

DEVELOPMENT AND EVALUATION OF HERBAL BASED NANO GEL OF PLANTAIN LEAVES FOR WOUND

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ABSTRACT

Wounds are injuries that involve a break in the skin or damage to the underlying tissues. They can be classified into several types based on their cause and healing pattern, including open or closed wounds, surgical or traumatic wounds, and acute or chronic wounds. The leaves of *Plantago major* have been traditionally used in Kazakhstan for wound healing and for managing various other health conditions. They have been used for problems affecting the skin, respiratory system, digestive system, reproductive system, and circulatory system, as well as for pain relief and infections. When applied externally, *P. major* exhibits anti-inflammatory, antimicrobial, antipruritic, and wound-healing properties. The crushed leaves or fresh plant juice can be used as traditional remedies to promote the healing of cuts, wounds, bruises, and earaches. Numerous researchers have developed poly-herbal topical formulations for treating skin infections and conditions such as acne, wounds, itching, fungal infections, psoriasis, and wrinkles. However, further research with robust scientific evidence is still required. Some of the studies on poly-herbal topical formulations have been summarized in the literature review. Topical formulations bypass liver metabolism, thereby enhancing the bioavailability of the drug, and provide a localized effect directly at the site of action.

Keywords: *Plantago major*, Nanoparticles, Bioavailability, Herbal extract, wound healing

INTRODUCTION

Wounds are injuries that involve a break in the skin or damage to the underlying tissues. They can be classified into several types based on their cause and healing pattern, including open or closed wounds, surgical or traumatic wounds, and acute or chronic wounds. [1] Unlike chronic wounds, which are commonly associated with underlying conditions such as diabetes or venous insufficiency, acute wounds resulting from abrasions or lacerations generally follow a predictable healing process. Chronic wounds often require a longer time to heal due to persistent inflammation, inadequate blood supply, or other factors that impair tissue repair.[2] Wound healing is a complex

biological process that occurs through several overlapping phases, including hemostasis, inflammation, proliferation, and remodeling. The efficiency of this process is influenced by various factors, such as the patient's age, nutritional status, underlying medical conditions, and genetic characteristics.[3] These factors influence cellular activity and the regeneration of damaged tissues during the healing process. External factors, including the condition of the wound environment, maintenance of appropriate moisture levels, infection prevention, and the selection of suitable wound dressings, can either promote or delay healing. Psychological factors, such as stress and mental well-being, may also indirectly affect wound repair by influencing immune function and the body's overall physiological resilience. Therefore, a comprehensive understanding of the interactions between different wound types and the factors that influence healing is essential for healthcare professionals to optimize wound management, improve patient outcomes and satisfaction, and reduce the healthcare costs associated with chronic wound care.[4] Wound healing is a complex natural process in which the body repairs damaged tissues after an injury. It involves many cellular and molecular activities inside and outside the cells that work together to restore the structure and normal function of the damaged tissue and promote recovery.[5,6] Wound healing usually takes place through four main stages: hemostasis, inflammation (0–3 days), proliferation (2–12 days), and remodeling (3–6 months). Each stage plays an important role in the repair and recovery of the damaged tissue.(FIG.1). [7] The two main types of wounds are acute wounds and chronic wounds. Acute wounds include surgical, mechanical, thermal, and chemical injuries, while chronic wounds include bed sores, ischemic wounds, venous stasis ulcers, pressure ulcers, and diabetic ulcers.[8,9] Wound dressings play an important role in the wound-healing process, especially in chronic wounds, which usually take a longer time to heal.[10] For effective wound healing, wound dressings should have important properties such as being non-toxic, protective, highly absorbent, and allowing oxygen to pass through. These properties help prevent infection and further injury and promote faster wound healing.[11] Various traditional systems of medicine, such as Ayurveda, Unani, Chinese medicine, and Siddha, are commonly used for the treatment and healing of skin injuries and damage.[12] For example, *Moringa oleifera* seeds are widely valued for their nutritional and medicinal properties. They contain several important phytochemical compounds that may support and promote the wound-healing process.[13] Modern wound dressings are made from synthetic and natural polymers, such as alginate, chitosan, starch, silicone, and hydrocolloid gels. These materials help promote faster wound healing because of their antimicrobial, antibacterial, and growth factor-supporting properties.[15-17] Smart wound dressings, composed of biopolymers and nanoparticles, offer several advantages in wound management. They can promote wound healing through drug delivery systems (DDS) and help recreate the natural environment of damaged tissue.[18] Active dressings are an emerging type of modern wound-healing material that possesses non-toxic, biodegradable, and biocompatible properties. They help protect the wound and prevent or fight infections, thereby supporting the healing process.[19] They possess antioxidant properties that help reduce excessive oxidation and control inflammation, thereby supporting and promoting the wound-healing process.[20]

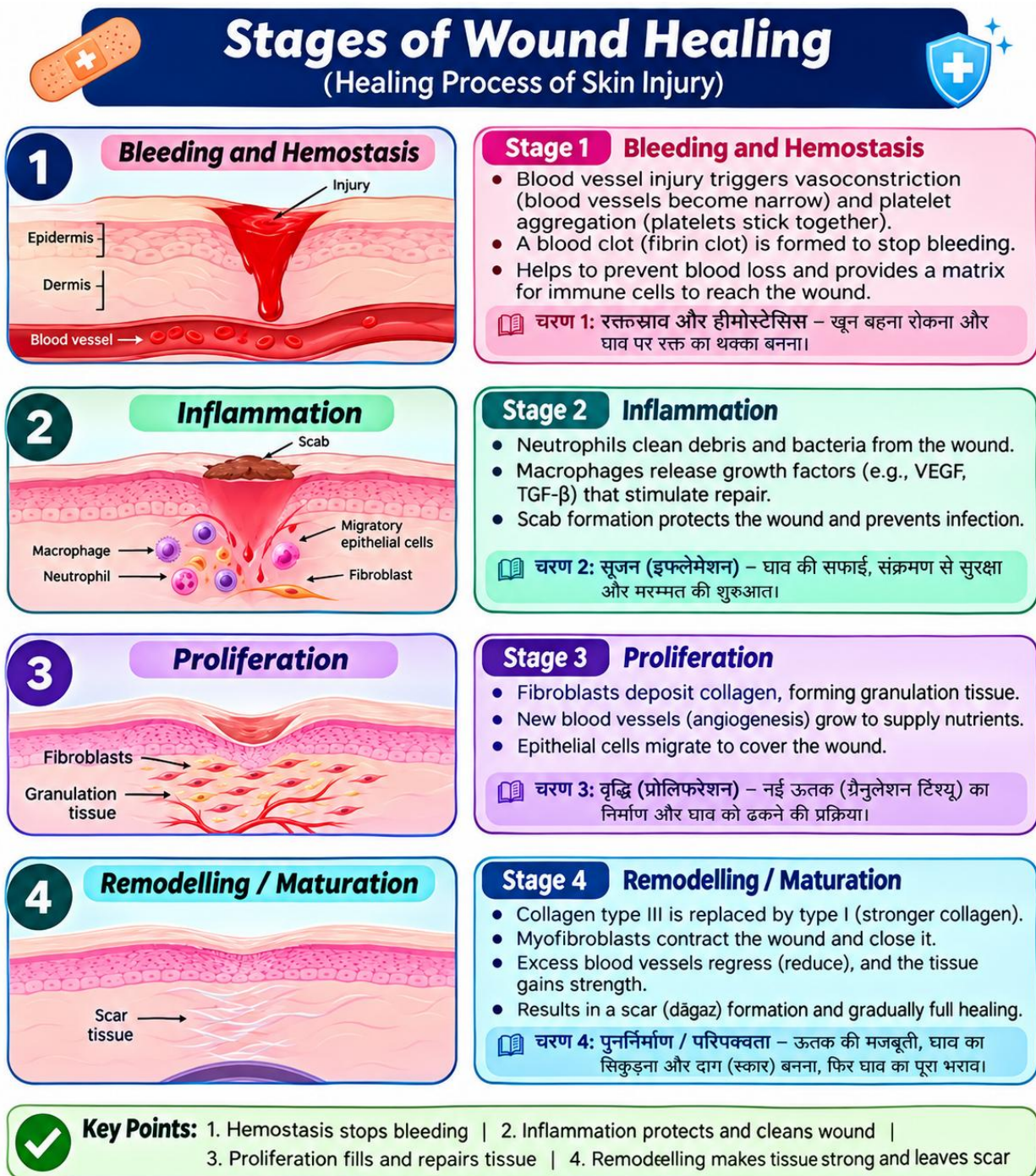


Fig.1. Four major phases of wound healing.

PLANT PROFILE

PLANTAIN (*Plantago major*)

The leaves of *Plantago major* have been traditionally used in Kazakhstan for wound healing and for managing various other health conditions. They have been used for problems affecting the skin, respiratory system, digestive system, reproductive system, and circulatory system, as well as for pain relief and infections. When applied externally, *P. major* exhibits anti-inflammatory, antimicrobial, antipruritic, and wound-healing properties. The crushed leaves or fresh plant juice can be used as traditional remedies to promote the healing of cuts, wounds, bruises, and earaches.[21] Throughout human history, people have used natural remedies and medicinal plants to maintain health and treat various diseases. Over the centuries, these plants have been considered relatively safe and associated with minimal side effects when used appropriately.[22] The therapeutic benefits of medicinal plants have been recognized worldwide, leading to extensive scientific research to evaluate and confirm their pharmacological activities. The growing interest in medicinal plants has also been encouraged by the increasing use and development of pharmacopoeial, non-pharmacopoeial, and synthetic drugs.[23]

Category	Classification
Kingdom	Plantae (Plants)
Phylum	Tracheophyta (Vascular Plants)
Class	Magnoliopsida
Order	Lamiales
Family	Plantaginaceae (Plantain Family)
Genus	<i>Plantago</i>
Species	<i>Plantago major</i>
Common Name	Common Plantain, Broadleaf Plantain

Table 1: Scientific Classification of Plantain (*Plantago major*)



Fig.1: Plantain (*Plantago major*)

Traditional Uses: Some uses of *Plantago major* L. in traditional medicine

S.No.	Traditional use	Part of plant	Country	References
1.	Skin Abscesses	Leaves,	Hawaii, Norway, Turkey	[24], [25], [26]
2.	Acne	Leaves, wood	Guatemala	[27]
3.	Anti-inflammatory	Leaves, juce	Madeira	[28]
4.	Desinfectant for wounds	Leaves, wood	Denmark, Norway	[29], [25]
5.	Haemostatic on wounds	Leaves,	India	[30], [31]
6.	Wound healing	Leaves, wood	Canary Islands, Chile, Turkey	[32], [33], [34]
7.	Ulcer	Leaves, wood	Brazil, Norway, Turkey	[25], [26], [35]

Table 2: Uses of *Plantago major* L. in traditional medicine

Morphological characteristics

Roots: Numerous fibrous, primarily adventitious roots arising from a short, stout, erect rootstock or short rhizome.

Stems: The plant is essentially stemless aboveground, with a short, stout, truncate rootstock.

Leaves:

Arrangement: Spirally arranged in a dense, basal rosette that often lies flat against the ground in trampled areas.

Blade Shape: Ovate to broadly elliptic or oval-shaped.

Dimensions: 3 to 18 cm long and 2 to 11 cm broad (exceptionally larger).

Margins & Apex: Smooth, wavy, or with occasional blunt, uneven teeth; apex is acute to rounded.

Venation: Distinctly parallel with 3 to 7 (rarely 9) conspicuous longitudinal arched veins running the length of the blade.

Petiole: Distinct, robust petiole often nearly as long as the leaf blade itself.

Flowers:

Inflorescence: Dense, slender, cylinder-shaped spikes (resembling a rat tail) measuring 1 to 20 cm long.

Peduncle: Borne upright on leafless, slender flowering stalks/scapes measuring 2 to 18 cm (rarely up to 70 cm) tall.

Individual Flowers: Minute (about 1 to 3 mm across), inconspicuous, greenish-brown or yellowish-white petals with prominent purple or pinkish stamens

Fruit and Seeds

Fruit: Small, oval-to-rounded capsules (2.5 to 4 mm tall) that split open transversely near the middle.

Seeds: Numerous (typically 6 to 11 or more per capsule depending on subspecies), minute, glossy, dark brown to blackish oval seeds.

Chemical constituents and their biological activities

Carbohydrates:

The seeds contain several types of sugars, including the monosaccharides glucose, fructose, xylose, and rhamnose, along with the disaccharide sucrose and the trisaccharide planteose [O- α -d-Galp-(1 $\rightarrow$ 6)-O- β -d-Fruf-(2 $\rightarrow$ 1)- α -d-Glcp]. [36]. Planteose functions as a storage carbohydrate, serving as an energy reserve in the seeds. [37]

The outer seed coat contains water-absorbing polysaccharides that swell and produce a highly viscous mucilage. Cold-water extraction of the seeds yields polysaccharides containing 61% xylose, 13.2% arabinose, and 24% galacturonic acid. The hot-water extract of the remaining material consists mainly of xylose (78%), along with arabinose (13.2%), galactose (3%), and galacturonic acid (6.2%).[36]. Samuelsen et al. (1999a) The polysaccharides obtained from the 50°C water extract contain 39.7% xylose, 13.1% arabinose, 17.2% galacturonic acid, 15.5% glucuronic acid, 2.1% rhamnose, 2.5% galactose, and 9.9% glucose. The acidic fractions are mainly heteroxylans, consisting of β -(1 $\rightarrow$ 4)-linked and β -(1 $\rightarrow$ 3)-linked xylose units in the main polymer chain. Small side chains, including individual xylose and arabinose residues and the disaccharides α -L-Araf-(1 $\rightarrow$ 3)- β -D-Xylp and α -D-GlcpA-(1 $\rightarrow$ 3)- β -D-Xylp, are attached to the 2 or 3 positions of the β -(1 $\rightarrow$ 4)-linked xylose residues in the backbone. [38],[39]

S.No.	Polysaccharide	References
1.	<i>In leaves</i>	
a.	Plantaglucide Pectic acid, galactoarabinan, Galactan	[40],[41]
b.	PMII Pectin with smooth and hairy regions	[42]
c.	PMIa Arabinogalactan type II	[43]
d.	Glucomannan	[44]
2.	<i>In Seeds</i>	
a.	Starch	[45]
b.	Acidic heteroxylans	[45]

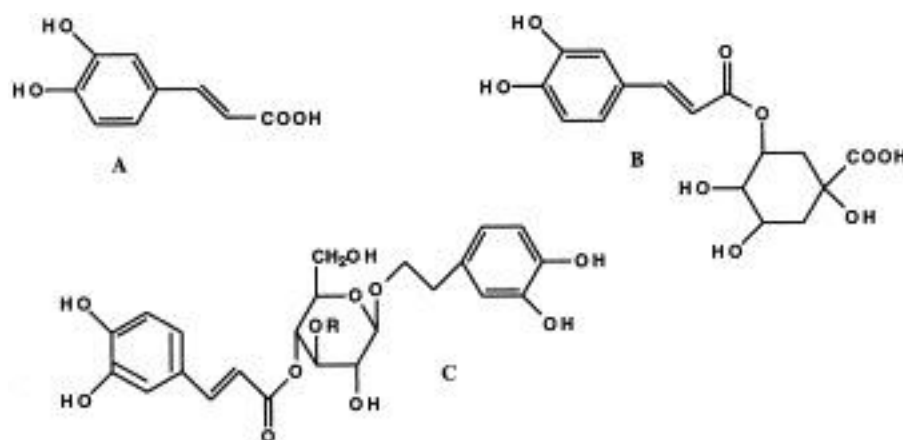
Table.2: Polysaccharides in *Plantago major* L.**Lipid:**

Fatty acids, both free and after hydrolysis of triglycerides, have been isolated from the seeds and are listed in Table 3 . According to Ahmed et al. (1968) 64.8% of the fatty acids are unsaturated.

S.No.	Fatty acid	% of Total Fatty acid	References
1.	Myristic acid	14:0	[46]
2.	Palmitic acid	16:0	[47], [46]
3.	Stearic acid	18:0	[47], [46]
4.	Oleic acid	18:1	[47], [46]
5.	Linoleic acid	18:2	[47], [46]
6.	Linolenic acid	18:3	[47], [46]
7.	Arachidic acid	20:0	[47]
8.	Behenic acid	22:0	[47]
9.	Lignoceric acid	24:0	[48]
10.	9-Hydroxy- <i>cis</i> -11-octadecenoic acid	18:1	[47]

Table 3.Fatty acids isolated from the seeds of *Plantago major* L.**Caffeic acid derivatives:**

The ethyl and methyl esters of caffeic acid were isolated from the methanolic extract [48], and chlorogenic and neochlorogenic acid were isolated from the aqueous extract. [49]. According to Noro et al. (1991) plantamajoside is the main caffeic acid derivative in *P. major* L., and only small amounts of acteoside (synonym to verbascoside) are present. [50]. . According to Mølgaard (1986), plantamajoside and acteoside are not found together in the same plant. In Denmark, there are two subspecies of *P. major*, *P. major* ssp. *major* and ssp. *spleiosperma*. [51]. Plantamajoside is present in both subspecies, while acteoside is found only in ssp. *Spleiosperma*. [51]. Plantamajoside is glycosylated with glucose to the central glucose while in acteoside it is glycosylated with rhamnose (Fig. 2).

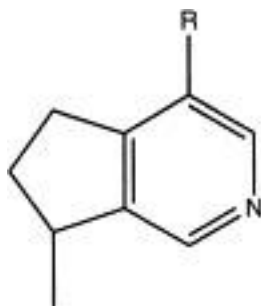


Caffeic acid derivatives in *P. major* L. (A) Caffeic acid, (B) chlorogenic acid, (C) Plantamajoside R=Glc, acteoside R=Rha.

Fig.2. Caffeic acid derivatives

Alkaloids:

P. major has been tested positive for alkaloids (Rojas, 1968, Smolenski et al., 1974)[52],[53]. Schneider (1990) identified them as indicain and plantagonin (Fig. 1).[54]



Alkaloids in *P. major* L. Indicain: R=CHO; plantagonin: R=COOH.

Fig.2: Alkaloids

Flavonoids

According to Kawashty et al. (1994) the amount of each flavonoid isolated from Egyptian *P. major* can be ranged as follows: luteolin 7-glucoside>hispidulin 7-glucuronide>luteolin 7-diglucoside>apigenin 7-glucoside≈nepetin 7-glucoside>luteolin 6-hydroxy 4'-methoxy 7-galactoside.[55]. Skari et al. (1999b) isolated plantaginidin and homoplantaginidin in addition to several flavonoids having structures that have not been found in *P. major* earlier. Their structures remain to be published.[56]

Iridoid glycosides

The iridoid glycosides isolated from *P. major* are listed in Table 6 , and the structure formulas are given in Fig. 3 . The major iridoid glycoside found is aucubin, but its content varies over the seasons. The highest aucubin level registered (1.3% in dried leaves) was in June. *P. major* contains less aucubin than *P. lanceolata*. [57] Three unusual iridoid glycosides with 8,9 double bonds, majoroside.[58] 10-hydroxymajoroside and 10-acetoxymajoroside have been isolated from the aerial parts of the plant .[59]

S.No.	Iridoidglycoside	Part of plant	%	References
	Asperuloside	Flowers	0.023	[60]
	Aucubin	Leaves	0–1.3	[57]
	Catapol	Aerial parts	0.003	[61]
	Gardoside	Aerial parts	0.001	[61]
	Geniposidic acid	Aerial parts	0.005	[61]
	Majoroside	Aerial parts	0.004	[58]
	10-Actoxymajoroside	Aerial parts	0.03	[59]
	10-Hydroxymajoroside	Aerial parts	0.02	[59]
	Melittoside	Aerial parts	0.004	[61]

Table 6. Iridoidglycosides from *Plantago major* L.

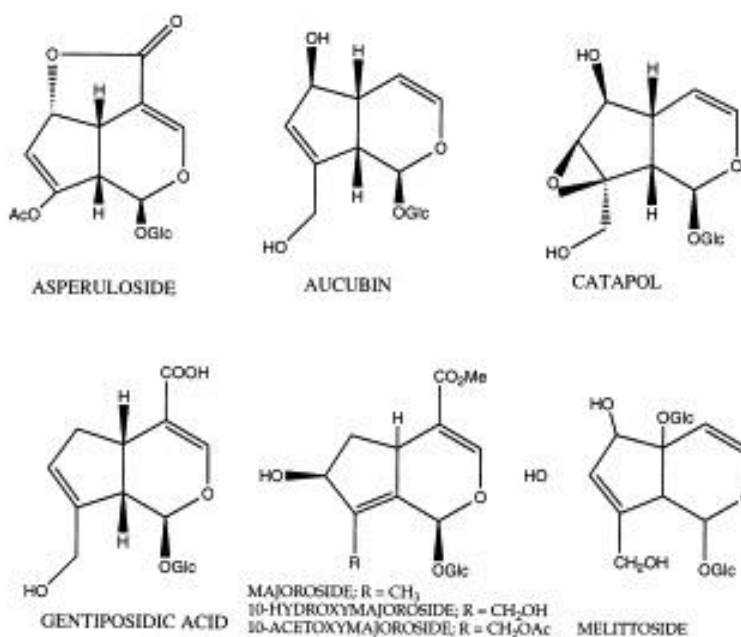


Fig. 3. Iridoid glycosides from *P. major* L.

INTRODUCTION TO NANOPARTICALES

Numerous researchers have developed poly-herbal topical formulations for treating skin infections and conditions such as acne, wounds, itching, fungal infections, psoriasis, and wrinkles. However, further research with robust scientific evidence is still required. Some of the studies on poly-herbal topical formulations have been summarized in the literature review. Topical formulations bypass liver metabolism, thereby enhancing the bioavailability of the drug, and provide a localized effect directly at the site of action.[62]

Inflammation is a complex biological response triggered to eliminate injury or harmful stimuli, including pathogens, damaged cells, or irritants. This response often results in physical symptoms such as fever, pain, and swelling, due to processes like vasodilation, increased vascular permeability, and plasma leakage. Normally, the body regulates inflammation by downregulating proinflammatory proteins, upregulating anti-inflammatory proteins, and reversing the vascular changes that initially recruited immune cells.[63]

Wounds are injuries that disrupt the skin or other tissues, including cuts, scrapes, scratches, and punctures. They may occur due to accidents, as well as from surgical procedures, sutures, or stitches. Wound healing is a complex biological process involving hemostasis, inflammation, proliferation, and remodeling. This process engages numerous cell types, including neutrophils, macrophages, lymphocytes, keratinocytes, fibroblasts, and endothelial cells.[64]

HERBAL-BASED NANOGEL FORMULATION

Herbal-based nanogel formulations involve creating nanogels using natural or plant-derived ingredients. This approach combines nanotechnology with herbal medicine to produce nanoscale hydrogel particles capable of encapsulating or delivering herbal compounds and extracts, potentially improving their therapeutic effectiveness and bioavailability.

The typical steps involved in formulating herbal-based nanogels include:

Selection of herbal ingredients: Active herbal compounds or extracts with known medicinal properties are chosen. These can be derived from various plant parts, such as leaves, stems, roots, or flowers, depending on the intended therapeutic effects.[65]

Nanogel preparation: Nanogels are synthesized using biocompatible polymers or natural hydrogel-forming agents, such as chitosan, alginate, gelatin, or hyaluronic acid. These polymers are crosslinked or self-assembled to form nanoscale hydrogel particles capable of encapsulating the herbal ingredients.[66]

Encapsulation of herbal compounds: The herbal extracts are incorporated into the nanogel matrix during formulation. This can be achieved by dispersing the herbs in the polymer solution or using techniques like coacervation, emulsion, or nanoprecipitation.[67]

Characterization and optimization: The prepared nanogels are analyzed for particle size, stability, drug-loading efficiency, and release characteristics. Formulation parameters, including polymer concentration, crosslinking density, and herbal content, may be optimized to achieve the desired properties.[68]

Evaluation of bioactivity and efficacy: Herbal nanogels are tested through in vitro and in vivo studies to assess the release kinetics of the encapsulated compounds, their interaction with target cells or tissues, and their therapeutic effectiveness.[69]

ADVANTAGES OF HERBAL-BASED NANOGEFORMULATIONS

Herbal-based nanogels offer multiple benefits due to the integration of nanotechnology with herbal medicine:

Improved bioavailability: The nanoscale size of nanogels enhances the solubility and permeability of herbal compounds, leading to better cellular uptake and increased therapeutic efficacy.[70]

Controlled and sustained release: Nanogels enable gradual release of herbal compounds over time, maintaining therapeutic levels and extending the duration of action.[71]

Targeted delivery: By modifying surface properties or adding targeting ligands, nanogels can be directed to specific tissues or cells, improving therapeutic outcomes while minimizing off-target effects.[72]

Protection and stability: The hydrogel matrix protects herbal compounds from degradation and oxidation, preserving their integrity and effectiveness over time.[73]

Synergistic effects: Multiple herbal ingredients can be incorporated into a single nanogel formulation, producing synergistic therapeutic effects and broadening the spectrum of activity.[74]

Reduced side effects: Herbal compounds generally have lower risks of adverse effects compared to synthetic drugs. Nanogel formulations allow localized or controlled delivery, further minimizing potential systemic side effects.[75]

Natural and sustainable approach: Using herbal ingredients and biocompatible polymers makes these formulations environmentally friendly and aligns with the growing demand for natural healthcare solutions.[76]

Compatibility with traditional medicine: Herbal nanogels modernize the delivery of traditional remedies, enhancing their efficacy and facilitating their integration into contemporary healthcare practices.[77]

HERBAL-BASED NANOGEL FORMULATIONS FOR WOUND TREATMENT

Herbal-based nanogel formulations have emerged as a promising approach for wound management. Combining herbal compounds with nanogel technology provides several benefits in promoting wound healing:

Improved wound healing properties: Herbal constituents in nanogels often exhibit natural wound healing abilities, including tissue regeneration, inflammation reduction, promotion of new blood vessel formation, and support for granulation tissue development. Incorporating these compounds into nanogels can amplify their healing effects.[78]

Controlled release of active ingredients: Nanogels allow for the sustained and controlled release of herbal bioactive compounds at the wound site, enhancing their bioavailability, efficacy, and prolonging therapeutic action.[79]

Maintaining a moist healing environment: The hydrogel nature of nanogels helps preserve moisture at the wound site, preventing excessive drying and supporting optimal conditions for natural healing.[80]

Protection and barrier function: Nanogels create a protective layer over the wound, shielding it from external contaminants, reducing infection risk, and maintaining an ideal moist environment.[81]

Targeted delivery of herbal compounds: Nanogels can be engineered to deliver herbal ingredients directly to the wound surface. Through surface modification or incorporation of targeting ligands, they ensure localized and efficient delivery of active compounds.[82]

Anti-inflammatory and antimicrobial benefits: Many herbal components have inherent anti-inflammatory and antimicrobial properties. Nanogels provide sustained release of these compounds, helping to reduce inflammation and prevent infection.[83]

Minimized scarring and improved cosmetic outcomes: Certain herbal ingredients in nanogels can reduce scar formation and enhance the aesthetic appearance of healed wounds, improving overall cosmetic outcomes.[84]

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