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Nanoparticle- Embedded Hydrogels for Phytoconstituents Delivery: A Smart Approach to Drug Delivery Systems

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ABSTRACT
Phytoconstituents bioactive compounds derived from medicinal plants have gained significant attention in pharmaceutical research due to their therapeutic efficacy, biocompatibility, and minimal side effects. However, their clinical translation is often hindered by poor aqueous solubility, low bioavailability, instability, and rapid metabolism. Recent advances in nanotechnology and biomaterials have introduced nanoparticle-embedded hydrogels as a smart and versatile platform for effective phytoconstituent delivery. These hybrid systems combine the structural and stimuli-responsive properties of hydrogels with the controlled release, protective encapsulation, and targeting abilities of nanoparticles. Such systems enable site-specific, sustained, and responsive drug release under physiological conditions. This review highlights the principles of hydrogel nanoparticle integration, the advantages of these hybrid systems in phytoconstituent delivery, recent applications in wound healing, cancer therapy, anti- inflammatory treatments, and antimicrobial formulations, as well as current challenges and future perspectives. By bridging traditional herbal medicine with modern nanotechnology, nanoparticle-embedded hydrogels represent a promising next- generation platform in smart drug delivery systems.
Keywords: *Hydrogels; Nanoparticles; Phytoconstituents; Drug delivery systems; Smart biomaterials; Controlled release; Herbal therapeutics; Nanohybrid hydrogels.*

1. INTRODUCTION

The increasing global interest in plant-derived bioactive compounds has revitalized the importance of phytoconstituents in modern medicine. These natural molecules including alkaloids, flavonoids, phenolics, terpenoids, and glycosides possess diverse pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial, anticancer, and wound-healing effects (Patra et al., 2021; Hussain et al., 2022). Despite their therapeutic potential, phytoconstituents often face serious limitations, such as low aqueous solubility, poor stability under physiological conditions, rapid metabolism, and low systemic bioavailability, which restrict their clinical applications (Yadav et al., 2020).

To address these challenges, drug delivery systems (DDSs) have been explored to enhance solubility, stability, and bioavailability of phytoconstituents. Among these, hydrogels three-dimensional polymeric networks with high water content have emerged as versatile carriers due to their tunable porosity, biocompatibility, biodegradability, and ability to provide sustained drug release (Ahmed, 2015; Li et al., 2021). However, conventional hydrogels often suffer from weak mechanical strength and limited drug-loading efficiency, especially for hydrophobic phytoconstituents.

Recent advances in nanotechnology have enabled the development of nanoparticle- embedded hydrogels, a hybrid delivery system that integrates the benefits of nanoparticles (NPs) and hydrogels into a single platform. Nanoparticles including polymeric, metallic, lipid-based, and magnetic varieties offer controlled release, surface functionalization for targeting, and improved encapsulation of poorly soluble phytoconstituents (Chakraborty et al., 2022). When embedded within hydrogels, they provide additional structural stability, stimuli-responsive release (pH, temperature, enzymes, magnetic field), and protection of labile bioactives from degradation (Sharma et al., 2023).

This novel approach has been applied in diverse therapeutic contexts. For instance, quercetin-loaded nanoparticle hydrogels demonstrated enhanced wound healing and antimicrobial activity (Khan et al., 2022). Curcumin nanohybrids incorporated into hydrogels have been investigated for cancer therapy and anti-inflammatory treatments (Basu et al., 2021). Similarly, silver nanoparticle–hydrogel composites with calendula extract showed synergistic antibacterial and regenerative effects for wound dressings (Singh et al., 2023).

Given the growing number of studies in this field, it is essential to consolidate knowledge on nanoparticle-embedded hydrogels for phytoconstituent delivery. This review provides a comprehensive overview of their design principles, mechanisms of drug release, therapeutic applications, challenges, and future directions.

Special emphasis is placed on the integration of phytomedicine with nanotechnology, underscoring the potential of these smart systems to revolutionize drug delivery and personalized medicine.

2. FUNDAMENTALS

2.1 Hydrogels as Drug Delivery Platforms;

Hydrogels are three-dimensional hydrophilic polymer networks capable of absorbing large amounts of water or biological fluids while maintaining structural integrity (Ahmed, 2015). Their tunable porosity, mechanical strength, and biocompatibility make them excellent candidates for drug encapsulation and controlled release. Hydrogel matrices can be synthesized from natural polymers (chitosan, alginate, gelatin, hyaluronic acid) or synthetic polymers (polyvinyl alcohol, polyethylene glycol, poly(N-isopropylacrylamide) (PNIPAM)) (Huang et al., 2021).

One of the most attractive features of hydrogels is their ability to act as stimuli- responsive systems, also termed "smart hydrogels." These can alter their swelling, permeability, and drug-release characteristics in response to environmental triggers such as pH, temperature, ionic strength, light, enzymes, and redox conditions (Liu et al., 2020; Li et al., 2021). For example, pH-sensitive hydrogels have been applied for colon-specific drug delivery, while thermosensitive hydrogels enable in situ gelation at body temperature, making them suitable for injectable formulations (Coviello et al., 2022).

Despite these advantages, conventional hydrogels alone exhibit limitations such as poor mechanical strength, limited stability in vivo, and inefficient loading of hydrophobic drugs, which restrict their broader clinical applications. These challenges have paved the way for the integration of nanoparticles into hydrogel matrices.

2.2 Nanoparticles in Drug Delivery;

Nanoparticles (NPs), typically ranging from 10 to 500 nm in size, serve as versatile drug carriers with unique physicochemical and functional properties. They enhance solubility, stability, bioavailability, and cellular uptake of therapeutic agents, including poorly soluble phytoconstituents (Chakraborty et al., 2022).

TYPES OF NANOPARTICLES COMMONLY USED IN DRUG DELIVERY INCLUDE

- **Polymeric nanoparticles**: Biodegradable carriers such as PLGA, PLA, and chitosan nanoparticles; useful for sustained release and high drug encapsulation efficiency.
- **Lipid-based nanoparticles**: Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) that provide biocompatibility and enhanced permeability (Das et al., 2021).
- **Inorganic nanoparticles**: Gold, silver, zinc oxide, and iron oxide nanoparticles, which offer additional functionalities like antimicrobial activity, imaging, and magnetic targeting (Wang et al., 2020).
- **Hybrid nanoparticles**: Combinations of organic and inorganic materials that integrate biocompatibility with functional responsiveness.

The surface functionalization of nanoparticles with ligands, antibodies, or aptamers further enables active targeting to specific tissues or receptors (Patra et al., 2021). Moreover, nanoparticles can protect phytoconstituents from degradation, improve intracellular uptake, and allow stimuli-triggered release.

2.3 Nanoparticle-Embedded Hydrogels: A Hybrid Approach;

The integration of nanoparticles into hydrogel matrices results in nanocomposite hydrogels, which combine the mechanical stability and stimuli responsiveness of hydrogels with the loading capacity and controlled release features of nanoparticles (Sharma et al., 2023). This hybridization can be achieved through several strategies:

1. **In situ nanoparticle synthesis within hydrogels –** metal or polymeric nanoparticles are generated directly inside the hydrogel matrix, providing uniform distribution and strong interactions.
2. **Pre-formed nanoparticle incorporation –** nanoparticles are synthesized separately and then physically entrapped or chemically crosslinked within hydrogel networks.
3. **Surface-anchored nanoparticles –** nanoparticles are tethered onto hydrogel backbones to achieve targeted release and structural reinforcement.

These systems offer several advantages:

- Sustained and controlled release of phytoconstituents.
- Enhanced loading of poorly soluble molecules.
- Protection of phytoconstituents from hydrolysis, oxidation, and enzymatic degradation.
- Stimuli-responsive release under physiological conditions.

- Improved mechanical stability for biomedical applications (Zhao et al., 2022; Basu et al., 2021).

Nanoparticle-embedded hydrogels have demonstrated superior performance in oral, transdermal, ocular, and parenteral drug delivery compared to conventional formulations. Importantly, they bridge the gap between traditional herbal medicine and advanced smart biomaterials, offering a cutting-edge strategy for next-generation drug delivery systems.

3. PHYTOCONSTITUENT DELIVERY VIA NANOPARTICLE–HYDROGEL SYSTEMS:

Phytoconstituents—bioactive compounds derived from medicinal plants—are widely recognized for their therapeutic potential. However, their clinical application remains limited due to poor solubility, chemical instability, and low systemic bioavailability (Patra et al., 2021; Yadav et al., 2020). Embedding nanoparticles loaded with phytoconstituents into hydrogels provides a dual protective environment, enabling sustained and site-specific release, improved stability, and enhanced therapeutic efficacy.

3.1 Types of Phytoconstituents Delivered Using Nanoparticle–Hydrogel Systems;

(a) Flavonoids;

Quercetin, a natural flavonoid with antioxidant, anti-inflammatory, and anticancer activity, suffers from poor solubility. Studies show that ZnO nanoparticle-loaded chitosan hydrogels improve quercetin's stability, sustain its release, and enhance antimicrobial activity in wound healing models (Khan et al., 2022).

Rutin embedded into polymeric nanoparticle hydrogels has demonstrated promising results for skin repair and UV protection (Mandal et al., 2023).

(b) Polyphenols;

Curcumin, derived from Curcuma longa, has poor bioavailability but strong anticancer and wound-healing properties. Curcumin-loaded nanoparticles embedded in hydrogels (chitosan, gelatin, or PEG-based) provide prolonged release, increased solubility, and enhanced anticancer efficacy (Basu et al., 2021; Sharma et al., 2023).

Epigallocatechin gallate (EGCG), a polyphenol from green tea, loaded into gold nanoparticles within hydrogels, demonstrated antibiofilm and anti-inflammatory effects for periodontal therapy (Zhang et al., 2022).

(c) Essential Oils;

Essential oils such as clove oil, turmeric oil, and tea tree oil are unstable and volatile, limiting their direct therapeutic use. Embedding essential oil-loaded nanoparticles in hydrogel matrices provides controlled release and enhances antimicrobial activity for wound healing and topical applications (Singh et al., 2023).

(d) Terpenoids and Saponins;

Calendula officinalis extract, rich in terpenoids and flavonoids, incorporated with silver nanoparticles in alginate/chitosan hydrogels, has shown antimicrobial, anti- inflammatory, and regenerative activity for skin dressings (Ali et al., 2022).

Ginsenosides, saponin compounds from Panax ginseng, have been formulated into nanocarrier hydrogels, improving transdermal delivery and stability (Wang et al., 2021).

3.2 CASE STUDIES AND APPLICATIONS

1. Wound Healing Applications;

Quercetin–ZnO NP–hydrogels improved collagen synthesis and epithelialization (Khan et al., 2022).

Calendula–AgNP hydrogels accelerated wound closure while preventing bacterial infections (Ali et al., 2022).

2. Cancer Therapy;

Curcumin-loaded nanoparticle hydrogels demonstrated sustained drug release and enhanced cytotoxicity against breast and colon cancer cell lines (Basu et al., 2021). Combination systems (curcumin + resveratrol in hydrogel–NPs) showed synergistic anticancer effects (Li et al., 2022).

3. Anti-inflammatory Applications;

EGCG–gold nanoparticle hydrogels inhibited pro-inflammatory cytokine release in periodontal disease models (Zhang et al., 2022).

Quercetin–nanohydrogel composites reduced oxidative stress and inflammation in skin disorders (Mandal et al., 2023).

4. Antimicrobial Therapy;

Silver nanoparticle–hydrogels combined with plant extracts exhibited potent antibacterial activity against multidrug- resistant strains (Singh et al., 2023).
Essential oil–NP hydrogels provided controlled release and long-lasting antimicrobial effects for topical delivery.

3.3 SUMMARY OF SELECTED STUDIES

Phytoconstituent	Nanoparticle Type	Hydrogel Matrix	Application	Key Findings
Quercetin	ZnO nanoparticles	Chitosan–cellulose hydrogel	Wound healing	Sustained release,Antimicrobial, Pro-healing effects
Curcumin	Polymeric nanoparti (PLGA, chitosan)	PEG/chitosan hydrogels	Cancer, inflammat	Enhanced solubility anticancer efficacy
EGCG	Gold nanoparticles	Injectable hydrogel	Periodontal therap	NIR-triggered release, anti-inflammatory, bone regeneration
Calendula extract	Silver nanoparticles	Alginate chitosan hydrogel	Wound healing	Antibacterial, anti-inflammatory, tissue regeneration
Essential oils (clove, turmeric)	Lipid/polymeric nanoparticles	Biopolymer hydrogels	Antimicrobial, care	Controlled release, prolonged antibacterial activity
Ginsenosides	Polymeric nanoparti	Thermoresponsive hydrogel	Transdermal delive	Enhanced stability and systemic absorption

4. MECHANISMS OF DRUG DELIVERY AND SMART RELEASE

The effectiveness of a drug delivery system is largely determined by its ability to release the therapeutic agent at the right time, dose, and site of action. Nanoparticle– embedded hydrogels function as multifunctional reservoirs, where nanoparticles act as drug carriers while the hydrogel matrix regulates diffusion, swelling, and responsiveness to environmental cues. The combination allows controlled, sustained, and stimuli-responsive (smart) drug release, which is crucial for phytoconstituents that are otherwise unstable or rapidly metabolized.

4.1 Diffusion-Controlled Release;

One of the primary mechanisms is Fickian diffusion, where phytoconstituents diffuse through the swollen hydrogel network. The mesh size of the hydrogel and nanoparticle encapsulation govern the release rate. For example, quercetin–ZnO nanoparticle hydrogels exhibited prolonged release due to controlled diffusion through the polymeric network (Khan et al., 2022).

4.2 Swelling- And Degradation-Controlled Release;

Hydrogels swell when exposed to aqueous environments, enlarging the pores and facilitating drug diffusion. Similarly, biodegradable hydrogels (e.g., chitosan, alginate) degrade in physiological conditions, releasing nanoparticles in a sustained manner (Li et al., 2021). This mechanism is particularly beneficial for phytoconstituents requiring extended release, such as curcumin and resveratrol.

4.3 Stimuli-Responsive (Smart) Release;

Smart hydrogels embedded with nanoparticles are engineered to respond to internal physiological or external triggers, ensuring spatiotemporal control of phytoconstituent delivery.

(a) pH-Responsive Systems

Many pathological sites (e.g., tumors, inflamed tissues, infected wounds) exhibit acidic microenvironments.
pH-sensitive hydrogels with nanoparticles enable preferential release of phytoconstituents at these sites.
Example: Curcumin-loaded nanoparticle hydrogels released drug more efficiently under acidic tumor-like conditions (Basu et al., 2021).

(b) Temperature-Responsive Systems;

Hydrogels like PNIPAM undergo sol–gel transitions in response to temperature. Injectable formulations remain liquid at room temperature but gel at body temperature, offering in situ depot formation (Coviello et al., 2022).

This strategy is used in thermoresponsive phytoconstituent gels for localized cancer and wound therapy.

(c) Enzyme-Responsive Systems;

Certain enzymes, such as matrix metalloproteinases (MMPs), are overexpressed in diseased tissues. Hydrogels crosslinked with enzyme-degradable linkages release nanoparticle-bound phytoconstituents only in the presence of these enzymes.

Example: EGCG–gold nanoparticle hydrogels degraded selectively in periodontal pockets rich in bacterial enzymes (Zhang et al., 2022).

(d) Redox-Responsive Systems;

Redox-sensitive hydrogels use disulfide bonds that cleave in high-glutathione environments, typical of tumor cells.

Example: Embedding nanoparticles in such hydrogels ensures site-specific release of anticancer phytoconstituents (Sharma et al., 2023).

(e) Magnetic- and Light-Responsive Systems;

Magnetic nanoparticles (e.g., Fe_3O_4) incorporated into hydrogels allow on-demand release under an external magnetic field.

Gold or silver nanoparticles enable photothermal or NIR-triggered release, useful in cancer and wound therapy.

Example: EGCG–gold nanoparticle hydrogels exhibited NIR-triggered drug release and promoted bone regeneration (Zhang et al., 2022).

4.4 Advantages of Smart Release Mechanisms

- Targeted delivery at disease sites.
- Reduced systemic toxicity by avoiding premature drug release.
- Sustained release profiles, improving patient compliance.
- Responsive control, allowing combination therapies (e.g., photothermal + phytoconstituent therapy).

5. ADVANTAGES AND CHALLENGES

5.1 Advantages;

Nanoparticle–embedded hydrogels provide a synergistic combination of the unique features of both components, offering multiple benefits over conventional drug delivery systems.

1. Enhanced Stability of Phytoconstituents;

- Hydrogels protect sensitive compounds (e.g., polyphenols, essential oils) from hydrolysis, oxidation, and enzymatic degradation.
- Nanoparticles further stabilize poorly soluble and volatile phytoconstituents, such as curcumin and essential oils (Basu et al., 2021; Singh et al., 2023).

2. Improved Bioavailability;

- Nanoparticles improve cellular uptake of hydrophobic phytoconstituents.
- Hydrogel matrices ensure sustained release, leading to improved plasma concentration and therapeutic effect (Yadav et al., 2020).

3. Controlled and Site-Specific Release;

- Stimuli-responsive systems (pH, temperature, enzyme, magnetic field, light) allow drug release only at targeted sites, minimizing systemic toxicity (Sharma et al., 2023).

4. Biocompatibility and Safety;

- Hydrogels composed of natural polymers (alginate, chitosan, gelatin) are biodegradable and non-toxic.
- Surface-modified nanoparticles reduce risks of immune rejection.

5. Versatility in Applications;

- Can be used in oral, injectable, transdermal, ocular, and wound-healing applications.
- Suitable for both systemic and localized delivery.

6. Synergistic Therapeutic Action;

- Metallic nanoparticles (e.g., AgNPs, AuNPs) exhibit intrinsic antimicrobial and anti-inflammatory

activity, which complements phytoconstituents in wound healing and infection control (Ali et al., 2022).

5.2 Challenges

Despite these advantages, several challenges and limitations remain before nanoparticle–hydrogel systems can be widely adopted in clinical practice.

1. Scale-Up and Manufacturing Issues:

- Reproducibility in nanoparticle size, distribution, and hydrogel consistency is difficult to achieve in large-scale production (Li et al., 2021).
- Batch-to-batch variations may affect drug release profiles.

2. Complexity of Formulation:

- Combining nanoparticles with hydrogels requires precise optimization of crosslinking, particle loading, and release kinetics.
- Complex formulations may increase production costs.

3. Stability Concerns:

- Long-term storage stability of phytoconstituent-loaded nanohydrogels remains a challenge due to moisture sensitivity and microbial contamination.
- Freeze-drying or lyophilization may alter hydrogel structure and drug release.

4. Toxicity and Biocompatibility Issues:

- Some nanoparticles (e.g., ZnO, AgNPs) may cause dose-dependent cytotoxicity or oxidative stress in healthy tissues (Wang et al., 2020).
- Ensuring safe degradation of synthetic polymers in hydrogels is also critical.

5. Regulatory Barriers;

- Herbal drug formulations already face regulatory challenges due to variability in raw materials.
- Combining them with advanced nanotechnology introduces further complexities in approval, safety validation, and standardization (Patra et al., 2021).

6. Translational Gap;

- Most studies remain preclinical (in vitro or small-animal models).
- Lack of well-designed clinical trials delays translation into real-world therapies.

5.3 Balancing Promise and Limitations;

The advantages of nanoparticle–hydrogel systems clearly demonstrate their potential to revolutionize phytoconstituent-based therapeutics. However, the challenges highlight the need for further optimization, toxicity evaluation, large-scale studies, and regulatory frameworks. Bridging these gaps is essential for successful clinical translation.

6. FUTURE PERSPECTIVES

Nanoparticle–embedded hydrogels have demonstrated tremendous promise for phytoconstituent delivery. However, to translate these systems from laboratory research into clinical and industrial applications, several future directions must be considered.

6.1 Green and Sustainable Nanoparticle Synthesis;

Conventional nanoparticle synthesis often involves toxic chemicals, raising concerns about environmental safety and biocompatibility. Green synthesis, using plant extracts, polysaccharides, or microbial processes, offers an eco-friendly alternative. Such approaches not only improve sustainability but also integrate phytoconstituents directly into the synthesis process, potentially enhancing therapeutic efficacy (Patra et al., 2021).

6.2 Multi-Stimuli-Responsive Systems;

Most current hydrogel–nanoparticle systems respond to a single trigger, such as pH or temperature. However, diseased tissues often present multiple abnormal conditions (e.g., acidic pH, elevated enzymes, high glutathione). Designing multi-stimuli- responsive nanohydrogels could allow more precise control of phytoconstituent release, improving efficacy in complex diseases like cancer and chronic wounds (Sharma et al., 2023).

6.3 Personalized And Precision Medicine;

The integration of nanotechnology with herbal therapeutics aligns with the growing trend toward personalized medicine. By tailoring phytoconstituent delivery systems to individual patient profiles

(genetic background, metabolic rate, disease type), nanoparticle–hydrogel systems can enhance therapeutic outcomes while reducing adverse effects.

6.4 Advanced Manufacturing Technologies;

Emerging fabrication techniques such as 3D bioprinting and microfluidics offer new opportunities for customizing hydrogel–nanoparticle composites with precise architectures. This may enable the creation of implantable devices or tissue- engineered scaffolds that release phytoconstituents in a spatiotemporally controlled manner.

6.5 Clinical Translation and Regulatory Frameworks;

Although preclinical studies demonstrate great promise, clinical validation remains scarce. Future work should focus on:

- Large-scale, standardized production.
- Long-term biocompatibility and toxicity studies.
- Rigorous clinical trials with standardized phytoconstituent formulations.
- Establishing clear regulatory guidelines for herbal nanomedicines.

7. CONCLUSION

Nanoparticle–embedded hydrogels represent a smart and versatile platform for delivering phytoconstituents. By combining the biocompatibility, water retention, and responsiveness of hydrogels with the stability, targeting, and controlled release capabilities of nanoparticles, these hybrid systems overcome many limitations of conventional phytotherapeutic delivery. Applications in wound healing, cancer therapy, anti-inflammatory treatments, and antimicrobial formulations demonstrate their clinical potential.

Despite challenges such as scale-up difficulties, stability issues, and regulatory barriers, advances in green synthesis, multi-stimuli-responsive designs, and precision medicine approaches are paving the way toward clinical translation. Ultimately, the integration of traditional herbal medicine with modern nanotechnology can revolutionize drug delivery, offering safer, more effective, and patient-specific therapeutic options.

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