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Role of herbal hydrogels in chronic wound management

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Abstract-

This review highlights the pathophysiology of chronic wounds, limitations of traditional therapies, and the emerging role of herbal hydrogel systems as advanced wound dressings. It underscores their potential as cost-effective, multifunctional, and biologically active platforms for improving chronic wound management. **Chronic wounds** represent a significant clinical challenge due to their prolonged healing time, high recurrence rates, and association with comorbid conditions such as diabetes, vascular disorders, and obesity. These wounds arise primarily from disruptions in the normal wound healing cascade, particularly the persistence of the inflammatory phase, leading to excessive production of reactive oxygen species (ROS), proteolytic enzymes, and pro-inflammatory cytokines. This results in extracellular matrix degradation, impaired cellular function, and delayed tissue regeneration. Conventional wound dressings often fail to adequately address the complex microenvironment of chronic wounds, including infection, biofilm formation, moisture imbalance, and poor perfusion. **Hydrogels** have emerged as promising biomaterials in wound management due to their high-water content, biocompatibility, and ability to mimic the extracellular matrix. They provide a moist environment, facilitate gas exchange, and support cellular migration and proliferation. Recent advancements have focused on the incorporation of herbal bioactive compounds into hydrogel systems to enhance therapeutic efficacy. Herbal hydrogels combine the structural and physicochemical advantages of polymeric hydrogels with the pharmacological properties of natural compounds such as curcumin, Aloe vera, Centella asiatica, honey, neem, and green tea. These phytoconstituents exhibit potent antimicrobial, antioxidant, and anti-inflammatory activities, which are critical for addressing the underlying pathological mechanisms of chronic wounds. Furthermore, **herbal hydrogels** enable controlled and sustained release of bioactive agents, improve their stability, and enhance bioavailability at the wound site. Studies have demonstrated improved outcomes with herbal hydrogel formulations, including accelerated wound contraction, enhanced collagen deposition, increased angiogenesis, and reduced healing time compared to conventional treatments. Despite these advantages, challenges such as variability in herbal composition, lack of standardization, and limited clinical evidence remain barriers to widespread clinical application.

Keywords- Aloe vera hydrogel, Chronic wounds, Herbal hydrogels, Hydrogel drug delivery, Wound healing, etc.

Introduction-

There are various series of events that take place in the restoration of skin barrier. Wound is a major problem in our society nowadays and need to be get advanced treatment. There are four different phases in which the wound healing can be processed, these are hemostasis, inflammation, proliferation and remodeling. There are specific cells that perform different types of activities to fulfill these four stages process such as platelets, immune cells, keratinocytes, fibroblast and endothelial cells. If there is any type of the disruption occurs in the functioning of these cells, the stages of wound healing become prolonged and known as chronic wound. We can say that there are various types of chronic wounds such as diabetic wounds, arterial and Venous disease wounds and the people who are facing obesity conditions they have also chronic wound conditions [1].

If go through by the definition of chronic wounds, this is a condition in the four phases of wound healing get disturbed and inflammation phase becomes prolonged and convert in a pathological inflammation condition due to which the healing mechanism gets delayed and does not process in a coordinated way with other phases [2]. These wounds are identified by the chronic conditions and frequent relapse and they are cause of major disabilities.

Poor wound healing and disruption of the extracellular matrix (ECM) are key factors in ulcer development. Common ulcer types include pressure, venous, arterial, and diabetic ulcers. While their underlying causes differ, they share common features. A major reason these wounds become chronic is a prolonged inflammatory phase that does not resolve. This leads to excessive infiltration of inflammatory cells into the wound site, which drives further ECM breakdown. In such wounds, neutrophils are overactive and generate high levels of reactive oxygen species (ROS). ROS damage both the provisional matrix and cell membranes, pushing cells toward senescence. Neutrophils also release enzymes like neutrophil elastase and MMP-8. These degrade essential growth factors such as PDGF and TGF-β, as well as ECM components. As a result, ECM destruction continues while the remaining cells lose the growth factor signals needed to rebuild it, causing compounding tissue damage. Beyond enzyme release, neutrophils and macrophages in chronic wounds also produce pro-inflammatory cytokines, similar to what occurs during normal healing [3][4].

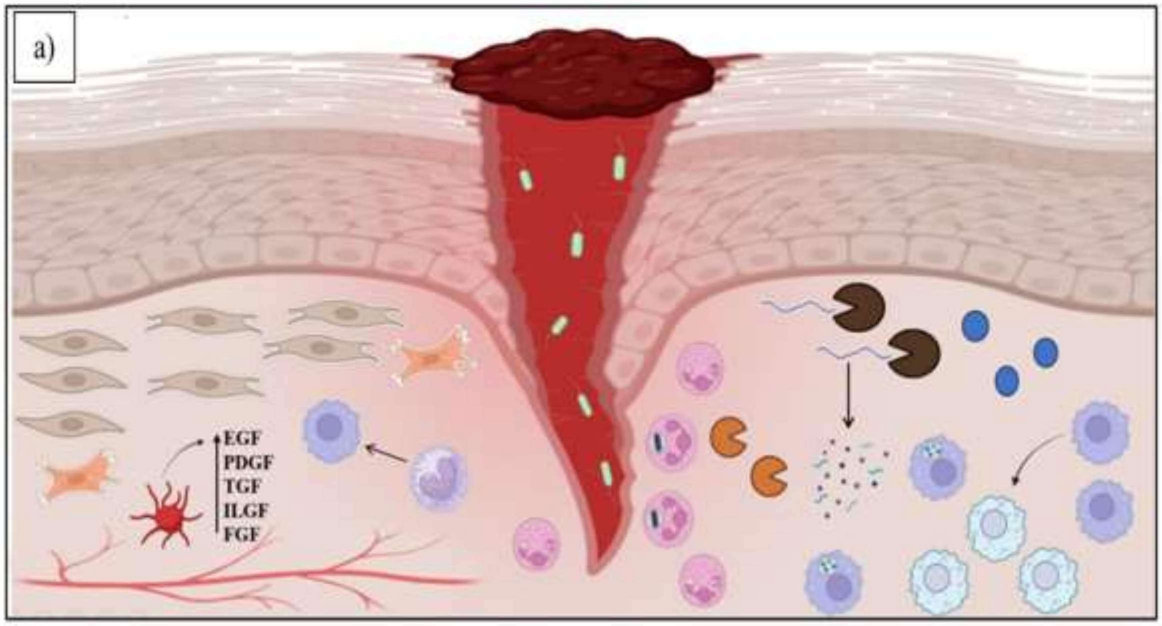

Fig. 1. Pathophysiology of normal wound healing [5]

Phases of wound healing [6-9]-

- **Haemostasis**

The wound healing cascade begins when skin injury causes blood to leak from damaged vessels. This exposes platelets to fibrillar collagen, fibronectin, and extracellular matrix proteins that are normally absent from the vascular lumen. The exposure triggers platelet activation, leading to adhesion, aggregation, and degranulation. During degranulation, α-granules release mediators such as TGF-α, TGF-β, PDGF, VEGF, serotonin, thromboxane A2, and cyclic AMP. These substances promote vasoconstriction to limit blood loss. Simultaneously, both the intrinsic and extrinsic coagulation pathways are initiated. Thrombin converts fibrinogen into fibrin, forming a fibrin-platelet clot. This clot controls bleeding and provides a temporary scaffold for migrating cells. With hemostasis achieved, subsequent wound healing stages can proceed: inflammation, angiogenesis, re-epithelialization, and extracellular matrix deposition/remodeling.

- **Inflammation-**

The inflammatory phase starts about 30–40 minutes after injury and can continue for 2–3 weeks. Early on, neutrophils move from blood vessels into the wound in response to several chemotactic factors. Platelets and mast cells are two primary sources of these chemoattractant: platelets release PDGF and TGF-β, whereas mast cells secrete TNF, histamines, leukotrienes, and interleukins (IL). Other chemotactic signals present at this stage include kallikrein, fibrinopeptides, cellular debris, and components from invading pathogens. Neutrophils sense the chemoattractant TGF-β, and rapid chemotaxis is triggered through the cell surface. This activates TGF-β serine/threonine receptors and the Smad signaling pathway, allowing cells to detect a TGF-β concentration gradient and migrate toward the source [5].

- **Proliferation-**

Re-epithelialization begins within hours after injury at the advancing edge of the epidermis. This process restores the epidermal barrier, which helps block infection, limit water loss, and maintain temperature regulation. To enable migration and proliferation of epithelial cells into the wound, matrix metalloproteinases (MMPs) and plasmin are secreted at the front of the epidermal tongue where they break down extracellular matrix components. Epithelial cells express high levels of MMP-9, which cleaves type IV collagen in the basal lamina and type VII collagen in anchoring fibrils, allowing keratinocytes to detach from the basal lamina and begin migrating. As keratinocytes move beyond the leading edge, they produce MMP-1 to degrade type I and III collagen, supporting continued cell movement. Studies using knockout models demonstrate that plasmin generated by tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) is upregulated in keratinocytes and plays an essential role in wound healing.

- **Remodelling**

The remodeling phase starts during the first week post-injury and may extend for up to 2 years. During this stage, collagen is synthesized, broken down, remodeled, and reorganized into bundles that form a mature scar. Typically, type III collagen is substituted by type I collagen, while hyaluronan in the basement membrane is replaced by heparan sulphate, and by dermatan and chondroitin sulphate within the interstitium. The shift from type III to type I collagen is regulated by the balance of MMPs and TIMPs. These enzymes degrade extracellular matrix components through hydrolysis. MMP-1 and MMP-8 cleave triple-helical collagens at Gly-Ile/Leu bonds, producing fragments that MMP-2 and MMP-9 then further degrade. TIMPs directly inhibit MMPs by binding in a 1:1 ratio, blocking the MMP active site. The MMP:TIMP ratio is carefully regulated, since disruption leads to either excess matrix deposition or degradation. Chronic wounds illustrate this imbalance clearly: elevated MMP production causes ECM breakdown, delaying healing or preventing closure entirely.

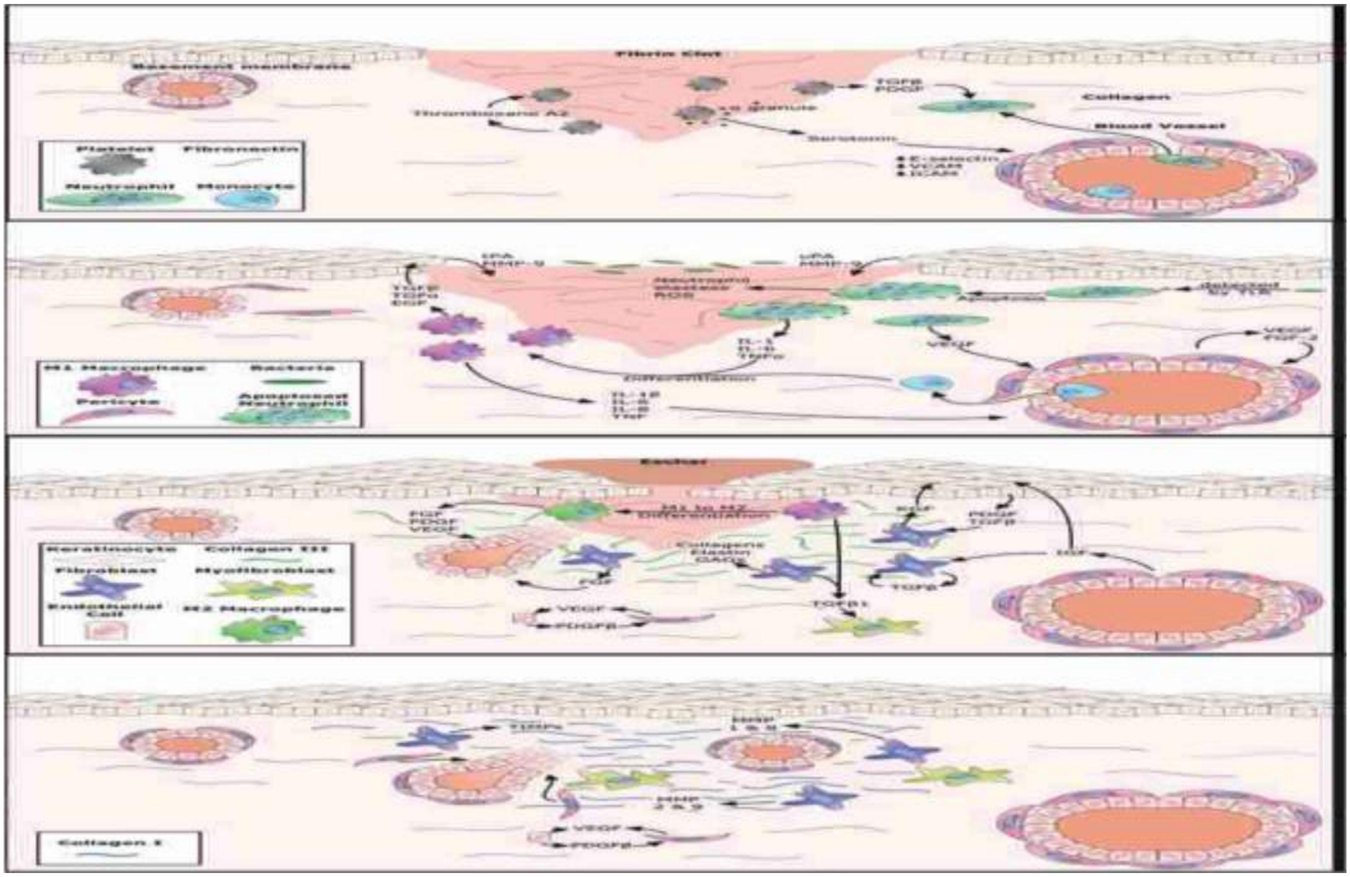

Fig. The four phases of the wound healing process [10]

Difficulties or challenges with chronic wounds [11-14]-

- ✓ **Prolonged Inflammatory Phase:** Chronic wounds often stall in inflammation and fail to advance into proliferation and remodeling stages.
- ✓ **Persistent Microbial Colonization:** Ongoing bacterial presence, frequently polymicrobial, hinders healing and raises risk of complications.
- ✓ **Biofilm Development:** Bacterial biofilms shield microbes from antibiotics and host immune defenses.

- ✓ **Inadequate Perfusion/Ischemia:** Poor blood flow restricts oxygen and nutrient supply needed for tissue repair.
- ✓ **Comorbid Conditions:** Diseases such as diabetes mellitus compromise immune response and impair regeneration.
- ✓ **Sensory Neuropathy:** Reduced sensation results in undetected trauma and late intervention.
- ✓ **Excessive Inflammatory Response:** High levels of cytokines and proteases break down growth factors and extracellular matrix components.
- ✓ **Exudate Imbalance:** Excess wound fluid causes skin maceration, while insufficient moisture leads to tissue desiccation.
- ✓ **Chronic Pain:** Persistent discomfort from wounds negatively impacts daily function and quality of life.
- ✓ **High Recurrence Rates:** Conditions like venous ulcers frequently reopen even after initial closure.
- ✓ **Economic Burden:** Extended care, advanced dressings, and hospital stays create substantial treatment costs.
- ✓ **Antimicrobial Resistance:** Repeated antibiotic use promotes resistant strains, making infections harder to treat.
- ✓ **Poor Treatment Adherence:** Inconsistent patient compliance with care plans slows or prevents healing.
- ✓ **Limitations of Conventional Dressings:** Standard wound care products often fail to address complex wound environments.
- ✓ **Psychosocial Effects:** Living with chronic wounds can lead to depression, anxiety, and social withdrawal.

Hydrogels-

Hydrogels are polymer networks that are highly swollen with water and have a strong capacity for water absorption. Their ability to swell under physiological conditions makes them well suited for biomedical uses. The network’s hydrophilicity comes from functional groups such as hydroxyl, carboxyl, amide, primary amide, and sulphonic moieties present along the polymer backbone or as side chains [15]. Hydrogels with substantial hydrophobic content can also be produced by blending or copolymerizing hydrophilic and hydrophobic polymers, or by forming interpenetrating networks (IPN) or semi-interpenetrating polymer networks (s-IPN) of hydrophobic and hydrophilic polymers [16]. Based on side-group chemistry, hydrogels are categorized as neutral or ionic. For neutral hydrogels, swelling is driven by the thermodynamic contribution of water–polymer mixing to the total free energy, together with the elastic response of the polymer network. They are further described as affine or phantom depending on their mechanical and structural features [17]. Classification by preparation method distinguishes homopolymer from copolymer hydrogels. They can also be grouped by network physical structure into amorphous, semi-crystalline, hydrogen-bonded, supramolecular, and hydrocolloidal aggregates. Stimuli-responsive hydrogels represent a key class; their swelling changes with the surrounding physical environment, enabling diverse applications. Hydrogels may be derived from natural or synthetic polymers (Table 1). Multiple methods for synthesizing biomedical hydrogels have been reported. In chemically cross-linked gels, polymer chains are connected through ionic or covalent bonds [18].

Hydrogels can be derived from natural polymers including cellulose, alginate, chitosan, gelatin, and dextran, or from synthetic polymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and polyethylene glycol (PEG). The physicochemical characteristics that determine a dressing’s clinical performance are influenced by the monomer type (natural vs. synthetic), the polymer chain structure (covalent bond stability and intermolecular interactions), and molecular weight. The polymerization method used also affects these properties [19-20].

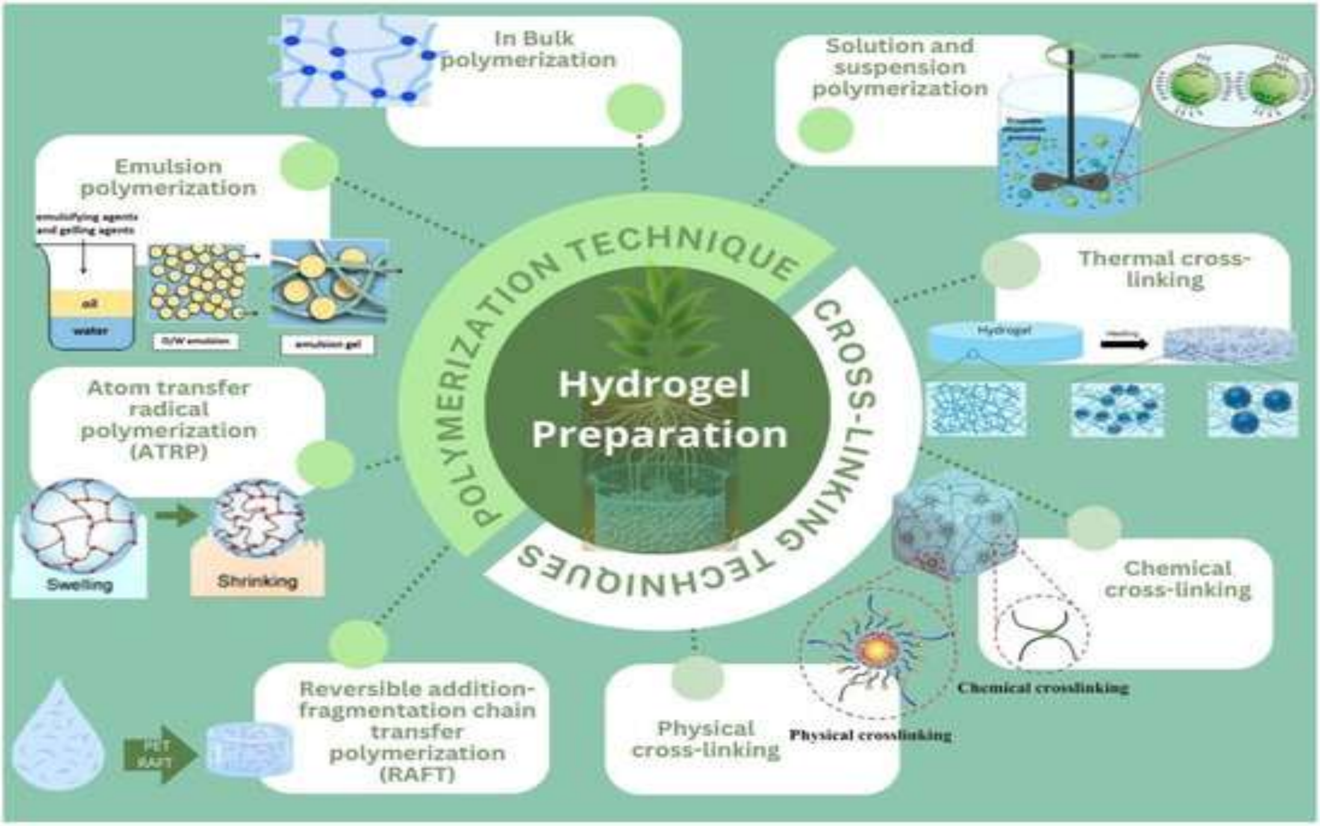

Fig 3- Hydrogel preparation [21]

Importance of hydrogels in chronic wounds-

Hydrogels have found broad success in biomedical applications because of their high-water content and resulting biocompatibility. Recent work highlights their potential in tissue engineering, as synthetic extracellular matrix (ECM) substitutes, and as three-dimensional scaffolds. *Hossein Khani et al*. examined the proliferation and differentiation of mesenchymal stem cells (MSC) within a 3D nanofiber network formed by self-assembling peptide-amphiphile (PA) molecules [22]. The 3D network was produced by combining cell suspensions in media with a dilute aqueous PA solution. In a separate study, a hybrid scaffold composed of two biopolymers — a hydrogel formed via self-assembly of PA with cell suspensions, and a collagen sponge reinforced with poly (glycolic acid) fibres — was used to improve bone formation. A new injectable 3D scaffold containing encapsulated growth factor was created by mixing aqueous PA solution with a basic fibroblast growth factor (bFGF) suspension. *Hossein Khani et al.* demonstrated that subcutaneous co-injection of aqueous PA and bFGF suspension in mice generated a transparent 3D hydrogel at the injection site, which markedly promoted angiogenesis around the area, unlike injection of bFGF alone or PA alone. Other promising biomedical and pharmaceutical uses of hydrogels include materials that regulate enzyme activity, agents that destabilize phospholipid bilayers, substrates for reversible cell attachment, nanoreactors with precisely positioned reactive groups in 3D space, smart microfluidic systems with responsive hydrogels, and energy-conversion platforms. The soft, hydrophilic character of hydrogels makes them especially suitable for novel drug delivery systems [23]. Modulating hydrogel swelling behaviour can serve as a trigger for controlled drug release. With appropriate design, hydrogels can support sustained, targeted, or stealth delivery of biomolecules. They can be engineered for bio adhesiveness to enhance drug targeting, particularly across mucosal membranes for non-invasive administration. In vivo, hydrogels exhibit a key “stealth” property due to hydrophilicity, which prolongs circulation time of delivery devices by reducing host immune recognition and phagocytic uptake. Dinarvand’s group developed poly(lactide-co-glycolide)-based hydrogel nanoparticles with surface modifications to extend the blood circulation half-life of drug carriers [24-27].

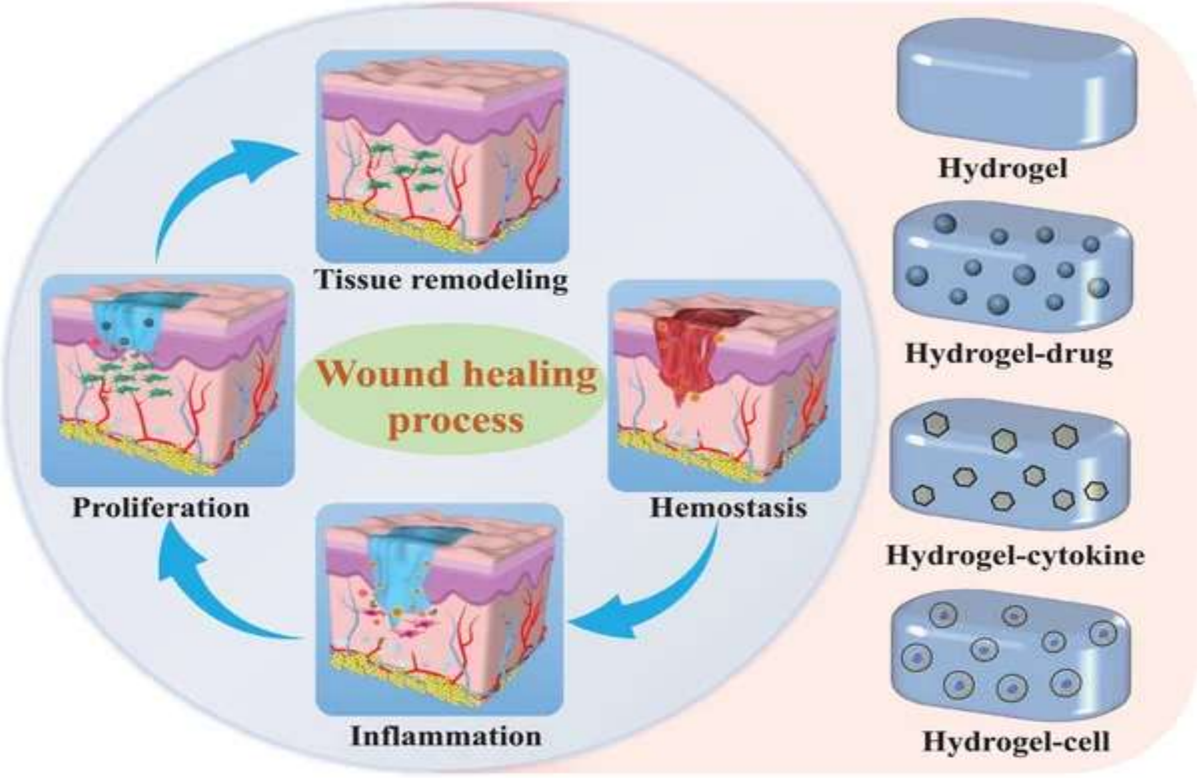

Fig 4- Hydrogel wound healing process in 4 stages [28]

Fig 5- Hydrogel wound dressing [29]

Herbal hydrogels used in various chronic wounds-

Herbal hydrogels are increasingly recognized as advanced dressings for chronic wounds including diabetic foot ulcers, pressure ulcers, and burns. Hydrogels consist of three-dimensional hydrophilic polymer networks that hold substantial amounts of water, maintaining a moist environment that supports wound healing. Because they resemble the extracellular matrix, they promote cell migration, proliferation, and tissue repair [30]. Recent studies have investigated loading herbal bioactive agents into hydrogel matrices to improve therapeutic performance. Frequently reported herbal hydrogels include those based on curcumin, Aloe vera, Centella asiatica, honey, neem (*Azadirachta indica*), and green tea (*Camellia sinensis*) [31]. These systems display strong antimicrobial, antioxidant, and anti-inflammatory activities that address major issues in chronic wounds such as infection, oxidative damage, and persistent inflammation. Curcumin-incorporated hydrogels are noted for pronounced anti-inflammatory and antioxidant effects that enhance wound contraction and collagen deposition. Aloe vera hydrogels offer soothing, hydrating, and re-epithelialization benefits, making them suitable for burns and diabetic wounds. *Centella asiatica* hydrogels stimulate fibroblast proliferation and collagen synthesis to aid tissue regeneration. Honey-based hydrogels provide broad-spectrum antimicrobial action and osmotic activity that assists wound debridement. Neem and green tea hydrogels likewise deliver notable antibacterial and antioxidant effects that help control infection and speed healing [32]. Polysaccharide carriers like chitosan, alginate, and hyaluronic acid are commonly used to fabricate these herbal hydrogels owing to their biocompatibility and biodegradability. Such systems allow controlled, sustained release of phytochemicals at the wound site, improving stability and therapeutic efficacy [33]. Encapsulation also protects labile plant compounds from degradation and increases bioavailability. In multiple chronic wound models, herbal hydrogels have shown faster wound closure, greater angiogenesis, higher collagen production, and shorter healing times versus standard dressings. Despite these encouraging outcomes, issues including variability in herbal constituents, insufficient standardization, and limited clinical data continue to limit broad clinical adoption. Still, herbal hydrogels present a promising, cost-efficient approach for chronic wound care [34-36].

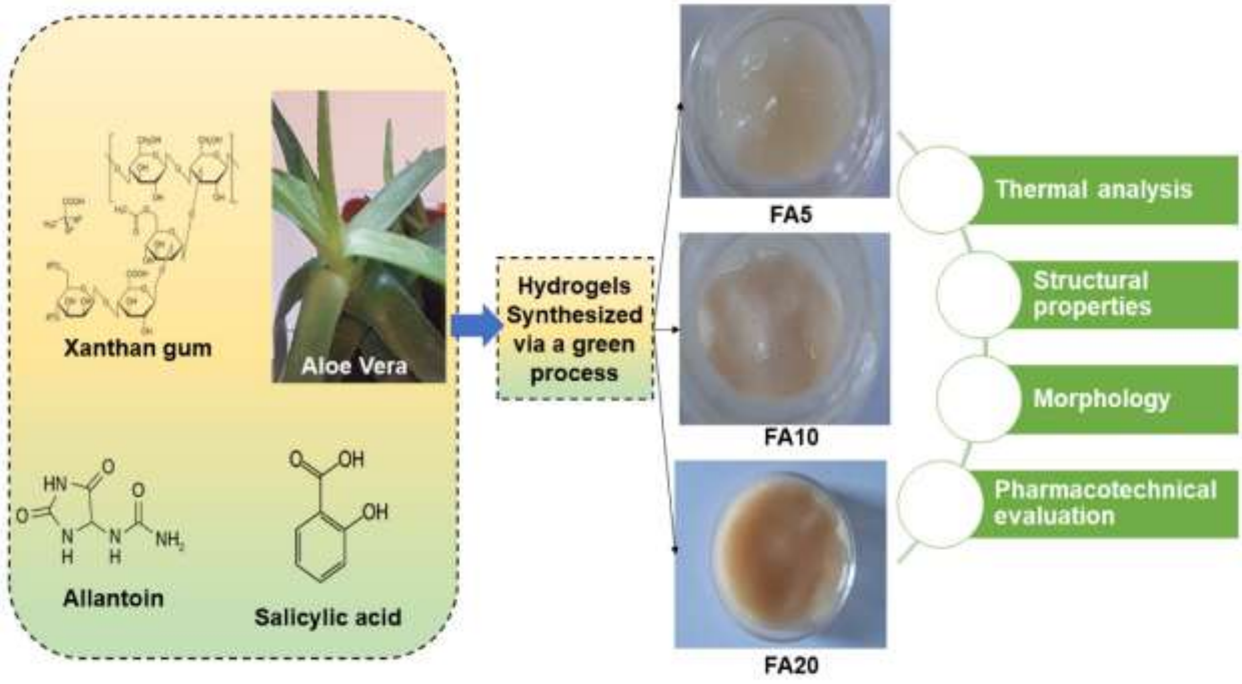

Fig 6- Aloevera herbal hydrogel for wound healing [37]

Curcumin hydrogel is developed from the principal bioactive constituent of turmeric (Curcuma longa). It displays notable anti-inflammatory and antioxidant activity, which supports collagen production and speeds up wound contraction. Because it effectively reduces oxidative stress, it is commonly applied in the management of diabetic wounds [38-39].

Aloe vera hydrogel is prepared from the mucilaginous gel of Aloe barbadensis. It delivers strong moisturizing and soothing effects at the wound site, while also promoting re-epithelialization and lowering inflammation. Due to these properties, it is frequently used for treating burn injuries and chronic ulcers [40-41].

***Centella asiatica* hydrogel** is formulated using extracts from Centella asiatica, commonly known as Gotu kola. It promotes fibroblast proliferation and enhances collagen synthesis, while also stimulating angiogenesis to support tissue regeneration. These properties make it effective for managing chronic wounds and reducing scar formation [42].

Honey-based hydrogel is created by integrating natural honey within a polymeric network. It exhibits potent antimicrobial activity and osmotic debridement effects, while also sustaining a moist wound environment that lowers the risk of infection. These characteristics make it suitable for managing infected chronic wounds and ulcers [43].

Neem hydrogel is developed from extracts of *Azadirachta indica*. It demonstrates strong antibacterial and antifungal activity that helps manage wound infection and inflammation. This makes it appropriate for treating chronic wounds with a high microbial burden [44].

Green tea hydrogel is formulated with polyphenols extracted from Camellia sinensis. It exhibits pronounced antioxidant and anti-inflammatory properties that help lower oxidative stress and promote tissue repair. These effects make it beneficial for enhancing healing in chronic non-healing wounds [45-46].

Conclusion-

Chronic wounds continue to impose a substantial burden on healthcare systems and significantly affect patients' quality of life due to their prolonged healing time, susceptibility to infection, and high recurrence rates. The underlying pathology of these wounds is complex, involving persistent inflammation, excessive protease activity, microbial colonization, biofilm formation, and impaired angiogenesis. As highlighted in the document, disruptions in the tightly regulated phases of wound healing—hemostasis, inflammation, proliferation, and remodeling—lead to delayed or incomplete tissue repair. Conventional wound management strategies, including standard dressings and systemic antibiotics, often fail to address these multifactorial challenges effectively.

In this context, hydrogels have gained considerable attention as advanced wound dressing materials due to their unique physicochemical properties. Their high-water content, biocompatibility, and ability to maintain a moist wound environment make them particularly suitable for chronic wound care. Moreover, hydrogels can mimic the extracellular matrix, thereby promoting cell adhesion, proliferation, and tissue regeneration. Their versatility allows for the incorporation of therapeutic agents, making them effective drug delivery systems.

The integration of herbal bioactive compounds into hydrogel matrices represents a promising advancement in wound care. Herbal hydrogels combine the structural benefits of hydrogels with the therapeutic properties of natural phytoconstituents, offering a multifunctional approach to wound healing. Compounds such as curcumin, Aloe vera, Centella asiatica, honey, neem, and green tea have demonstrated significant antimicrobial, antioxidant, and anti-inflammatory effects. These properties directly target key factors responsible for chronic wound persistence, including oxidative stress, infection, and prolonged inflammation. Additionally, the controlled and sustained release of these bioactives from hydrogel systems enhances their stability and bioavailability, leading to improved therapeutic outcomes.

Evidence from various studies indicates that herbal hydrogels can accelerate wound closure, enhance collagen synthesis, promote angiogenesis, and reduce healing time compared to conventional treatments. They also offer advantages such as reduced toxicity, cost-effectiveness, and improved patient compliance. However, despite their promising potential, several challenges must be addressed before their widespread clinical adoption. These include variability in herbal extract composition, lack of standardized formulations, limited large-scale clinical trials, and regulatory concerns.

Future research should focus on the standardization of herbal components, optimization of hydrogel formulations, and extensive clinical evaluation to validate their safety and efficacy. Advances in nanotechnology, biomaterials, and tissue engineering may further enhance the performance of herbal hydrogels, enabling the development of next-generation wound care systems. Overall, herbal hydrogels represent a novel and effective strategy for managing chronic wounds, with the potential to significantly improve patient outcomes and reduce the global burden of wound-related complications.

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