



Review Article

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NANO-PHYTO PUNCTURE: ENHANCING HERBAL BIOAVAILABILITY THROUGH NANOTECHNOLOGY

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ABSTRACT

Nano-phytopuncture represents a novel integrative therapeutic strategy that synergizes traditional pharmacopuncture with advanced nanotechnology to overcome the pharmacokinetic limitations of herbal compounds. Conventional herbal extracts used in pharmacopuncture often suffer from poor water solubility, rapid metabolism, and low systemic bioavailability, leading to inconsistent clinical efficacy. Integrating nanocarrier systems such as polymeric nanoparticles, lipid-based carriers (SLNs [Solid Lipid Nanoparticles], NLCs [Nanostructured Lipid Carriers], liposomes), inorganic nanoparticles (gold, iron oxide), and nanogels can significantly improve solubility, stability, targeted delivery, and sustained release of phytochemicals. These carriers enhance lymphatic uptake, utilize passive EPR (Enhanced Permeability and Retention) and active targeting, and enable stimuli-responsive release, thereby improving therapeutic concentrations at target sites while minimizing systemic toxicity. Preclinical studies highlight promising applications in managing cancer, infections, inflammation, neurological disorders, and iron deficiency. However, translational challenges remain, including the need to standardize herbal-nanoformulations, develop GMP-compliant scale-up processes, and conduct rigorous safety and toxicology assessments. Surface modifications such as PEGylation and chitosan coating help reduce immunogenicity and enhance circulation time. Yet, the lack of robust clinical trials and regulatory frameworks specific to these hybrid systems continues to hinder their clinical integration. This review critically evaluates current nanotechnological approaches applied in pharmacopuncture, with emphasis on formulation strategies, mechanisms of enhanced bioavailability, therapeutic efficacy, and translational bottlenecks. This review on nano-phytopuncture offers valuable insights for young researchers engaged in drug discovery and the development of phytonano formulations by bridging traditional herbal therapeutics with cutting-edge nanotechnology. It serves as a comprehensive knowledge platform that explains how nanocarrier systems can be strategically employed to overcome longstanding challenges in herbal pharmacokinetics, such as low bioavailability, instability, and non-specific distribution.

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INTRODUCTION

Conventional pharmacopuncture, while rooted in the synergistic principles of herbal medicine and acupuncture, often faces significant limitations that hinder its therapeutic potential [1]. Many herbal extracts used in pharmacopuncture suffer from poor water solubility, instability in the gastrointestinal or systemic environment, and rapid metabolism, all of which contribute to low bioavailability and inconsistent clinical outcomes [2]. These challenges reduce the effective concentration of active constituents at target sites, limiting their efficacy in treating chronic or complex conditions. Nanotechnology offers a transformative solution by encapsulating herbal compounds in nanocarriers such as liposomes, solid lipid nanoparticles, and polymeric particles. These systems not only protect sensitive phytochemicals from degradation but also improve solubility, prolong systemic circulation, and facilitate targeted or sustained release at specific tissues or cellular receptors [3].

By overcoming key pharmacokinetic barriers, nanocarriers enhance both the stability and bioefficacy of herbal extracts, positioning nano-phytopuncture as a promising advancement in integrative medicine that aligns modern delivery technologies with traditional therapeutic wisdom [4]. This review focuses on the emerging integration of nanotechnology into pharmacopuncture to improve the delivery and therapeutic impact of herbal formulations. A key area of interest is the use of various nano-carrier systems that have shown promise in enhancing the bioavailability, stability, and targeting capabilities of herbal compounds [5]. Among these, polymeric nanoparticles are widely studied for their controlled release properties and compatibility with biological systems. Lipid-based carriers, including liposomes, SLNs, and NLCs, are particularly effective in enhancing solubility and promoting absorption through lymphatic pathways [6]. Metallic and inorganic nanoparticles, such as those made from gold, silver, or iron oxide, offer additional benefits through targeted delivery, magnetic responsiveness, and potential imaging applications [7].

By exploring these different nano-carrier platforms, this review aims to present a comprehensive understanding of how nanotechnology can address the inherent limitations of traditional pharmacopuncture, such as poor solubility and low systemic absorption. The objective is to highlight the transformative potential of nano-phytopuncture and provide

insights into future research and clinical opportunities in this evolving field. This review critically evaluates current formulation strategies in nano-phytopuncture and how these approaches enhance the pharmacological performance of herbal compounds.

It examines how nano-carriers influence the pharmacokinetics of active ingredients, particularly absorption, distribution, metabolism, and excretion, compared with traditional formulations. Furthermore, the review explores the therapeutic applications of nano-phytopuncture across various clinical areas, highlighting how improved delivery mechanisms can lead to better outcomes in managing conditions such as inflammation, pain, infections, and even cancer. Equally important is assessing safety profiles, focusing on potential cytotoxicity, immunogenicity, and the long-term effects of repeated administration. Lastly, the review considers the translational potential of these nano-formulations, including challenges in standardization, large-scale production, regulatory approval, and clinical implementation. Through this comprehensive analysis, the review aims to provide a clear picture of both the promises and limitations of nano-phytopuncture, laying the groundwork for future advancements in research and clinical practice.

2. METHODOLOGY

This review used a comprehensive literature search of PubMed, Scopus, Web of Science, and Google Scholar to identify relevant publications on nano-phytopuncture, pharmacopuncture, herbal nanocarriers, and phyto-nanodelivery systems. The search strategy combined keywords such as "pharmacopuncture", "nano-phytopuncture", "nanocarriers", "polymeric nanoparticles", "lipid nanoparticles", "herbal drug delivery", "phyto-nanodelivery", "targeted delivery", and "bioavailability enhancement". We used Boolean operators ("AND", "OR") to optimize the search.

We considered original research articles, systematic reviews, meta-analyses, and relevant clinical studies published in English between 2005 and 2025. We included studies on nanocarrier-based herbal drug delivery, pharmacokinetic enhancement, targeted delivery, therapeutic applications, and safety. We excluded conference abstracts, duplicate publications, editorials, and studies lacking adequate methodological details. We also screened the reference lists of eligible articles to identify relevant publications.

3. TYPES OF NANO-CARRIERS IN PHYTO-NANODELIVERY

3.1. Polymeric nanoparticles

Polymeric nanoparticles are among the most widely studied nanocarrier systems for enhancing herbal drug delivery in pharmacopuncture because of their versatility, biocompatibility, and ability to provide controlled, sustained release [8,9]. Researchers typically prepare these nanoparticles using methods such as emulsion-diffusion, ionic gelation, and nanoprecipitation. In the emulsion-diffusion method, a polymer is dissolved in a volatile organic solvent and emulsified in an aqueous phase, then the solvent diffuses out and evaporates, forming nanoparticles [10,11]. Ionic gelation involves the crosslinking of natural polymers such as chitosan with counterions (e.g., tripolyphosphate), allowing mild preparation conditions suitable for temperature-sensitive herbal compounds. Nanoprecipitation, also known as solvent displacement, is a simple and scalable technique in which a polymer and herbal extract solution prepared in a water-miscible organic solvent is rapidly introduced into an aqueous phase, resulting in spontaneous nanoparticle formation through solvent diffusion [12–14]. These methods offer considerable flexibility for encapsulating a wide range of phytochemicals while preserving their physicochemical stability and biological activity.

Furthermore, researchers can tailor the resulting nanoparticles for particle size, surface charge, encapsulation efficiency, and drug-release characteristics, making them particularly suitable for localized administration in pharmacopuncture. Their ability to protect herbal bioactive compounds from degradation and provide sustained release at the site of administration substantially enhances the therapeutic potential of traditional herbal formulations [15]. Several notable examples demonstrate the effectiveness of polymeric nanoparticles in improving the delivery and therapeutic performance of herbal compounds used in pharmacopuncture. One such example is piperine-loaded nanocapsules, which have shown nearly a threefold enhancement in therapeutic efficacy compared with non-encapsulated piperine. This improvement is primarily attributed to enhanced solubility, protection against rapid metabolic degradation, and prolonged systemic availability of the encapsulated phytoconstituent [16]. Another example is curcumin encapsulated in a PLGA-chitosan {Poly (lactic-co-glycolic acid)-Chitosan} nanoparticle system, which provides sustained drug release and improved bioavailability. Curcumin

possesses potent anti-inflammatory and antioxidant activities but is limited by poor aqueous solubility and rapid systemic elimination following conventional administration [17]. Incorporating curcumin into biodegradable PLGA-chitosan nanoparticles enhances its stability while enabling gradual, localized release at the target site. These examples illustrate how polymeric nanoparticles can overcome major pharmacokinetic limitations associated with herbal compounds and substantially improve their therapeutic efficacy when used in nano-phytopuncture. Polymeric nanoparticles offer several advantages that make them well suited for nano-phytopuncture, particularly for enhancing localized delivery of herbal bioactive compounds [18]. One of their principal advantages is the ability to provide controlled and sustained drug release, allowing phytochemicals to be released gradually rather than as an immediate burst. This sustained release helps maintain therapeutic concentrations at the target site for extended periods, thereby reducing dosing frequency and potentially improving therapeutic outcomes [19]. Additionally, polymeric nanoparticles protect encapsulated phytochemicals from premature degradation within the local tissue microenvironment following pharmacopuncture administration. Their controlled release characteristics promote sustained local drug retention, prolonged diffusion through the interstitial matrix, and gradual uptake into surrounding capillary and lymphatic networks. These properties enhance localized therapeutic exposure while minimizing rapid systemic clearance and reducing off-target effects [20]. Moreover, researchers can engineer polymeric nanoparticles for targeted delivery by modifying their surface with specific ligands or functional groups, enabling selective accumulation in inflamed or diseased tissues while minimizing exposure to healthy tissues. Such targeted delivery improves therapeutic efficacy and reduces the likelihood of adverse effects [21]. Collectively, these attributes make polymeric nanoparticles a highly promising platform for improving the efficacy, safety, and precision of herbal therapies administered through nano-phytopuncture [22].

3.2. Lipid-based systems

Lipid-based nanocarriers have emerged as one of the most effective delivery platforms in nano-pharmacopuncture because they improve the solubility, stability, and bioavailability of herbal phytoconstituents [23]. These carriers enhance intestinal and lymphatic absorption, partially bypassing hepatic first-pass metabolism and increasing the systemic availability of bioactive

compounds that are otherwise poorly absorbed or rapidly metabolized after oral administration [24]. Consequently, lipid-based systems offer an efficient strategy to improve the therapeutic performance of herbal medicines while enabling sustained and targeted drug delivery. Among these carriers, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have received considerable attention because of their favorable physicochemical characteristics and controlled drug-release capabilities. SLNs consist of a solid lipid core stabilized by surfactants, providing excellent drug protection, high physical stability, and prolonged release of encapsulated phytochemicals. However, the highly ordered crystalline structure of SLNs may limit drug loading. To overcome this limitation, researchers developed NLCs by incorporating both solid and liquid lipids within the lipid matrix. This less ordered internal structure enhances drug loading capacity, reduces drug expulsion during storage, and enables more flexible and sustained release profiles, making NLCs particularly suitable for delivering a broad range of herbal bioactive compounds. In addition to SLNs and NLCs, other lipid-based nanocarriers, including liposomes and micelles, have demonstrated significant potential for herbal drug delivery [25].

Liposomes are phospholipid bilayer vesicles that can encapsulate both hydrophilic and lipophilic phytoconstituents, protecting them from enzymatic degradation, improving stability, and enhancing cellular uptake. For example, berberine-loaded liposomes have shown improved accumulation in cardiac tissue, enhancing therapeutic efficacy for cardiovascular disorders. Micelles, self-assembled nanostructures formed from amphiphilic molecules, are particularly effective at solubilizing poorly water-soluble herbal compounds and facilitating their transport across biological membranes, thereby improving absorption and bioavailability [26]. Lipid-based nanoparticle preparation involves several established techniques, including high-pressure homogenization, microemulsion methods, solvent emulsification-evaporation, ultrasonication, and hot or cold homogenization. Among these, high-pressure homogenization is the most widely employed because it consistently produces nanoparticles with a narrow particle size distribution, high physical stability, and excellent encapsulation efficiency. During formulation, lipophilic phytoconstituents are typically dissolved in the molten lipid phase, whereas hydrophilic compounds are dispersed or dissolved in the aqueous phase before homogenization. This formulation strategy promotes

efficient drug encapsulation, enhances stability, and enables sustained release of the incorporated herbal compounds. Overall, lipid-based nanocarriers offer substantial advantages for nanopharmacopuncture by improving the pharmacokinetic and pharmacodynamic properties of herbal medicines. Their ability to enhance bioavailability, protect phytoconstituents from degradation, provide controlled release, and facilitate targeted delivery makes them promising platforms for maximizing the therapeutic efficacy of herbal pharmacopuncture formulations [27].

3.3. Inorganic and metallic nanoparticles

Inorganic and metallic nanoparticles such as gold, silver, silica, and iron oxide (magnetic) nanoparticles represent a cutting-edge frontier in nano-phytopuncture, offering multifunctional capabilities that extend beyond conventional drug delivery [28]. Researchers can precisely engineer these nanocarriers to improve targeted delivery and controlled release of herbal compounds, enhancing therapeutic efficacy while minimizing off-target effects [29]. Researchers can synthesize inorganic nanoparticles through chemical, physical, or biological (green synthesis) approaches. Among these, green synthesis using plant extracts has gained considerable attention because naturally occurring phytochemicals act as both reducing and stabilizing agents, eliminating the need for hazardous chemicals during nanoparticle fabrication. Furthermore, herbal compounds may either participate directly in nanoparticle synthesis or be subsequently conjugated to or adsorbed onto the nanoparticle surface, thereby improving nanoparticle stability, targeting capability, drug-loading efficiency, and controlled-release characteristics. Among inorganic nanocarriers, gold nanoparticles are highly valued for their excellent biocompatibility, facile surface functionalization, and ability to conjugate with targeting ligands that facilitate selective accumulation in diseased tissues. Silver nanoparticles possess intrinsic broad-spectrum antimicrobial activity and can act synergistically with herbal extracts to enhance antimicrobial efficacy against pathogenic microorganisms [30]. Silica nanoparticles provide a highly stable, porous matrix that can encapsulate substantial quantities of phytochemicals while enabling sustained, controlled drug release. Magnetic iron oxide nanoparticles offer additional multifunctional advantages, including magnetic targeting, externally controlled drug delivery, and magnetic hyperthermia, in which localized heat generated under an alternating magnetic field enhances

therapeutic efficacy, particularly in cancer treatment. Moreover, these magnetic nanoparticles can simultaneously serve as diagnostic imaging agents, enabling the integration of therapy and diagnosis, a concept widely known as theranostics [31].

Collectively, these inorganic and metallic nanocarriers provide a versatile platform that not only improves the pharmacokinetic performance of herbal compounds but also enables the integration of targeted therapy, controlled drug release, diagnostic imaging, and precision medicine within nano-phytopuncture. Several compelling examples illustrate the therapeutic potential of metallic and inorganic nanoparticles for enhancing herbal drug delivery. One prominent example is curcumin-conjugated gold nanoparticles (AuNPs), which have shown significantly improved targeting efficiency and preferential accumulation in tumor tissues [32,33]. The unique physicochemical properties of gold nanoparticles, including their excellent biocompatibility and ease of surface modification, facilitate efficient delivery of curcumin, a natural polyphenolic compound with potent anticancer activity but inherently poor bioavailability to malignant cells, thereby enhancing therapeutic efficacy while reducing systemic toxicity [34]. Another notable example involves iron oxide (Fe_3O_4) nanoparticles coated with chitosan and loaded with quercetin, a flavonoid known for its potent antioxidant and anticancer properties. This multifunctional nanoparticle system has demonstrated enhanced cellular uptake, improved intracellular drug delivery, and superior anticancer efficacy in various experimental models. Furthermore, the magnetic properties of Fe_3O_4 nanoparticles enable externally guided magnetic targeting, increasing delivery precision while minimizing adverse effects on healthy tissues [35]. These examples underscore the potential of integrating herbal bioactive compounds with metallic and inorganic nanoparticles to overcome the pharmacokinetic limitations of phytochemicals and develop multifunctional therapeutic systems capable of targeted drug delivery, controlled release, diagnostic imaging, and enhanced treatment outcomes in nano-phytopuncture and related biomedical applications [36].

3.4. Nanogels and hydrogels

Nanogels are a versatile, innovative class of nanocarriers characterized by crosslinked, three-dimensional polymer networks that can absorb and retain large amounts of water or biological fluids [37]. This unique structure allows nanogels to

swell and respond to environmental stimuli, making them well-suited for controlled, sustained release of herbal compounds. Because of their high water content and soft nature, nanogels are highly biocompatible and can be administered through multiple routes, including oral, nasal, and topical applications, expanding their therapeutic versatility [38]. Their ability to protect sensitive herbal actives from enzymatic degradation and harsh physiological conditions further enhances the stability and bioavailability of phytochemicals. Moreover, nanogels can be engineered to respond to specific triggers such as pH, temperature, or ionic strength, enabling site-specific drug release and improved targeting of diseased tissues [39]. This controlled delivery not only maximizes therapeutic efficacy but also minimizes systemic side effects. Overall, nanogels offer a promising platform for advancing nano-phytopuncture by combining the benefits of hydrogels with nanoscale precision, making them an exciting area of research for modern herbal medicine delivery systems [40]. Hydrogels are three-dimensional, hydrophilic polymer networks that can hold large amounts of water while maintaining their structure, making them excellent carriers for sustained drug delivery in herbal medicine. A notable example is the chitosan-Panax hydrogel, which has shown the ability to provide controlled, prolonged release of active compounds over 10 days [41]. This extended-release profile is particularly advantageous in pharmacopuncture, as it ensures a steady therapeutic concentration of the herbal extract at the target site, reducing the need for frequent administrations and improving patient compliance. The natural polymer chitosan offers biocompatibility and biodegradability and enhances mucoadhesive properties, facilitating better retention at the site of injection or application [42]. Additionally, combining it with Panax extracts leverages the herb's adaptogenic and immunomodulatory effects, making the hydrogel a multifunctional delivery platform. Hydrogels like this exemplify how integrating traditional herbal medicine with advanced biomaterials can overcome pharmacokinetic limitations, enhance stability, and optimize therapeutic outcomes in nano-phytopuncture treatments [43].

4. MECHANISMS OF ENHANCED BIOAVAILABILITY

4.1. Improved solubility and stability: One of the primary mechanisms through which nanocarriers enhance the bioavailability of herbal compounds is by significantly improving their solubility and stability [44]. Many phytochemicals naturally possess poor water solubility, which

severely limits their absorption in the gastrointestinal tract and reduces their overall therapeutic effectiveness. Nanocarriers address this challenge by encapsulating these compounds in specialized structures such as liposomes, polymeric nanoparticles, or lipid-based carriers, increasing their dispersibility in bodily fluids [45]. This encapsulation also protects the active ingredients from harsh gastric acids and enzymatic degradation, which commonly break down herbal molecules before they can exert their effects. Furthermore, by shielding phytochemicals from premature metabolism, nanocarriers prolong the drug's circulation time, allowing sustained therapeutic levels and improved tissue targeting [46]. Together, these factors contribute to a more efficient delivery system that maximizes the amount of active compound reaching the intended site of action, ultimately enhancing the overall bioavailability and clinical efficacy of herbal treatments administered via pharmacopuncture [47].

4.2. Passive (EPR) and active targeting: Nanocarriers improve the targeting of herbal compounds through both passive and active mechanisms, significantly enhancing therapeutic precision and efficacy. Passive targeting primarily relies on the Enhanced Permeability and Retention (EPR) effect, in which nanoparticles accumulate in inflamed or tumorous tissues due to leaky vasculature and poor lymphatic drainage [48]. This allows the nanocarriers to concentrate the herbal actives directly at disease sites without affecting healthy tissues, reducing systemic side effects. Beyond this, active targeting involves functionalizing nanocarrier surfaces with specific ligands, such as antibodies, peptides, or small molecules, that bind selectively to receptors overexpressed on target cells [49]. For example, a folate-chitosan-quercetin nanoparticle system uses folate as a targeting ligand to exploit cancer cells' high affinity for folate receptors, ensuring enhanced uptake and retention within tumor cells [50]. This ligand-mediated approach not only increases cellular internalization but also improves the therapeutic index of the encapsulated herbal compound by delivering it precisely where it is needed most. Combining passive and active targeting strategies in nano-phytopuncture therefore represents a powerful approach to maximize treatment efficacy while minimizing unwanted effects [51].

4.3. Stimuli-responsive release: Stimuli-responsive release systems represent a sophisticated advancement in nano-phytopuncture, enabling herbal compounds to be released in

response to specific environmental triggers such as pH, temperature, or magnetic fields [52]. These smart nanocarriers are engineered to remain stable during circulation but undergo structural changes or degradation when exposed to particular stimuli at the target site, allowing for precise control over drug release timing and location. For example, nanoparticles coated with materials sensitive to acidic pH can exploit the lower pH environment commonly found in inflamed or tumor tissues, triggering the release of encapsulated herbal actives exactly where they are needed [53]. Similarly, temperature-sensitive coatings can respond to localized hyperthermia, releasing their payload once they reach a certain temperature threshold. Magnetic nanoparticles, such as superparamagnetic iron oxide (SPIO), offer the unique capability of externally controlled release through alternating magnetic fields, which generate localized heat and induce drug liberation [54]. This combination of internal and external triggers enables highly targeted, efficient therapy, minimizing systemic exposure and side effects while maximizing the therapeutic impact of herbal medicines delivered via pharmacopuncture [55].

4.4. Lymphatic uptake

After pharmacopuncture administration, nanoparticles deposited in interstitial tissue may enter peripheral lymphatic capillaries through pressure-driven interstitial fluid drainage. Unlike orally administered lipid nanoparticles, which access the lymphatic system through chylomicron-mediated intestinal absorption, injectable nano-phytopuncture formulations rely primarily on particle size, surface characteristics, and local interstitial transport for lymphatic uptake [56]. Nanoparticles within an optimal size range preferentially enter lymphatic capillaries rather than blood capillaries, allowing gradual drainage from the injection site into regional lymph nodes before entering the systemic circulation. This peripheral lymphatic transport prolongs local residence time, facilitates sustained release of encapsulated phytochemicals, and enables gradual systemic distribution without dependence on gastrointestinal absorption pathways. By promoting controlled lymphatic drainage, solid lipid nanoparticles (SLNs) help maintain prolonged therapeutic concentrations of herbal bioactive compounds at the injection site while simultaneously facilitating their systemic availability through the lymphatic network. This transport pathway reduces rapid systemic clearance, enhances exposure of lymphoid and inflamed tissues to the therapeutic agents, and minimizes fluctuations in drug concentration. Consequently, SLNs

represent an effective delivery platform for hydrophobic phytochemicals by improving localized tissue retention, sustained therapeutic release, and overall bioavailability, thereby enhancing the therapeutic potential of nano-phytopuncture treatments [57].

5. THERAPEUTIC APPLICATIONS AND CASE STUDIES

5.1. Antimicrobial potential of nano-phytopuncture systems

In vitro investigations have demonstrated that composite silver-curcumin nanoparticles (often termed Cur-AgNPs or cAgNPs) disrupt established biofilms of both *Pseudomonas aeruginosa* and *Staphylococcus aureus*. A concentration of approximately 100 µg/mL of the hybrid formulation eradicated nearly 50% of mature biofilms, whereas curcumin nanoparticles alone required approximately 500 µg/mL to achieve the same level of disruption. Microscopic analyses using scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM) revealed substantial damage to the biofilm architecture, supporting a synergistic antimicrobial mechanism. Importantly, the combined formulation remained non-toxic to human bronchial epithelial cells, indicating a favorable safety profile [58]. In related studies, ultrasound-fabricated Cur-AgNPs (approximately 25–35 nm) demonstrated significantly greater antimicrobial activity than silver nanoparticles alone, with minimum inhibitory concentration (MIC) values decreasing from approximately 20 mg/L for pure AgNPs to approximately 5 mg/L for Cur-AgNPs against both Gram-positive and Gram-negative bacteria. The enhanced antimicrobial activity was attributed to increased Ag⁺ ion release and reactive oxygen species (ROS) generation, with curcumin acting as both a reducing and stabilizing (capping) agent that promoted silver accumulation at the bacterial membrane [59]. These mechanisms resulted in oxidative stress, membrane disruption, and subsequent bacterial cell death. Furthermore, Cur-AgNPs reduced the secretion of pro-inflammatory cytokines (IL-6 and TNF-α) in human macrophages. They exhibited selective toxicity, with MIC values remaining substantially below the cytotoxic concentrations observed in keratinocytes (cell death occurring only at approximately 156 mg/L). Although these antimicrobial findings clearly demonstrate the enhanced therapeutic potential of nano-herbal formulations, the reported studies employed conventional in vitro experimental models rather than pharmacopuncture-based delivery. Consequently, the observed antimicrobial efficacy cannot be directly extrapolated to localized acupoint administration, highlighting the need for

dedicated pharmacopuncture investigations to evaluate nanoparticle retention, local tissue distribution, controlled release, and antimicrobial efficacy within the unique microenvironment of pharmacopuncture injection sites.

5.2. Anticancer efficacy of nano-phytopuncture strategies

Nanotechnology-enabled piperine nanocapsules have markedly enhanced the therapeutic potential of this phytoconstituent by improving its bioavailability and biological activity. In an investigation against *Trypanosoma evansi*, piperine-loaded nanocapsules reduced the half-maximal inhibitory concentration (IC₅₀) from 14.45 µM for free piperine to 5.04 µM, representing an approximately threefold improvement in antiparasitic efficacy. This enhanced activity was accompanied by increased reactive oxygen species (ROS) generation within the parasite, with minimal cytotoxicity toward host mammalian cells, demonstrating an improved therapeutic index [60]. Similarly, curcumin-loaded magnetic nanoparticles (MNP-CUR) have shown considerable promise in pancreatic cancer models. These formulations, consisting of iron oxide nanoparticle cores encapsulating curcumin, demonstrated dose-dependent cellular internalization into Panc-1 and HPAF-II cell lines, significantly inhibited cell proliferation and colony formation *in vitro*, increased serum bioavailability by approximately 2.5-fold compared with free curcumin, and effectively suppressed tumor growth while improving survival in HPAF-II xenograft mouse models without inducing hematological toxicity [61]. Collectively, these studies demonstrate that nano-encapsulation substantially enhances the antiparasitic and anticancer efficacy of phytochemicals by improving cellular uptake, enabling controlled drug release, reducing effective therapeutic doses, and increasing overall bioavailability. These advantages highlight the potential of nano-herbal formulations as targeted therapeutic platforms with reduced systemic toxicity. Similarly, these anticancer studies primarily evaluated intravenous or conventional systemic routes of administration rather than pharmacopuncture-based delivery. While the findings confirm improved bioavailability and therapeutic efficacy of nano-herbal formulations, further investigations are needed to determine nanoparticle behavior after localized pharmacopuncture injection, including tissue retention, sustained local drug release, interstitial diffusion, lymphatic transport, and acupoint-specific pharmacodynamic responses. Such studies are essential for translating promising outcomes of conventional nanomedicine into clinically applicable nano-phytopuncture therapies.

5.3. Neuroprotective and anti-inflammatory potentials of phyto-nanocarrier systems

Recent experimental studies have demonstrated that quercetin-loaded superparamagnetic iron oxide nanoparticles ($\text{Fe}_3\text{O}_4@ \beta$ -cyclodextrin) markedly reduce seizure episodes, neuronal loss, and astrocyte activation in PTZ-induced kindled epilepsy models. These neuroprotective effects have been attributed to improved quercetin solubility, enhanced brain bioavailability, and the potent antioxidant and anti-inflammatory properties intrinsic to this flavonoid [62]. Mechanistic studies further indicate that flavonoids regulate multiple neuroinflammatory signaling pathways, including NF- κ B, MAPK, and Nrf2, thereby enhancing endogenous antioxidant defenses and attenuating oxidative stress in epileptic brain tissue. These beneficial effects are significantly potentiated when flavonoids are delivered using magnetic nanoparticle-based delivery systems, which improve stability, cellular uptake, and targeted brain delivery [63]. Meanwhile, Fe_3O_4 nanoparticles coated with Astragalus polysaccharides ($\text{Fe}_3\text{O}_4@ \text{APS}$) have demonstrated therapeutic efficacy in rodent models of iron deficiency anemia by simultaneously providing iron supplementation and stimulating hematopoiesis. In addition to their therapeutic function, these nanoparticles also serve as T_2 -weighted magnetic resonance imaging (MRI) contrast agents, enabling real-time visualization of nanoparticle biodistribution and therapeutic response [64].

Collectively, these studies show that herbal compound-loaded Fe_3O_4 nanoparticle systems provide multifunctional therapeutic and diagnostic capabilities, offering anti-epileptic, antioxidant, anti-inflammatory, and neuroprotective effects, along with enhanced formulation stability, controlled drug release, targeted delivery, and non-invasive imaging. These multifunctional properties highlight the considerable potential of phyto-nanocarrier systems for managing neurological and hematological disorders. These neuroprotective findings provide encouraging evidence for nano-herbal delivery; however, none of the cited investigations specifically examined pharmacopuncture administration. Future studies should evaluate whether localized acupoint deposition produces prolonged therapeutic effects through sustained nanoparticle retention, controlled release within the interstitial tissue, and modulation of local neuroimmune signaling at pharmacopuncture sites. Such investigations would provide valuable insights into the translational potential of nano-phytopuncture for neurological disorders.

6. SAFETY, BIOCOMPATIBILITY, AND REGULATORY CHALLENGES IN PHYTO-NANOMEDICINE

The safety and toxicological profile of nanoparticles used in nano-phytopuncture is strongly influenced by their size, surface charge, and shape, which play critical roles in determining their interactions with biological systems [65]. For instance, smaller nanoparticles, particularly silver nanoparticles (AgNPs) under 20 nanometers, have been shown to exhibit significantly higher cytotoxicity compared to their larger counterparts. This increased toxicity largely stems from their higher surface area-to-volume ratio, which facilitates greater cellular uptake and reactive oxygen species (ROS) generation, potentially leading to oxidative stress and cell damage [66]. Additionally, nanoparticle surface charge affects stability in biological fluids, protein binding, and cellular membrane interactions; positively charged particles tend to interact more strongly with negatively charged cell membranes, which can increase cytotoxic effects [67]. Nanoparticle shape also influences biological fate, as rod-shaped or irregularly shaped particles may induce different levels of inflammation or immune responses than spherical ones. Understanding these physicochemical parameters is essential for designing safer nanocarriers that balance therapeutic efficacy with minimal adverse effects.

Furthermore, regulatory frameworks are evolving to address these complexities, emphasizing the need for comprehensive toxicological evaluations and standardized testing protocols to ensure the safe clinical translation of nano-phytopuncture technologies [68]. Surface functionalization of nanoparticles plays a crucial role in improving their safety profile by reducing immunogenicity and enhancing biological clearance, key factors in minimizing adverse reactions during nano-phytopuncture treatments. Techniques such as PEGylation, the attachment of polyethylene glycol (PEG) chains, and chitosan coating are widely used to modify nanoparticle surfaces, creating a hydrophilic, sterically stabilized barrier that prevents protein adsorption and immune recognition. This “stealth” effect reduces the likelihood of triggering immune responses such as inflammation or rapid clearance by the mononuclear phagocyte system, thereby prolonging the circulation time of the therapeutic payload [69]. Chitosan, a natural biopolymer, not only enhances biocompatibility but also offers mucoadhesive properties and can facilitate targeted delivery through its positive charge interacting with negatively charged cell membranes [70]. By improving nanoparticle stability and evading immune detection, surface functionalization strategies ensure safer and

more effective delivery of herbal compounds. These modifications are also essential considerations for regulatory approval, as they help address potential toxicity concerns and support the development of clinically translatable nano-phytopuncture formulations with predictable pharmacokinetics and reduced side effects [71]. Despite the promising advances in nano-phytopuncture, significant regulatory gaps remain that challenge the consistent development and clinical translation of these technologies. One major issue is the lack of standardized protocols for herbal extracts, whose chemical composition can vary widely because of factors such as plant source, extraction methods, and batch differences, leading to inconsistent therapeutic outcomes. Additionally, reproducibility in nano formulation metrics such as particle size, zeta potential, and drug-loading efficiency is critical, as these parameters directly influence the safety, efficacy, and stability of the nanocarriers [72]. However, variability in manufacturing processes often results in discrepancies that complicate quality control and regulatory assessment. Furthermore, comprehensive toxicology guidelines tailored to nano-phytopuncture products are urgently needed to address their unique physicochemical properties and biological interactions [73]. Current regulatory frameworks are not fully equipped to evaluate the complexity of these hybrid herbal-nanoparticle systems, creating uncertainty in safety evaluation and approval pathways. Addressing these gaps through standardized herbal extract characterization, rigorous nanoformulation quality control, and dedicated toxicological protocols is essential to build regulatory confidence and facilitate the safe, effective integration of nano-phytopuncture into mainstream healthcare[74].

7. TRANSLATIONAL CHALLENGES AND FUTURE DIRECTIONS

7.1 Standardization: One of the foremost translational challenges in advancing nano-phytopuncture lies in the standardization of formulations, particularly in achieving consistent physicochemical parameters despite the inherent variability of herbal extracts [75]. Herbal materials are complex mixtures whose composition can fluctuate based on factors such as plant species, growing conditions, harvesting time, and extraction techniques. This variability poses significant obstacles to reproducibly controlling critical nanoformulation characteristics such as particle size, surface charge, encapsulation efficiency, and release-profile parameters essential for predictable biological behavior and therapeutic efficacy [76]. Without robust standardization protocols, batch-

to-batch differences may lead to inconsistent clinical outcomes and hinder regulatory approval. Addressing this challenge requires integrating advanced analytical tools for detailed phytochemical profiling with stringent manufacturing practices that tightly regulate both the herbal and nanomaterial components. Developing well-defined quality control frameworks and harmonized standards will be crucial to translating nano-phytopuncture from laboratory innovation to reliable, scalable therapies with broad clinical impact [77].

7.2 Scale-up and GMP compliance: Scaling up the production of nano-herbal formulations while ensuring Good Manufacturing Practice (GMP) compliance presents a critical challenge in the clinical translation of nano-phytopuncture therapies [78]. Laboratory-scale methods that produce consistent, high-quality nanoparticles may not translate directly to industrial-scale manufacturing because maintaining precise control over critical parameters such as particle size distribution, surface chemistry, and drug-loading efficiency is complex. Achieving reproducibility at scale requires robust process optimization, validated protocols, and advanced manufacturing technologies capable of producing nano-formulations with uniform characteristics batch after batch [79]. Additionally, strict adherence to GMP guidelines is essential to guarantee product safety, purity, and efficacy, as well as to satisfy regulatory requirements. This includes comprehensive documentation, rigorous quality control testing, and contamination prevention measures throughout the production cycle. Overcoming these scale-up hurdles is fundamental to delivering reliable, clinical-grade nano-herbal products that can meet the demands of healthcare systems, ultimately facilitating wider patient access to safe and effective nano-phytopuncture treatments [80].

7.3. Clinical evidence and trials: Despite the growing preclinical research supporting the potential of nano-phytopuncture, there remains a notable scarcity of in vivo animal studies and human clinical trials to validate its safety and efficacy comprehensively. Most current evidence is limited to laboratory or animal models, which, while promising, do not fully capture the complex pharmacodynamics and pharmacokinetics that occur in humans [81]. This gap highlights the urgent need for well-designed clinical trials that systematically evaluate how nano-herbal formulations behave within the human body, specifically their absorption,

distribution, metabolism, and excretion profiles, as well as their therapeutic effects over both short and long durations [82]. Furthermore, long-term safety data are crucial for identifying potential toxicities or adverse reactions associated with repeated or chronic administration of these nanoformulations. Addressing

these research gaps will provide the robust clinical evidence necessary to support regulatory approvals, optimize dosing regimens, and build healthcare providers' and patients' confidence in nano-phytopuncture as a reliable and effective treatment modality [83].

Table 1: Representative nano-herbal formulations with translational potential for parenteral nano-phytopuncture and precision phytomedicine

Nano-herbal formulation	Active phytochemical	Intended parenteral application	Primary evidence	Administration route	Major translational findings	Ref
PEGylated curcumin nanoparticles	Curcumin	Solid tumors	Preclinical + early translational studies	Intravenous	Enhanced circulation time, passive tumor accumulation through EPR effect, reduced systemic toxicity.	[84]
Liposomal curcumin	Curcumin	Advanced malignancies	Phase I clinical study + translational studies	Intravenous	Demonstrated acceptable safety, improved pharmacokinetics, and preliminary antitumor activity.	[85]
Polymeric curcumin nanoparticles	Curcumin	Inflammatory disorders	Human clinical evidence (oral) + parenteral preclinical studies	Intravenous (experimental)	Sustained release, macrophage targeting, suppression of NF- κ B and pro-inflammatory cytokines.	[86]
Albumin-based curcumin nanoparticles	Curcumin	Targeted cancer therapy	Translational studies	Intravenous	Improved cellular uptake, prolonged circulation, enhanced intracellular drug delivery.	[87]
Nano-silymarin	Silymarin	Hepatic injury and systemic inflammation	Human clinical studies + formulation research	Intravenous (experimental)	Increased aqueous solubility, enhanced hepatocyte uptake, reduced oxidative stress.	[88]
PLGA-loaded silymarin nanoparticles	Silymarin	Liver fibrosis	Preclinical translational studies	Intravenous	Improved hepatic accumulation and antifibrotic efficacy compared with free silymarin.	[89]
Berberine lipid nanoparticles	Berberine	Metabolic disorders	Translational studies	Intravenous	Improved bioavailability, mitochondrial protection, and anti-inflammatory activity.	[90]
Resveratrol polymeric nanoparticles	Resveratrol	Neurodegenerative disorders	Translational studies	Intravenous	Improved blood-brain barrier penetration and sustained antioxidant activity.	[91]
EGCG nanoparticles	Epigallocatechin gallate	Cancer and inflammatory diseases	Translational studies	Intravenous	Enhanced stability, prolonged plasma half-life, and improved cellular internalization.	[92]
Quercetin-loaded liposomes	Quercetin	Autoimmune and inflammatory diseases	Translational studies	Intravenous	Enhanced biodistribution, reduced oxidative damage, and improved anti-inflammatory efficacy.	[93]
Piperine nanocarriers	Piperine	Combination chemotherapy	Translational studies	Intravenous	Improved intracellular drug accumulation and reversal of multidrug resistance.	[94]
Magnetic phytochemical nanoparticles	Curcumin/Resveratrol	Image-guided targeted nano-phytopuncture	Experimental translational studies	Intravenous / Local injection	Magnetic guidance enabled localized delivery with reduced off-target exposure and improved therapeutic precision.	[95]

8. INNOVATION OPPORTUNITIES

Smart nanoparticles, including erythrocyte-mimetic and stimuli-responsive systems, offer a next-generation strategy in nano-phytopuncture by addressing critical limitations in conventional herbal drug delivery [96]. Erythrocyte-mimetic nanoparticles, designed to replicate red blood cells in morphology and surface properties, demonstrate immune evasion and prolonged circulation, enhancing the bioavailability of herbal compounds. Stimuli-responsive nanoparticles enable site-specific, controlled release of phytochemicals triggered by internal cues such as pH, enzymes, or external factors like light or ultrasound [97]. This responsive behavior ensures precise therapeutic delivery, reducing systemic toxicity and improving treatment efficacy. Integrating these smart nanocarriers into nano-phytopuncture frameworks aligns with the growing demand for precision medicine, allowing therapies to adapt dynamically to disease states and individual patient profiles. The fusion of traditional herbal knowledge with advanced, programmable nanotechnologies promises to optimize therapeutic performance and expand the clinical utility of phytomedicines in a targeted, efficient, and safer manner [98].

9. NANO-DEPOT FORMATION AND ACUPOINT MICROENVIRONMENT

One unique advantage of nano-phytopuncture is its ability to create a localized nanoparticle depot at acupuncture points after injection. Unlike conventional herbal pharmacopuncture, nanocarriers may remain within the interstitial extracellular matrix for extended periods, providing sustained release of bioactive phytochemicals while maintaining prolonged stimulation of local tissues. This depot effect may continuously activate sensory nerve endings, immune cells, and surrounding connective tissue, potentially extending both pharmacological and mechanical components of acupuncture therapy [99].

Furthermore, prolonged nanoparticle retention may influence interstitial fluid dynamics and extracellular matrix remodeling around the acupoint, thereby modifying local biochemical signaling involved in acupuncture-induced therapeutic responses. Although these mechanisms remain largely hypothetical, they offer a plausible explanation for the potential synergistic interaction between controlled nanocarrier drug release and traditional meridian stimulation. Future investigations combining imaging technologies, electrophysiological measurements, and pharmacokinetic studies are required to validate these proposed mechanisms and

establish nano-phytopuncture as a scientifically supported integrative therapeutic strategy [100].

10. CONCLUSION

Nano-phytopuncture represents a compelling convergence of traditional herbal medicine and modern nanotechnology, offering a transformative approach to overcoming the limitations of conventional pharmacopuncture. By enhancing the bioavailability of herbal compounds, these advanced nanoformulations improve the absorption, stability, and systemic delivery of active ingredients that are otherwise hindered by poor solubility or rapid metabolism. Moreover, the ability to achieve targeted precision, whether through ligand-based targeting, stimuli-responsive release, or biomimetic designs, ensures that therapeutic agents act more selectively at disease sites, thereby maximizing efficacy while minimizing off-target effects and systemic toxicity.

This precision not only elevates treatment effectiveness but also significantly reduces side effects commonly associated with herbal or conventional drug therapies. As a result, nano-phytopuncture holds great promise for safer, more efficient, and personalized treatment options, bridging ancient healing wisdom and cutting-edge biomedical innovation. With continued research, standardization, and clinical validation, this synergistic approach could redefine herbal therapy paradigms and broaden the horizons of integrative medicine. To fully realize the clinical potential of nano-phytopuncture, future research must prioritize overcoming several critical challenges. Chief among these is standardizing herbal extracts and nano-formulations to ensure consistent quality, reproducibility, and predictable therapeutic outcomes across batches and manufacturing scales.

Alongside this, a robust safety evaluation framework is essential to thoroughly assess the short- and long-term toxicological effects of these novel nanocarriers, considering their unique physicochemical properties and biological interactions. Such safety assessments should include detailed investigations into immunogenicity, biodistribution, metabolism, and potential organ accumulation. Equally important is conducting rigorous, well-designed controlled clinical trials that provide high-quality evidence on efficacy, pharmacokinetics, pharmacodynamics, and adverse effects in diverse patient populations. These clinical studies will help validate preclinical findings, refine dosing regimens, and build regulatory confidence, ultimately paving the way for safe, effective, and widely accepted nano-phytopuncture

therapies. Addressing these research imperatives will be crucial in bridging the gap between promising laboratory innovation and practical, scalable treatments that can meaningfully improve patient care.

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The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Poonam Sahu: Original drafting of the manuscript

Dr. Trilochan Satapathy: Revision and Supervision

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