



BIOPOLYMER-DIRECTED IN SITU NANOCRYSTAL HYDROGEL SYSTEMS: A REVIEW ON HERBAL APPROACHES FOR ENHANCED ANTI-INFLAMMATORY THERAPY

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ABSTRACT

Tissue damage, infections, and chronic illnesses all trigger inflammation, a complicated biological reaction. The development of safer therapeutic options is necessary since traditional anti-inflammatory medications, such as non-steroidal anti-inflammatory medicines (NSAIDs), can induce side effects, such as gastrointestinal discomfort and cardiovascular risks. The pharmacological potential and decreased toxicity of medicinal plants have drawn more and more attention. In ethnomedicine, *Achyranthes aspera* Linn., a traditional medicinal plant in the Amaranthaceae family, has been used extensively to treat infections, wounds, arthritis, and inflammatory conditions. Its medicinal properties are attributed to flavonoids, saponins, alkaloids, tannins, and triterpenoids, according to phytochemical studies. New approaches to increasing the bioavailability and effectiveness of bioactive chemicals obtained from plants have been made possible by

recent developments in nanotechnology. Among them, hydrogels based on biopolymers and drug delivery systems based on nanocrystals have shown promise for regulated drug delivery. The benefits of hydrogels and nanocrystals, such as increased solubility, prolonged drug release, better permeability, and focused therapeutic action, are combined in biopolymer-directed in situ nanocrystal loaded hydrogels. The phytochemistry, pharmacological properties, and anti-inflammatory processes of *Achyranthes aspera* are summarized in this

study along with recent developments in nanocrystal drug delivery systems, hydrogels based on biopolymers, and their use in herbal nanomedicine. Additionally included are formulation methodologies, characterisation procedures, and assessment approaches for hydrogel systems loaded with nanocrystals. Combining nanotechnology and herbal medicine might offer a new way to create potent anti-inflammatory treatments.

KEYWORDS: *Aspera Achyranthes*, Hydrogel made of biopolymers, The nanocrystals, Anti-inflammatory properties, Nanomedicine using herbs, Nanotechnology-based drug delivery system.

INTRODUCTION

The body uses inflammation as a defense mechanism against damage, infection, and damaging stimuli. On the other hand, chronic conditions including cancer, diabetes, heart disease, and arthritis can result from persistent or unchecked inflammation.^[71] Despite their widespread usage, conventional anti-inflammatory medications, such as corticosteroids and non-steroidal anti-inflammatory medicines (NSAIDs), can cause side effects include gastrointestinal ulcers, kidney damage, and cardiovascular problems. As a result, the demand to create safer and more potent anti-inflammatory treatments is growing.^[72,73] Traditional medicine has traditionally employed medicinal plants to treat a variety of inflammatory diseases. Among these, *Achyranthes aspera* Linn., sometimes referred to as "Apamarga," has drawn a lot of interest because of its diverse pharmacological properties. The plant is widely employed in Ayurvedic and traditional medical systems and is found across tropical and subtropical climates^[11,12] According to phytochemical research, *Achyranthes aspera* includes a number of bioactive substances that contribute to its pharmacological characteristics, such as flavonoids, alkaloids, tannins, saponins, phenolic compounds, and triterpenoids.^[14] *Achyranthes aspera* extracts have been shown in experiments to dramatically reduce inflammation in animal models, such as carrageenan-induced paw edema, indicating the plant's potential as a natural anti-inflammatory drug. Herbal medicines have therapeutic potential, but their quick metabolism, low bioavailability, and poor solubility frequently restrict their clinical use. Recent developments in nanotechnology have created new avenues for enhancing the therapeutic effectiveness and delivery of bioactive chemicals produced from plants. Drug delivery methods based on nanocrystals have shown promise in improving drug solubility, rate of dissolution, and bioavailability.^[22] Because of their superior biocompatibility, biodegradability, and capacity for controlled drug release, hydrogels—

especially those based on biopolymers—have drawn a lot of interest in pharmaceutical and biological applications. Enhanced drug stability, targeted distribution, and extended therapeutic effect may be made possible by the synergistic benefits of combining nanocrystals with hydrogel systems.^[21] The creation and assessment of biopolymer-directed in situ nanocrystal-loaded hydrogel systems of *Achyranthes aspera* for improved anti-inflammatory activity are the main topics of this review.^[16]

Pathophysiology of Inflammation

Immune cells, blood arteries, and chemical mediators are all involved in the intricate physiological reaction known as inflammation.^[71] The initiation, amplification, and resolution phases are the three main stages that it typically goes through. Histamine, prostaglandins, cytokines, and leukotrienes are among the inflammatory mediators released during the early phase of tissue damage. The afflicted area becomes red, hot, swollen, and painful as a result of these mediators' vasodilation and increased vascular permeability.^[76] Neutrophils, macrophages, and lymphocytes are examples of immune cells that move to the site of damage and produce more inflammatory mediators. Interleukins and tumor necrosis factor-alpha (TNF- α) are examples of cytokines that are important in controlling the inflammatory process. Chronic inflammatory disorders may result from prolonged inflammation.^[78,79]

Botanical Description of *Achyranthes aspera*

Taxonomy

Kingdom: Plantae Family: Amaranthaceae Genus: *Achyranthes*

Species: *Achyranthes aspera*

Morphology

The upright perennial herb *Achyranthes aspera* can reach a height of one meter. The plant features little seeds, greenish blooms clustered in spikes, and simple leaves.^[2] It is extensively found in tropical and subtropical areas, such as Southeast Asia, Africa, and India.

Distribution

In tropical areas, the plant is widely distributed along roadsides, in agricultural fields, and in wastelands.

Ethnomedical Significance

Traditional medicine has made considerable use of *Achyranthes aspera* to treat a wide range

of illnesses.^[1]

Conventional applications consist of:

- Arthritis treatment
- Healing of wounds
- Skin conditions
- Respiratory conditions
- Digestive issues

The herb, known as Apamarga in Ayurvedic medicine, is used to relieve pain and inflammatory diseases.

Phytochemical Constituents

Numerous bioactive substances have been found in *Achyranthes aspera*, according to phytochemical research.

Principal components consist of:

- Alkaloids
- Flavonoids
- Saponins
- Glycosides
- Terpenoids
- Phenolic substances

The pharmacological actions of the plant are attributed to more than fifty chemical components that have been identified from various portions of the plant. These phytochemicals are essential for their anti-inflammatory, antioxidant, antibacterial, and anticancer properties.

Pharmacological Activities

- Anti- Inflammatory Activity

Achyranthes aspera has been shown in several studies to have strong anti-inflammatory properties. Plant extracts have been shown to considerably^[7] decrease inflammation in animal models of paw edema caused by carrageenan.

- Activity of Antioxidants

The plant's phenolic chemicals and flavonoids give it a significant antioxidant action.

- Activity Against Microbes

Plant extracts have demonstrated antimicrobial efficacy against a range of diseases.

- Activity Against Diabetes

Plant extracts have been shown in studies to lower blood glucose levels.^[3]

Mechanism of Anti-Inflammatory Action

Achyranthes aspera's anti-inflammatory properties are mostly explained by its capacity to block inflammatory mediators including prostaglandins and cytokines.

The plant's flavonoids and saponins, which stabilize cell membranes and block inflammatory enzyme pathways, play a major role in this function.^[10]

Challenges in Herbal Drug Delivery

Herbal medications have a number of delivery issues despite their medicinal advantages. Poor water solubility, which causes decreased dissolution and restricted absorption in the body, is one of the main drawbacks. Furthermore, a lot of phytochemicals might break down during storage or metabolism since they are chemically unstable. Rapid excretion from the body, which lowers bioavailability and therapeutic effectiveness, presents another difficulty. The consistency of herbal formulations is further impacted by standardization issues and plant extract variability. These difficulties demonstrate the necessity for sophisticated formulation techniques, such as systems based on nanotechnology, to improve the efficacy and delivery of herbal medications.

Nanocrystal Drug Delivery Systems

Pure medicine particles, known as nanocrystals, are usually between 10 and 1000 nanometers in size. They are made up of the active medicinal component stabilized by appropriate polymers or surfactants. Because their smaller particle size greatly improves the surface area, nanocrystals are especially helpful for medications that are poorly soluble.^[24] Increased surface area improves the drug's saturation solubility and dissolution rate, which increases bioavailability. Oral, topical, and parenteral distribution are among the methods by which nanocrystal compositions can be delivered.^[25,26] These benefits have made nanocrystal technology a key tactic for enhancing the effectiveness of poorly soluble herbal medicines.

Biopolymer-Directed Nanocrystal Systems

Natural polymers generated from plants, animals, or microbes are known as biopolymers. Because of their low toxicity, biocompatibility, and biodegradability, they are frequently

utilized in medicinal formulations.^[41]

Natural polymers are employed as stabilizing agents throughout the nanocrystal formation process in biopolymer-directed nanocrystal systems. These polymers aid in maintaining a steady nanoscale size and stop medication particles from aggregating. Additionally, the medication formulation's stability and controlled release are enhanced by the inclusion of biopolymers.^[46] Chitosan, alginate, gelatin, pectin, and cellulose derivatives are a few examples of frequently utilized biopolymers. Drug molecules can interact with these polymers to improve distribution to the intended location.^[47]

Common Biopolymers Used in Drug Delivery

Pharmaceutical nanotechnology makes use of a number of natural biopolymers. Because of its superior biocompatibility, mucoadhesive qualities, and capacity to improve drug permeability, chitosan is employed extensively. Another significant polymer that is frequently utilized for controlled drug release is alginate, which forms hydrogels when calcium ions are present. Hydrogel formulations frequently contain gelatin, a protein-based polymer with strong film-forming qualities. Plant-derived polysaccharides with good swelling and gel-forming properties include pectin and xanthan gum. These polymers aid in the formation of hydrogel matrices for long-term drug administration in addition to stabilizing nanocrystals.

In Situ Nanocrystal Formation

The method of forming nanocrystals directly inside the formulation system as opposed to preparing them separately is known as "in situ" nanocrystal formation. This method keeps nanocrystals stable and stops them from aggregating while being stored. Techniques like solvent evaporation and antisolvent precipitation are frequently used to create in situ nanocrystal systems. Nanosized crystals are formed when the medication is first dissolved in an appropriate solvent and then quickly precipitated in the presence of stabilizing polymers.

This technique increases the formulation's overall stability and gives greater control over the distribution of particle sizes.

Hydrogel Drug Delivery Systems

Hydrogels are networks of three-dimensional polymers that can absorb a lot of water without losing their structural integrity. Because of their great biocompatibility and capacity for regulated drug release, they are extensively employed in pharmaceutical applications^[32]

Hydrogels are frequently used for topical, transdermal, and wound healing treatments. They can be made from natural or synthetic polymers. They are perfect for administering medications at the site of inflammation because of their softness and flexibility, which enable them to closely resemble biological tissues.^[35]

Nanocrystal-Loaded Hydrogel Systems

The benefits of hydrogel drug delivery systems and nanocrystal technology are combined in nanocrystal-loaded hydrogels, which incorporate drug nanocrystals into a hydrogel matrix that serves as a reservoir for sustained drug release.^[39] The hydrogel prevents the nanocrystals from aggregating and offers a controlled release of the drug over an extended period of time.^[55] This system improves drug penetration through the skin and increases therapeutic efficacy in inflammatory conditions.

Preparation Methods

Nanocrystal hydrogel systems are created using a variety of methods. A popular technique for creating nanocrystals is antisolvent precipitation, which involves dissolving the medication in a solvent and quickly combining it with an antisolvent.^[56] Mechanical methods for reducing particle size to the nanoscale include wet milling and high-pressure homogenization.^[40] Another method that breaks down particles into tiny sizes using ultrasonic radiation is called ultrasonication. These techniques aid in the creation of stable nanocrystals that may be added to hydrogel compositions.

Characterization of Nanocrystal Hydrogel Systems

An essential first step in assessing the effectiveness and quality of nanocrystal hydrogel compositions is characterization. The stability and dispersion of nanocrystals may be assessed with the use of particle size and zeta potential studies.^[62,63] The shape and surface properties of nanocrystals can be determined by morphological study utilizing transmission electron microscopy (TEM) or scanning electron microscopy (SEM). Drug-polymer interactions are studied using Fourier transform infrared spectroscopy (FTIR), and the drug's crystalline nature is ascertained using X-ray diffraction (XRD) and differential scanning calorimetry (DSC).^[66] Additionally assessed are the hydrogel's viscosity, swelling index, pH, and medication concentration.

In-Vitro and In-Vivo Evaluation

Drug release behavior and anti-inflammatory activity are assessed in vitro in controlled

laboratory settings. Diffusion methods are commonly used in drug release investigations to ascertain the drug's release characteristics from the hydrogel.^[68] In-vivo research evaluates the formulation's anti-inflammatory properties by testing it in animal models. Rats with paw edema caused by carrageenan are often used models.^[69] To investigate tissue reactions and validate the formulation's anti-inflammatory properties, histopathological investigation is also carried out.^[70]

Applications in Anti-Inflammatory Therapy

Systems of nanocrystal hydrogel have great promise for the treatment of a variety of inflammatory diseases. They can be used topically to treat wound healing, arthritis, and skin irritation. The hydrogel's regulated release of anti-inflammatory substances prolongs therapeutic benefits and lowers the frequency of medication administration. Compared to traditional anti-inflammatory treatments, herbal nanocrystal hydrogels using plant extracts like *Achyranthes aspera* may provide safer and more potent options.

Current Research and Recent Advances

Advanced drug delivery systems including stimuli-responsive hydrogels, smart nanocarriers, and tailored drug delivery platforms have been developed as a result of recent nanotechnology research. In an effort to enhance the therapeutic potential of plant-based medications, researchers are increasingly investigating herbal nanocrystal compositions. Numerous investigations have shown that the administration of herbal medications via hydrogel and nanocrystal systems enhances their anti-inflammatory properties.

Challenges and Limitations

Nanocrystal hydrogel systems have various drawbacks despite their benefits. These include stability problems during long-term storage, difficulty in large-scale manufacture, and regulatory obstacles related to herbal formulations. Furthermore, there aren't enough clinical trials to verify these cutting-edge medication delivery systems' effectiveness and safety in people.

CONCLUSION

An technique that shows promise for enhancing the therapeutic efficacy of herbal anti-inflammatory medicines is biopolymer-directed in situ nanocrystal hydrogel systems. Drug solubility, stability, and bioavailability are all improved by adding nanocrystals to hydrogel matrix. Incorporating medicinal plants with strong anti-inflammatory qualities, like

Achyranthes aspera, into cutting-edge nanotechnology-based delivery methods may result in safer and more efficient therapies for inflammatory illnesses. To fully investigate the potential of these novel formulations, more research and clinical investigations are needed.

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