trained on large molecular datasets can predict how well nanoparticles can pass through the skin and help choose the best plant-based compounds for transdermal delivery. Physics-informed neural networks that use transport equations and biological constraints provide both an understanding of the underlying mechanisms and the ability to make predictions. [43]

Bayesian optimization combined with Gaussian Process surrogates allows for a guided exploration of the possible combinations of nanoformulation parameters, identifying the best options in just 31 guided steps instead of over 80 experiments needed for a full analysis. [10] These AI-based methods cut development time by about two-thirds and enable the discovery of optimal formulations that traditional methods might miss. [17]

9.2 Integration with Gene-Editing Technologies

The combination of nanocarrier engineering with advanced gene-editing techniques, such as CRISPR/Cas9, offers exciting potential for precision herbal medicine. Nanocarriers loaded with CRISPR can deliver genetic modifications to specific targets, while herbal bioactive compounds can provide additional immune-modulating and anti-inflammatory effects. These combined strategies can address multiple disease mechanisms at once, offering therapeutic benefits that may not be possible with a single treatment. [42]

9.3 Bioelectronics Integration and Wearable Delivery

New technologies that include nanocarrier systems within bioelectronic and wearable devices allow for closed-loop drug delivery, which enables real-time monitoring and responsive therapeutic actions. Biodegradable and temporary electronic materials help solve longstanding issues related to removing devices and ensuring long-term compatibility with the body. These innovations are pushing the field toward scalable, non-invasive sensing methods such as smart textiles with embedded sensors, intelligent contact lenses, and subcutaneous bioresorbable systems that can easily integrate into digital health networks. [7]

9.4 Precision Medicine and Personalized Herbal Therapeutics

Future use of smart nanocarrier systems for herbal medicine will place greater focus on precision medicine, which customizes treatment plans to fit individual genetic makeup, disease characteristics, and how patients react to medications. [6] Clinical trials will involve grouping patients based on specific characteristics, along with thorough examination of drug interactions, immune responses, and disease progression, to gather essential information for creating better dosing plans and understanding the risks and benefits. [42]

Designing personalized nanocarriers that take into account specific patient factors, such as the composition of gut bacteria, genetic differences affecting drug processing, and the unique environment of a patient's disease, is becoming more feasible as manufacturing techniques improve and clinical insights grow. Combining data from various biological fields (genomics, proteomics, metabolomics) with nanocarrier

design supports a more precise therapeutic approach, connecting traditional herbal medicine with modern biomedical research.

10. Regulatory Pathways and Clinical Translation Considerations

Although nanoformulation technology offers significant benefits in drug absorption and effectiveness, moving herbal nanocarriers from the lab to the clinic involves navigating complex and changing regulatory guidelines. The FDA, European Medicines Agency (EMA), and regulatory bodies in Asia do not have detailed, unified guidance specifically about nanomedicines derived from plants, leading to confusion regarding the requirements for preclinical safety data, manufacturing controls, and product stability [17].While regulatory agencies have provided initial guidance for conventional nanomedicines (highlighting the importance of size, surface properties, and consistency between batches), the complexity of botanical materials-with variations in phytochemical content based on growing conditions, harvest times, and plant parts-introduces new regulatory challenges regarding standardization of raw materials and consistency of the final product [46].

Regulatory references from approved herbal monographs and traditional medicine registration procedures suggest that a unified quality-by-design (QbD) strategy, focusing on critical quality characteristics (CQAs) related to drug absorption and effectiveness, along with strong analytical methods to analyze the composition of herbal extracts, may help gain regulatory acceptance [17].

Establishing whether nanoformulated herbal products are equivalent to traditional formulations (when available) will likely become a standard regulatory expectation, requiring well-controlled clinical pharmacology studies to measure improvements in drug absorption, distribution in the body, and clinical outcomes. Co-operation across international organizations such as the International Council for Harmonisation (ICH) and WHO initiatives on traditional medicine standardization will be essential for creating globally consistent standards, speeding up the clinical application of these products while ensuring safety and effectiveness in different regulatory settings.

Smart nanocarriers offer a revolutionary way to overcome major pharmacokinetic challenges that have historically limited the usefulness of herbal treatments. By using advanced polymer chemistry, surface engineering, designs that respond to stimuli, and AI-based optimization, next-generation nanoformulations significantly improve oral absorption, targeted delivery to tissues, internalization by cells, and delivery of phytochemicals that were previously inefficient. The combination of technological progress with evolving regulatory policies and increasing clinical validation suggests that herbal nanomedicines will become more common and effective complements to traditional herbal therapy, offering patients access to plant-based remedies with greatly enhanced pharmacokinetic profiles and more predictable, dosage-controlled clinical effects.

CONCLUSION

Smart nanocarriers have fundamentally changed the potential of herbal medicines by overcoming long-standing pharmacokinetic barriers that previously limited their effectiveness. [3] The merging of nanotechnology with herbal medicine has created new opportunities for precise drug delivery, targeted treatment, and therapeutic adjustments triggered by physiological signals. Recent progress in polymeric, lipid-based, inorganic, and hybrid nanostructures shows how engineering at the nanoscale can control the stability of herbal compounds, improve their

absorption, and enable intelligent responses to body signals. [7]

Despite major advances, key challenges still hinder clinical application, such as inconsistent performance of nanomaterials across studies, difficulties in producing large quantities reliably, limited long-term safety data, and the lack of standard regulatory frameworks for multifunctional drug-device combinations enabled by nanotechnology. Over the next five to ten years, significant breakthroughs are expected from the integration of smart nanomaterials with bioelectronics, AI-assisted data analysis, and advanced wearable or implantable medical devices. [7] The development of highly selective nanosensors paired with AI-driven predictive algorithms could enable continuous, personalized monitoring with greater accuracy, while next-generation glucose-responsive nanocarriers and microneedle-based delivery systems will move the field toward truly patient-centered precision medicine. Creating uniform manufacturing guidelines, thorough methods for analyzing the physical and chemical properties, and consistent ways to assess effectiveness is necessary to guarantee dependable results and assist in moving nano-enhanced herbal treatments into clinical use. Working together across different fields, including materials science, pharmaceutical engineering, medical professionals, and regulatory specialists, will be key to turning these promising lab discoveries into real-world medical solutions that can enhance patient care worldwide, while making full use of the powerful healing benefits of traditional medicines within today's advanced precision medicine systems.

Disclosure Statement

No conflict of interest to declare by the authors

Author Contributions

Zalak D. Dave: conceptualization, methodology, project administration, supervision, writing original draft, review & editing.
Tisha K. Patel: conceptualization, validation, writing, review & editing.
Prachi R. Shah: review & editing.
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