



Herbal Polymer-Based Hydrogels for Wound Healing: A Comprehensive Review

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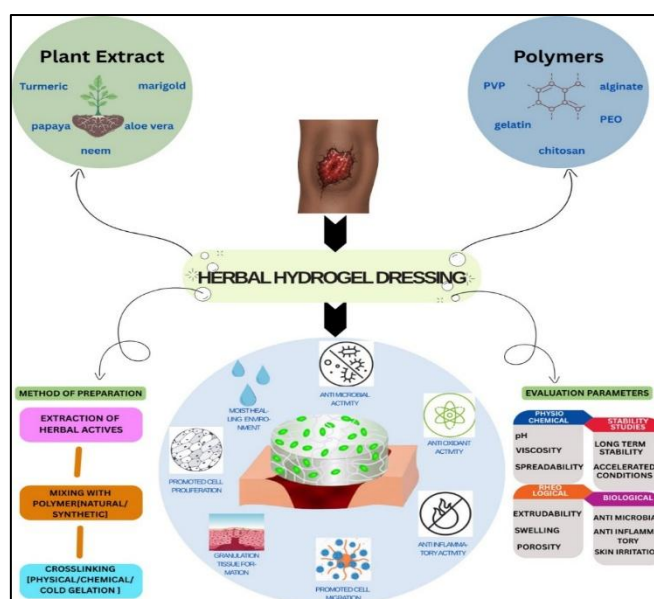
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ABSTRACT

Skin is highly vulnerable to injuries and microbial invasion, which can disrupt its structural integrity and delay the healing process. Wound healing is a complex and dynamic event involving overlapping stages of hemostasis, inflammation, proliferation, and remodeling. Conventional wound dressings and pharmaceutical approaches, such as synthetic antibiotics and antiseptics, often show limitations, including poor penetration into deep tissue, cytotoxic effects, and the growing problem of antimicrobial resistance. Additionally, biofilm formation by pathogenic microorganisms creates further barriers to effective treatment, prolonging recovery and increasing the risk of chronic wounds. Since ancient times, medicinal plants have been used in traditional medicine for their therapeutic effects in managing wounds and skin-related disorders. Herbal preparations are valued for their antimicrobial, antioxidant, and anti-inflammatory properties, while generally being safe and non-toxic for long-term application. They assist in wound healing by reducing microbial load, minimizing inflammation, and supporting tissue regeneration. Hydrogels, with their high-water content, softness, and biocompatibility, have recently gained attention as advanced wound dressing materials. They maintain a moist environment, protect the wound from external contaminants, and encourage fibroblast proliferation and migration. When herbal extracts are incorporated into hydrogel systems, they combine the natural bioactivity of plant-based compounds with the structural and functional advantages of hydrogels. This integration allows for sustained and localized delivery of herbal actives, enhancing antimicrobial defense, reducing oxidative stress, and accelerating tissue repair. Overall, herbal hydrogel formulations represent a promising bridge between traditional herbal medicine and modern wound management, offering safe, effective, and patient-friendly alternatives to conventional dressings.

Keywords:-Angiogenesis, Chronic Wound, Polymer, Anti-inflammatory, Herbal

Graphical Abstract:-





INTRODUCTION

The skin, the body's largest organ, plays a vital role in protection, fluid balance, immunity, and signal transduction. A wound is defined as any disruption in skin integrity caused by trauma or pathological conditions such as burns and diabetic ulcers. Wound healing is a complex process involving hemostasis, inflammation, proliferation, and remodeling, and disturbances in these phases may lead to delayed or chronic wounds.¹

Historically, natural products have been widely used in wound management. Ancient Egyptians applied honey-soaked linen dressings because of honey's antimicrobial and healing properties. Later, the concept of moist wound healing introduced by George Winter transformed modern wound care and led to the development of advanced dressings.²

Among these, hydrogels have gained considerable attention due to their biocompatibility, biodegradability, high water content, and ability to maintain a moist wound environment. Hydrogels also serve as effective carriers for controlled and sustained drug delivery. At the same time, herbal bioactive compounds such as curcumin and quercetin possess antimicrobial, antioxidant, and anti-inflammatory activities beneficial for wound healing. However, their poor solubility and stability limit their therapeutic effectiveness. Incorporating these compounds into hydrogels improves their stability, bioavailability, and sustained release.

Recent studies have demonstrated the effectiveness of herbal-loaded hydrogels in enhancing wound healing. Compared with conventional synthetic dressings, these systems offer multifunctional activity, better biocompatibility, and cost-effectiveness.

Therefore, this review focuses on hydrogel-based wound dressings containing herbal constituents, discussing wound healing mechanisms, strategies for herbal incorporation into hydrogels, and the challenges and future prospects of translating these systems into clinical applications.

2. Basics of Wounds: Definition and Types

A wound is an injury that disrupts the normal structure and function of living tissue, affecting its cellular, anatomical, or physiological integrity. Such disruptions can result from various causes, including physical trauma, chemical exposure, thermal injury, microbial invasion, or immune responses. Wounds may range from superficial breaches in the skin's epithelial layer to deeper injuries that extend into subcutaneous tissues, potentially impairing structures like muscles, tendons, blood vessels, nerves, internal organs, or bones.

Time is an important factor in injury management and wound repair. Thus, wounds can be clinically categorized according to their time frame of healing.

2.1 Acute Wounds

Acute wounds heal normally through an orderly healing process, resulting in functional and anatomical restoration. Healing generally occurs within 5–30 days. These wounds are mainly caused by mechanical trauma, surgical incisions, burns, chemical injuries, and electrical accidents.

2.2 Chronic Wounds

Chronic wounds fail to progress through the normal healing stages and do not heal in a timely manner. Prolonged inflammation, macrophage dysfunction, bacterial infections, and biofilm formation contribute to delayed healing. Biofilms promote tissue damage through enzymes and reactive oxygen species (ROS), preventing proper cell migration and repair. Common chronic wounds include diabetic ulcers, vascular ulcers, and pressure ulcers.³

2.3 Complicated Wounds

Complicated wounds involve both infection and tissue defects caused by trauma, surgery, or previous infections. The development of infection depends on microbial load, blood supply, and the patient's immune response. Common signs include redness, swelling, pain, warmth, and loss of function.

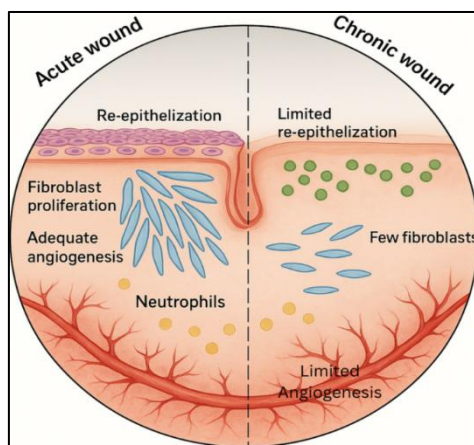


Figure 1 Illustration of differences in acute and chronic wounds in wound healing

3. Wound Healing Phases

Wound healing is a complex process that restores damaged tissue through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.

3.1 Hemostasis

Hemostasis is the immediate response to injury and aims to stop bleeding. Vasoconstriction reduces blood loss, while platelets aggregate at the wound site and interact with fibrin to form a stable blood clot. This clot seals the wound and provides a scaffold for cell recruitment and tissue repair.⁴

3.2 Inflammation

The inflammatory phase begins within the first 72 hours after injury. Neutrophils remove pathogens and necrotic tissue through reactive oxygen species (ROS) and enzymes. Macrophages later release cytokines and growth factors that regulate tissue repair, recruit fibroblasts, and promote angiogenesis and granulation tissue formation.

3.3 Proliferation

During proliferation, fibroblasts produce collagen and extracellular matrix components to strengthen the wound. Epithelial cells migrate to restore the epidermis, while myofibroblasts contract the wound. Angiogenesis also supplies oxygen and nutrients necessary for tissue regeneration.⁵

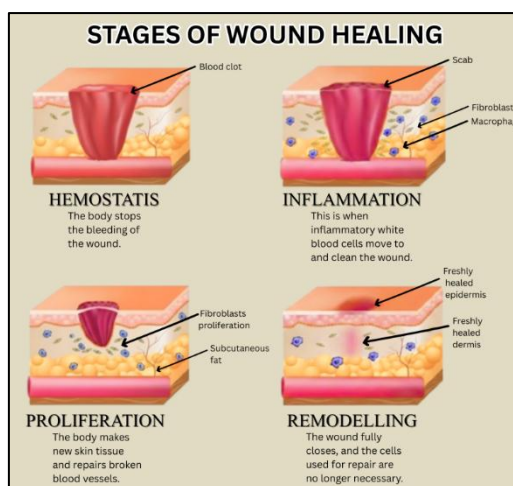


Figure 2 Illustration of four phases in the wound healing process.

3.4 Remodeling (Maturation)

The remodeling phase may continue for months or years. Collagen fibers reorganize and mature, increasing wound strength and improving scar organization. Over time, scars gradually flatten and fade, although the healed tissue may not regain full original strength.⁵

4. Factors Influencing Wound Healing

Wound healing is influenced by several systemic and local factors that may either promote repair or delay healing, leading to chronic wounds.

4.1 Systemic Factors

- Age:** Aging reduces angiogenesis, collagen synthesis, and re-epithelialization, slowing wound repair.⁶
- Stress:** Psychological and physiological stress increase glucocorticoid levels, suppressing immune responses and tissue repair.⁶
- Sex Hormones:** Estrogen promotes ECM production, regeneration, and anti-inflammatory activity, whereas androgens may delay healing.
- Diseases:** Diabetes impairs angiogenesis and causes oxidative stress, hypoxia, and neuropathy, resulting in chronic wounds. Obesity also increases the risk of infections, dehiscence, and ulcer formation due to poor blood supply in adipose tissue.
- Alcohol and Smoking:** Alcohol weakens immune function and increases infection risk, while smoking causes vasoconstriction and hypoxia, impairing tissue repair.

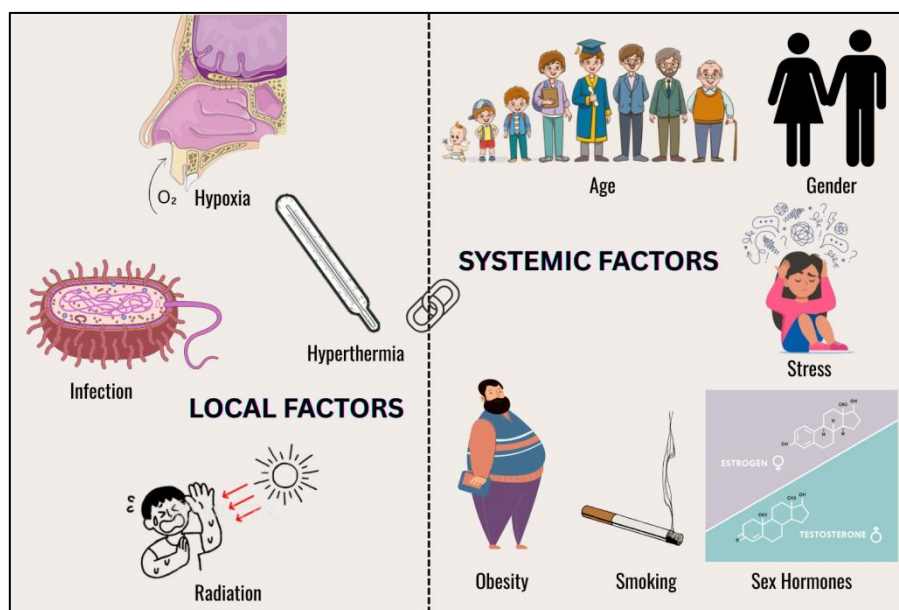


Figure 3 Factors affecting wound healing.

4.2 Local Factors

- Ischemia:** Reduces oxygen and nutrient supply to tissues.
- Repeated Injury:** Continuous trauma disrupts the healing process.
- Radiation:** Damages blood vessels and tissues, delaying repair.
- Hypothermia:** Decreases blood flow and cellular activity.



e. **Infection:** Prolongs inflammation and damages healthy tissue.

5. Hydrogels in Wound Healing

Hydrogels are widely used in wound healing due to their three-dimensional hydrophilic polymer network structure formed by physical or chemical cross-linking. Physically crosslinked hydrogels are stabilized by ionic interactions and hydrogen bonding, whereas chemically crosslinked hydrogels contain permanent covalent bonds, providing greater stability.

Their high water content, flexibility, and moisture-retaining ability help maintain a moist wound environment, support oxygen diffusion, manage exudates, and adapt to irregular wounds. Hydrogels are also biodegradable, biocompatible, and adhesive, providing temporary support for hemostasis, re-epithelialization, and wound stability.⁷⁻⁹

An important advantage of hydrogels is their ability to mimic the extracellular matrix (ECM), which supports cell adhesion, signaling, and tissue regeneration. Since ECM integrity is often damaged in acute and chronic wounds, hydrogels can act as dermal substitutes by promoting cell proliferation, ECM deposition, reduced scar formation, and overall tissue repair.

6. Natural and Synthetic Hydrogels

Hydrogel wound dressings are prepared using both natural and synthetic polymers. Natural polymers such as chitosan, gelatin, hyaluronic acid, and alginate provide biocompatibility and bioactivity, whereas synthetic polymers including polyethylene glycol, polyvinyl pyrrolidone, polyethylene oxide, and polyvinyl alcohol improve mechanical strength and stability.

Because hydrogels are highly elastic and may possess limited mechanical strength, multi-polymeric hydrogels are developed to enhance both strength and absorption capacity. Combining natural and synthetic polymers provides improved thermal, mechanical, and biological properties for wound healing applications.¹⁰

6.1 Natural Polymers

Natural polymers, or biopolymers, are obtained from plants, animals, fungi, bacteria, and algae. Due to their biocompatibility and bioactivity, they are considered suitable substitutes for the extracellular matrix (ECM) in wound healing applications.

Table 1. Natural Polymers used in Hydrogels

Polymer	Source	Key Properties	Role in Wound Healing	Reference
Chitosan	Derived from chitin (arthropod exoskeletons, fungal walls)	Biocompatible, biodegradable, antimicrobial, hemostatic	Promotes platelet adhesion, prevents microbial invasion, and enhances tissue regeneration	11
Gelatin	Derived from collagen	Biodegradable, low immunogenicity, supports cell adhesion	Maintains moist environment, absorbs exudates, and promotes cell proliferation	12
Hyaluronic Acid	ECM component found in vertebrates	High water-binding capacity and biocompatibility	Enhances cell migration, angiogenesis, and tissue regeneration	13
Alginate	Brown algae and bacterial sources	Highly absorbent, gel-forming, biocompatible	Maintains moisture, absorbs exudates, and supports chronic wound healing	14

6.2 Synthetic Polymers

Synthetic polymers are biocompatible and bioresorbable materials with reproducible properties due to controlled synthesis. Unlike natural polymers, they can be precisely engineered to obtain desired physical, chemical, mechanical, and kinetic properties for specific biomedical applications. However, they may have higher costs and structural differences compared to the natural extracellular matrix (ECM).

**Table 2. Synthetic Polymers used in Hydrogels**

Polymer	Key Properties	Role in Wound Healing	Reference
Polyethylene Glycol (PEG)	Hydrophilic, biocompatible, low immunogenicity, easily cross-linkable	Forms stable hydrogels, enhances cell proliferation, promotes wound closure, reduces scar formation, and enables growth factor delivery	15
Polyvinyl Alcohol (PVA)	Hydrophilic, biodegradable, semi-crystalline, strong mechanical properties	Maintains moist environment, improves oxygen permeability, and supports tissue regeneration when combined with bioactive polymers	16,17
Polyvinylpyrrolidone (PVP)	Water-soluble, biocompatible, heat-resistant, film-forming	Provides semi-permeable wound protection, supports oxygen transport, and exhibits enhanced antimicrobial activity in composite hydrogels	18
Polyethylene Oxide (PEO)	Water-soluble, viscoelastic, lubricating, highly absorbent	Absorbs wound exudates, forms gel-like structures, and supports healing in low to moderate exuding wounds	19

7. Nature's Remedies: Herbs with Wound-Healing Properties

Herbal medicines have long been used in traditional wound management because of their antimicrobial, anti-inflammatory, antioxidant, and tissue-regenerating properties. Medicinal plants such as turmeric, neem, aloe vera, papaya, moringa, honey, and calendula promote wound repair by enhancing collagen synthesis, reducing inflammation, preventing infection, and accelerating tissue regeneration.

Table 3. Medicinal Plants Used in Wound Healing

S. No.	Medicinal Plant	Part Used	Major Metabolites	Wound-Healing Applications	Reference
1	Turmeric (<i>Curcuma longa</i>)	Rhizomes	Curcumin, proteins, vitamin A	Chronic wound healing, anti-inflammatory activity	20
2	Neem (<i>Azadirachta indica</i>)	Leaves/whole plant	Azadirachtin, nimbin, nimbidin, flavonoids	Open wound healing, antimicrobial activity	21
3	Aloe vera (<i>Aloe barbadensis</i>)	Leaves	Acemannan, glucomannan, vitamins C & E	Open wound healing, collagen synthesis, angiogenesis	22
4	Papaya (<i>Carica papaya</i>)	Latex, fruit	Papain, chymopapain	Debridement, diabetic and burn wound healing	23
5	Drumstick tree (<i>Moringa oleifera</i>)	Leaves, seeds	Phenolics, beta-carotene, amino acids, vitamins	Excision and incision wound healing	24
6	Honey (<i>Apis mellifera</i>)	Bee secretion	Flavonoids, phenolic acids, fructose, glucose	Pressure ulcers, burns, post-surgical wound healing	25
7	Pot Marigold (<i>Calendula officinalis</i>)	Flowers	Carotenoids, flavonoids, coumarins, triterpenoids	Chronic and diabetic wound healing	26

8. Preparation of Herbal Hydrogels

The therapeutic effects of medicinal herbs can be utilized by incorporating their extracts into hydrogel formulations. Stable hydrogels require strong inter-chain interactions and efficient water retention within the polymeric network.

8.1 Physically Cross-Linked Hydrogels

Physically cross-linked hydrogels are formed through non-covalent interactions such as hydrogen bonding, electrostatic attraction, hydrophobic interaction, metal ion coordination, and freeze-thaw processing. These hydrogels are thermally reversible, highly water-sensitive, and suitable for short-term herbal drug delivery because they do not require toxic chemical cross-linkers.²⁷



Among these methods, freeze–thaw processing is widely used for preparing PVA-based herbal hydrogels. In this method, repeated freezing and thawing cycles create crystalline regions and hydrogen bonding within the polymer network, resulting in stable hydrogel formation.

Example: PVA/Guava Leaf Extract Hydrogel

Guava leaf extract (GLE) was prepared by maceration in ethanol, followed by concentration and freeze-drying to obtain a dry extract. Hydrogels were formed by mixing PVA and GLE in different ratios and subjecting the mixture to multiple freeze–thaw cycles (freezing at $-25\text{ }^{\circ}\text{C}$ and thawing at room temperature). This process produced stable, physically cross-linked hydrogels while preserving the biological activity of the herbal extract.²⁸

Table 4. Formulations of PVA/GLE Hydrogel Samples

Sample	PVA/GLE Weight Ratio	PVA Mass (g)	GLE Mass (g)
PGL0	10:0	15	0
PGL1	10:1	15	1.5
PGL2	10:2	15	3
PGL3	10:3	15	4.5
PGL4	10:4	15	6
PGL5	10:5	15	7.5

8.2 Chemically Cross-Linked Hydrogels

Chemically cross-linked hydrogels are formed through covalent bonds between polymer chains, resulting in strong, stable, and durable networks suitable for sustained drug release and wound healing applications.

8.2.1 Free Radical Polymerization In this method, monomers polymerize to form a 3D network, with herbal extracts entrapped within the matrix. It produces hydrogels with good mechanical strength and controlled release properties.²⁹

8.2.2 Enzyme-Mediated Cross-Linking A mild and biocompatible method where enzymes form covalent bonds between polymer chains, preserving the activity of herbal compounds.

8.2.3 Schiff's Base Reactions A simple cross-linking approach based on imine bond formation, producing injectable and self-healing hydrogels.

8.3 Irradiation-Based Cross-Linked Hydrogels

Irradiation-based cross-linking is a rapid and cost-effective method that uses UV light to form covalent bonds between polymer chains, producing stable hydrogel networks. Light-sensitive groups introduced into natural or synthetic polymers enable cross-linking upon irradiation.

This method is applicable to polymers such as chitosan, PVA, and PEG, and allows incorporation of herbal extracts during gel formation. The resulting hydrogels are stable, preserve bioactivity, and provide controlled release of herbal compounds.

8.4 Cold Gelation Method

Cold gelation is a simple technique where hydrophilic polymers swell in water without heat, forming hydrogels through neutralization or ionic interactions. It is especially suitable for heat-sensitive herbal extracts, ensuring stability and uniform incorporation of bioactive compounds.

Example: Carbopol-Based Herbal Hydrogel Carbopol 934P is dispersed in water and allowed to hydrate, followed by incorporation of herbal extracts under stirring. Gel formation is achieved by adjusting pH ($\approx 6-7$) using triethanolamine (TEA), resulting in a stable and homogeneous hydrogel.³⁰

**Table 5. Hydrogel Formulation with Different Extract Concentrations**

Ingredients	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9
Seed extract	5	5	5	5	5	5	5	5	5
Carbopol 934P	1.5	1	2	2	2	1	1	1.5	1.5
Aloe vera gel extract	2	1.5	1.5	2	1	1	2	1	1.5
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Distilled water (mL)	100	100	100	100	100	100	100	100	100

9. Evaluation of Herbal Hydrogels

9.1 Physicochemical Characterization

a. pH Measurement: Hydrogel pH is measured using a digital pH meter after dissolving in distilled water. Readings are taken in triplicate, and values close to skin pH are preferred to avoid irritation.³¹

b. Physical Appearance: Hydrogels are visually evaluated for color, clarity, odor, and uniformity to ensure proper formulation.

c. Homogeneity and Grittiness: The gel is checked by touch for smoothness and absence of coarse particles. Homogeneous, non-gritty gels are ideal for topical use.³¹

d. Spreadability: Spreadability determines ease of application. It is measured by placing gel between glass slides under a fixed weight and calculating:³²

$$S = (M \times L) / T$$

Where:

M is the weight applied (g),

L is distance moved

T is the time taken (sec).

e. Washability: Assesses how easily the gel can be removed with water; good washability improves user compliance.

f. In Vitro Diffusion Study: Performed using a Franz diffusion cell with suitable membrane and buffer at 37 °C. Drug release is analyzed over time to evaluate controlled release behavior.

9.2 Mechanical and Rheological Properties

a. Rheology / Viscosity: Rheological studies evaluate the flow behavior and viscosity of hydrogels using a rheometer or viscometer. These properties influence spreadability, stability, and patient compliance.³³

b. Extrudability: Extrudability measures the ease with which the gel is expelled from containers. Higher extrudability indicates better usability and uniform dosing.

c. Swelling Test: Swelling studies determine water uptake capacity and structural integrity. The swelling index is calculated as:

$$\text{Swelling Index (\%)} = (W_s - W_d) / W_d \times 100$$

where W_s is swollen weight and W_d is dry weight.

d. Porosity Test: Porosity evaluates the internal pore structure affecting drug loading and release. It is calculated using:



$$\text{Porosity (\%)} = (W_2 - W_1) / (\rho \times V) \times 100$$

where W_1 is dry weight, W_2 is soaked weight, ρ is solvent density, and V is volume.

9.3 Stability Studies

Stability studies assess the hydrogel's quality, efficacy, and safety under different storage conditions. Samples are stored at room temperature (25–30°C) and accelerated conditions (40°C, 75% RH) and evaluated for appearance, pH, viscosity, drug content, and microbial stability. These studies follow ICH guidelines and help determine shelf-life and overall stability.

9.4 Biological Evaluation

a. Skin Irritation Test: Assesses irritation potential using animal models by applying hydrogel on shaved skin and observing for erythema or edema. Non-irritant formulations are preferred for topical use.³⁴

b. Analgesic Activity: Evaluated using standard methods such as tail-flick and hot-plate tests, which measure the response time to thermal stimuli and indicate pain-relieving effects.

c. Anti-inflammatory Activity: Commonly assessed using the carrageenan-induced paw edema model. The percentage inhibition of inflammation is calculated as:

$$\% \text{ Inhibition} = (C_v - T_v) / C_v \times 100$$

where C_v is control paw volume and T_v is test paw volume.

d. Antimicrobial Activity: Determined using agar plate methods by measuring inhibition of microbial growth. Results are expressed as zone of inhibition or percentage reduction in growth.

10. Conclusions and Future Directions

Wound healing remains a complex clinical challenge due to the involvement of multiple biological processes and the structural complexity of skin. Herbal bioactive compounds—such as flavonoids, alkaloids, saponins, terpenoids, and phenolics—play a significant role by providing antioxidant, anti-inflammatory, and antimicrobial effects, while promoting key healing processes like fibroblast proliferation, collagen deposition, and angiogenesis. However, uncontrolled ROS can impair healing, highlighting the need for balanced therapeutic action.

To overcome limitations of herbal compounds (e.g., poor stability and bioavailability), their incorporation into hydrogel systems has gained importance. Both natural (chitosan, alginate, gelatin, hyaluronic acid) and synthetic polymers (PEG, PVA, PVP, PEO) provide biocompatible, moist, and ECM-like environments that enhance drug delivery and wound repair.

Overall, herbal–hydrogel systems offer a promising, safe, and effective approach for wound management, especially for chronic wounds. Future research should focus on standardization, optimization of formulations, and well-designed clinical studies to enable successful clinical translation.

Conflict of Interest

The authors declare no conflict of interest.

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