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Review Article

# Herbal Hydrogel for Wound Healing: A Review

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ABSTRACT

Wounds are inescapable events of life, which arise due to physical or chemical injury or microbial infections. Wound healing is a complex and protracted process of tissue repair and remodeling in response to injury. As per the conventional pharmaceuticals, the overuse of synthetic drugs for wound healing such as topical antibiotics create a development of antibiotic resistance because of inadequate penetration for deep skin infections. A recent study has shown that biofilm formation by certain bacteria has become an important virulence factor associated with the generation of secondary resistance because antimicrobials are not able to penetrate into the biofilm to completely eliminate the organisms. So, there is need of some alternatives to inhibit growth of bacteria on wounds. Since ancient time, plants are already proved to be a natural remedy for various ailments. Preparations from traditional medicinal plants are often used for wound healing purposes covering a broad area of different skin-related diseases. Herbal preparations can be more effective than conventional medicines and their non-toxic nature means that they can be administered over long periods. Herbal medicines in wound management involve disinfection, debridement, and provision of a suitable environment for aiding the natural course of healing. Today drug delivery experience several challenges, where hydrogel could be one potential answer to those. Hydrogel are one of the most popular types of wound dressings. Because they have been found to promote fibroblast proliferation by reducing the fluid loss from the wound surface and protect the wound from external noxae necessary for rapid wound healing. The major advantage of using hydrogels is that they are used as simple encapsulation of cells or drugs in homogenous materials. Hence this review explains the necessity of novel drug delivery system for herbal formulation to provide magnificent effect on wound healing capacity.

**Keywords:** Herbal medicine, wound, wound healing, synthetic and herbal treatment for wound healing, wound dressing and hydro gel.

## 1. INTRODUCTION

Nature has best owed on us a very rich botanical wealth and a large number of plants grow in different parts of the country. India is rich in all the 3 levels of biodiversity such as species diversity, genetic diversity and habitat diversity. In India thousands of species are known to have medicinal value and the use of different parts of several medicinal plants to cure specific ailments has been in vogue since ancient times. The medicinal plants have a great importance in human being as it shows diverse pharmacological

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properties. India has rich tradition of plant based knowledge of healthcare. The use of the plant based medication is gradually becoming popular throughout the world [1]. Although usage of these herbal medicines has increased, their quality, safety and efficiency are serious concerns in industrialized and developing countries. It is no wonder that the world's one-fourth population i.e. 1.42 billion people, are dependent on traditional medicines for the treatment of various ailments [2] because herbal remedies are getting increasing patient compliance as they are devoid of typical side effects of allopathic medicines. Recently considerable attention has been paid to utilize eco-friendly and bio-friendly plant based products for the prevention and cure of different human diseases. It is documented that most of the World's population has taken in traditional medicine, particularly plant drug for the primary health care. The Indian flora offers variety of plants having medicinal properties. These plants can be exploited to find out effective alternative to synthetic drugs. In India, medicines based on herbal origin have been the basis of treatment and cure for various diseases. Moreover, Indian folk medicine comprises numerous prescriptions for therapeutic purposes such as healing of wounds, inflammation, skin infections, leprosy, diarrhea, scabies, venereal disease, ulcers, snake bite, etc. More than 80% of the world's population still depends upon traditional medicines for various skin diseases. Herbal medicines in wound management involve disinfection, debridement and providing a moist environment to encourage the establishment of the suitable environment for natural healing process [3].

Wound is defined as disruption of cellular, anatomical, and functional continuity of a living tissue. It may be produced by physical, chemical,thermal, microbial, or immunological insult to the tissue. When skin is torn, cut, or punctured it is termed as an open wound and when blunt force trauma causes a contusion, it is called closed wound, whereas the burn wounds are caused by heat, radiation, chemicals, electricity, or sunlight. Wound healing is the interaction of a complex cascade of cellular and biochemical actions leading to the restoration of structural and functional integrity with regain of strength of injured tissues. It involves continuous cell-cell interaction and cell-matrix interactions that allow the process to proceed in different overlapping phases and processes including inflammation, wound contraction, reepithelialization, tissue remodelling, and formation of granulation tissue with angiogenesis. Various plant products have been used in treatment of wounds over the years. Wound healing herbal extracts promote blood clotting, fight infection, and accelerate the healing of wounds [4].

## 2. CLASSIFICATION OF WOUNDS: [5, 6]

Wounds are classified as open wounds and closed wounds on the basis of underlying cause of wound creation and as acute and chronic wounds on the basis of physiology of wound healing.

### 2.1 Open Wound:

Though an open wound blood escapes the body and bleeding is clearly visible. Open wound is further classified ii various types according to the object that occur the wound**.**

#### 2.1.1 Incised Wound:

It is an injury with no tissue loss and minimal tissue damage. It is caused by a sharp object such as knife. Bleeding in such cases can be profuse, so immediate action should be taken.

#### 2.1.2 Abrasions or Superficial Wounds:

It is caused by sliding fall onto a rough surface. During abrasion the topmost layer of the skin i.e. epidermis is scraped off that exposes nerve ending resulting in a painful injury. Blood loss similar to a burn can result from serious abrasions.

#### 2.1.3 Laceration Wound or Tears Wounds:

This is the nonsurgical injury in conjunction with some type of trauma, resulting in tissue injury and damage.

#### 2.1.4 Puncture Wounds:

They are caused by some object puncturing the skin, such as needle or nail. Chances of injection in them are common because dirt can enter into the depth of wound.

#### 2.1.5 Gunshot Wounds:

They are caused by a bullet or similar driving into or through the body.

#### 2.1.6 Penetration Wounds:

Penetration wounds are caused by an object such as a knife entering and coming out from the skin.

### 2.2 Closed Wound:

In closed wounds blood escapes the circulating system but remain in the body. It includes Contusion or bruises, heamatomas or blood tumor, Crush injury etc

#### 2.2.1 Contusions or bruises:

Bruises are caused by a blunt force trauma that damage tissue under the skin.

#### 2.2.2 Hematomas or blood tumor:

They are caused by damage to a blood vessel that consequently causes blood to collect under the skin.

#### 2.2.3 Crush injury:

Crush injury is caused when great or extreme amount of force is applied on the skin over long period of time.

#### 2.2.4 Acute Wounds:

Acute wound is a tissue injury that normally proceeds through an orderly and timely reparative process that result in sustained restoration of anatomic and functional integrity. Acute wounds are usually caused by cuts or surgical incisions and complete the wound healing process within the expected time frame [7].

#### 2.2.5 Chronic Wounds:

Chronic wounds are wounds that have failed to progress through the normal stages of healing and therefore enter a state of pathologic inflammation chronic wounds either requires a prolonged time to heal or problems such as

diabetes mellitus, Malnutrition, immunodeficiency or medications are the most frequent causes of chronic wounds [8].

## 3. PATHOLOGY OF WOUNDS [9]

Wounds are physical injuries that outcome in an opening or break of skin. Wound healing, or wound repair, is the body's regular procedure of recovering dermal and epidermal tissue. Most models suggest that the mechanics of dermal wound healing fall largely into four overlapping phases:

### 3.1. Haemostasis

Bleeding starts the process of haemostasis. Blood vessels contract, platelets aggregate and a clot is formed. Leucocytes are attracted to the injured area.

### 3.2. Inflammation

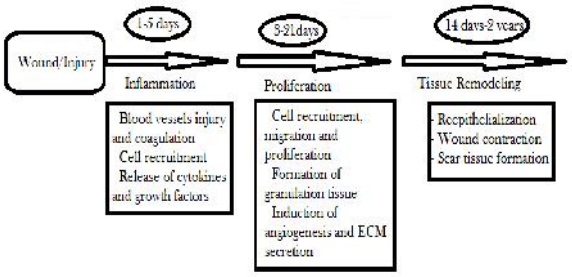
Prostaglandins and proteins are released, which cause vasodilation and inflammation. Neutrophils (whose function is phagocytosis of bacteria) and macrophages (which control the healing process) proliferate in the wound.

### 3.3. Granulation

New supporting tissue is formed like a scaffold, along with new blood vessel development, which is known as angiogenesis, and the wound begins to contract.

### 3.4. Epithelialisation

New skin cells emerge from the dermal edge and hair follicles, slowly bringing the wound edges together.




## 4. PHASES OF WOUND HEALING

### 4.1 The Inflammatory phase:

The inflammatory phase starts immediately after the injury that usually last between 24 and 48 hrs and may persist for up to 2 weeks in some cases the inflammatory phase launches the haemostatic mechanisms to immediately stop blood loss from the wound site. Clinically recognizable cardinal sign of inflammation, rubor, calor, tumor, dolor and function-laesa appear as the consequence. This phase is characterized by vasoconstriction and platelet aggregation to induce blood clotting and subsequently vasodilatation and phagocytosis to produce inflammation at the wound site [10].

### 4.2 Fibroblastic phase:

The second phase of wound healing is the fibroblastic phase that lasts upto 2 days to 3 weeks after the inflammatory phase. This phase comprises of three steps viz., granulation, contraction and epithelization. In the granulation step fibroblasts form a bed of collagen and new capillaries are produced. Fibroblast produces a variety of substances essential for wound repair including glycosaminoglycans and collagen. Under the step of contraction wound edges pull together to reduces the defects in the third step epithelial tissues are formed over the wound site [11].

### 4.3 Epithelization phase:

Epithelial cell migration is one of the vital processes of wound healing. The stem cells of epithelium must detach from the edges of the wound and migrate into wound. Normally dermal basal cells adhere to each other and to the underline basal layer of the dermis. Following mobilization, epithelial cells begin to enlarge and migrate down and across the wound. Transected hair follicles also contribute to the number of migrating epithelial cells. Epithelial cell migrating across wound usually move along the basal lamina or fibrin deposits, this phenomenon is called contact guidance and is an important factor in epithelial migration. Epithelial migration is followed by increased mitosis of epithelium. Recent evidence suggests that a water soluble heat labile substance called chalcone which is secreted at the wound site is responsible for regulation for mitosis [11].

### 4.4 Proliferative phase:

Proliferative Phase (2 days to 3 weeks) includes: Granulation stage: Fibroblasts lay bed of collagen fills defect and produces new capillaries, Contraction stage: Wound edges pull together to reduce defect. Epithelization stage: Crosses moist surface cell travel about 3 cm from point of origin in all directions [12].

### 4.5 Contraction phase:

Wound contraction is caused by the action of differentiated fibroblasts (myofibroblasts) in the granulation tissue, which contain filaments of smooth muscle actin. Contraction of these fibroblasts makes the wound margins move toward the center of the wound [13]. Wound contraction started sooner in ponies than in horses and it was significantly more pronounced in ponies. Additionally, it was significantly more pronounced in body wounds compared with the limb wounds. As a result, second intention wound healing was significantly faster in ponies than in horses, and significantly faster in body wounds than in metatarsal wounds. [14] Histology showed that myofibroblasts were more organized in the wounds of the ponies: the myofibroblasts in the newly formed granulation tissue were transformed into a regularly organized pattern within 2 weeks, in which the cells were orientated perpendicular to the vessels and parallel to the wound surface. This appears to be a more favorable condition for wound contraction to occur. In the horses, myofibroblast organization took much longer. No differences were found in the number of fibroblasts, the amounts of smooth muscle actin and collagen. Further research was performed to investigate whether the differences in wound contraction between horses and ponies were caused by differences in the inherent contraction capacity of fibroblasts or the local environment of the fibroblasts. It was found that no differences existed in the

inherent contraction capacity of fibroblasts from ponies and horses in vitro. However, the level of Transforming Growth Factor (TGF), the most important instigator of wound contraction, was significantly higher in the granulation tissue of pony wounds compared with horse wounds.

**4.7 Remodeling phase:**

This phase last for 3 weeks to 2 years. New collagen is formed in this phase. Tissue tensile strength is increased due to intermolecular cross-linking of collagen via vitamin-C dependent hydroxylation. The scar flattens and scar tissues become 80% as strong as the original [15]. The wound healing activities of plants have since been explored in folklore. Many Ayurvedic herbal plants have a very important role in the process of wound healing. Plants are more potent healers because they promote the repair mechanisms in the natural way. Extensive research has been carried out in the area of wound healing management through medicinal plants. Herbal medicines in wound management involve disinfection, debridement and providing a moist environment to encourage the establishment of the suitable environment for natural healing process**.**

## 5. ISSUES WITH WOUND HEALING PROCESS

**5.1 Maceration**

When moisture is trapped into the skin for a prolonged period, then skin will turn white or grey and will soften and wrinkle which is purely moisture dependent process occurred as a result of over-hydration [16]. Macerated skin is more permeable to microorganisms than intact skin. Due to inability of wound dressing to absorb moisture of the wound may lead to increase in area of wound infection.

**5.2 Skin stripping**

This is caused by the repeated removal of adhesive tapes and dressings from the skin. This process inflicts levels of damage to the layers of the stratum corneum, and may cause inflammatory skin damage [17].

**5.3 Bacterial and Fungal infection**

Alkaline wound fluid will promote the growth of both bacteria and fungus as it has pH from 5.5-9 [18]. A number of local factors such as damaged skin either excessively moist or dry, and changes in the temperature and normal acid balance of the skin increase a person's susceptibility to fungal infections. Most wounds are typically contaminated by bacteria which are normally harmless if the skin is intact. However, the protective barrier of skin is disrupted these normal floras are able to colonize the injured area.

**5.4 Antibiotic resistance to the pathogen**

Antimicrobial resistance has become a problem because of the overuse of antibiotics. Greater the overuse of antibiotics in the community, greater will be the resistance problem [19, 20.] Generally topical antibiotics create a development of antibiotic resistance because of inadequate penetration for deep skin infections. A recent study has shown that biofilm formation by certain bacteria has become an important virulence factor associated with the generation of secondary resistance because antimicrobials are not able to penetrate into the biofilm to completely eliminate the organisms.

**5.5 Nutritional deficiency**

Protein and glucose are required for all phases of wound healing, particularly important for collagen synthesis. Iron is required to transport oxygen. Minerals, like zinc and copper are important for enzyme systems and immune systems. Vitamins A, B complex, and C are responsible for supporting epithelization and collagen formation. Carbohydrates and fats provide the energy required for cell function [21].

**5.6 Oxygen deficiency**

Hypoxia is the important risk factor that interferes with wound healing. Hypoxia adversely affects the functions of neutrophil, macrophage, and fibroblast in repair phase. Both, oxygen-dependent and oxygen independent systems are required in order to kill microorganisms. Oxygen radicals derived from molecular oxygen are important in bacterial killing by oxidizing cell membranes. Collagen synthesis from fibroblasts also requires oxygen. If the tissue is hypoxic, procollagen hydroxylation suffers and mature collagen cannot be formed. Porous dressings usually used as wound dressing to absorb wound fluid and promote healing [22].

**5.7 Pain at dressing change**

Dressings applied on the wound are commonly allowed to remain intact until the second or third day. However, gauze materials are prone to adhere and can cause pain and trauma when they removed. The inappropriate selection of dressing materials for wound healing by secondary intention can results in significant pain and distress at dressing change. Hydrocolloids are less painful when removed because they adhere to the wound bed far less than gauze dressings [23].

## 6. TREATMENTS

**6.1 Some popular synthetic wound care drugs**

| Drug name | Drug class |
|---|---|
| Silver sulfa diazine | Sulfa antibiotics |
| Santyl | Collagen specific enzyme |
| Urea | Keratolytics |
| Thermazene | Sulfa antibiotics |
| Hibiclens | Antiseptic |
| Sarna | Local Anaesthetic |
| Silver nitrate | Antiseptic |
| Atrapro | Skin Barrier Emollient |

**6.2 Limitations**

- Cytotoxic drugs interfere with cell proliferation and may cause neutropenia, making the patient more susceptible to wound infection
- Some topical antibiotics create a development of antibiotic resistance because of inadequate penetration for deep skin infections

- Long-term use of corticosteroids may suppress fibroblast and collagen synthesis
- Non-steroidal anti-inflammatory drugs (NSAIDs) suppress the normal inflammatory response and may affect healing by causing vasoconstriction [24].
- Surgical techniques such as inadequate skin closure, rough handling and prolonged theatre time have been shown to delay healing [25].
- Failure to accurately identify abnormalities of healing
- Inappropriate use of antiseptics, hypochlorites and antibiotics
- Poor dressing choice: high exudate levels, which are not managed effectively by the dressing, cause maceration and subsequent breakdown [26]. Conversely, if the wound surface is too dry, the cells will become desiccated and may die causing further delay
- Failure to provide appropriate pressure relief will contribute to tissue breakdown

**Table 1: Some Indian plants with wound healing activity with their models:** [27]

| SL.NO | PLANT NAME | PART USED | MODEL STUDIED |
|---|---|---|---|
| 1 | Ageratum conyzoides | Root | Excision wound model |
| 2 | Andrographis paniculata | Leaf | Excision wound model |
| 3 | Bryophyllum pinnatum | Leaf | Excision wound model |
| 4 | Centella asiatica | Plant | Excision wound model |
| 5 | Datura alba | Leaf | Burn wound |
| 6 | Eucalyptus globules | Leaf | Excision wound model |
| 7 | Ficus deltoidea | Whole plant | Excision wound model |
| 8 | Gentiana lutea | Rhizomes | Excision,Incision,dead space |
| 9 | Hemigraphis colorata | Leaf paste | Excision wound model |
| 10 | Ixora coccinea | Flower | Dead space |
| 11 | Jatropha curcas | Bark | Excision,Incision,Dead space |
| 12 | Kalanchoe pinnata | Leaf | Excision wound model |
| 13 | Lanata camara | Leaf | Burn wound |
| 14 | Laura nobilis | Aqueous | Excision and Incision model |
| 15 | Moringa olifera | Leaf | Exicision,Incision |
| 16 | Nelumbo nucifera | Rhizome | Excision,Incision |
| 17 | Ocimum sanctum | Leaves | Excision,Incision,Dead space |
| 18 | Rubia cardifolia | Root | Excision wound model |
| 19 | Vinca rosea | Leaf | Excision wound model |
| 20 | Wedalia calendulaceae | Plant | Incision and Excision |

The direct application of herbal medication shows poor bioavailability due to drug degradation, poor penetration through skin and drug loss etc. miraculous prosperity of novel drug delivery system like localized action, controlled, sustained and targeted delivery may instigate the drug in novel form.

## 7. WOUND DRESSING

Wound dressings are used to avoid all shortcomings which occurred during wound healing process. Dressing can be classified as primary dressings which are in physical contact with the wound surface, secondary dressings that cover the primary dressing. In general, dressings are divided into two; traditional and modern dressings. Cotton wool, natural or synthetic bandages and gauzes are referred to as traditional dressings, while modern dressings include hydrocolloids, alginates, hydro gels, semi permeable adhesive film, foams, biological dressings and tissue engineered skin substitutes. Among that hydro gels are more popular due to ease of application and better percutaneous absorption than other semisolid preparation.

Hydro gels are three-dimensional cross-linked polymer network that can respond to the fluctuations of the environmental stimuli (pH, temp, ionic strength, electric field, presence of enzyme etc.) and swell or shrink accordingly. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility. Hence these biomaterials are widely used in different field of pharmaceutical and biomedical engineering [28].These biomaterials can incorporate large quantum of biological fluids and swell. Today, drug delivery experience several challenges where hydro gel could be one potential answer to those. Unique biocompatibility, flexible methods of synthesis and tailor able physical properties have made the hydro gels to be used as a drug delivery device to tissue engineering scaffolds. As scaffolds they should provide structural integrity like tissue constructs and as a drug carrier it should have sufficient mechanical strength to control and protect the drug and proteins until they are delivered to the specific sites of the biological system. Hence, the evaluation of swelling, mechanical and biocompatible properties consider more attention before the hydro gels are applied.

Hydro gels are capable of delivering genetically engineered pharmaceuticals, *viz.* protein and peptides and improve the therapeutic efficacy and safety of drugs administered by conventional methods. Depending on the preparation methods this three dimensional architecture of hydro gels could be homo-polymeric, co-polymeric, semi-interpenetrating and interpenetrating polymer networks. Recently, thermoplastic co-polymeric biodegradable hydro gels with optimum mechanical strength have been designed for biomedical applications including drug delivery system [29].

Hydro gels due to their unique biocompatibility, flexible methods of synthesis, range of constituents and desirable physical characteristics, are widely used in different biomedical fields. They can serve as scaffolds which provide structural integrity to tissue constructs, control drug and

protein delivery to tissues and serve as adhesives or barriers between tissue and material surfaces. Hence, the properties of hydro gels are important for tissue engineering and other areas of biomedical field.

## 8. PROPERTIES OF HYDROGEL

Hydrophilic gels called hydro gels can be used as a carrier for drug and other therapeutic bio-molecule only if it is biodegradable, biocompatible and non-toxic *in situ*. Thus once the biomaterials are prepared one must evaluate the characteristic properties like swelling behavior, mechanical properties and toxicity studies etc so that the hydro gel could be used successfully in the concerned biomedical field.

### 8.1 Swelling properties

All polymer chains in hydro gels are cross linked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For this reason, there is no concept of molecular weight of hydro gels and therefore, sometimes called infinitely large molecules or super macromolecules. A small change in environmental condition may trigger fast and reversible changes in hydro gel. The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical texture of the hydro gel. These changes may occur at macroscopic level as precipitate formation, changes in size and water content of hydro gels.

### 8.2 Mechanical properties

Mechanical properties of hydro gels are very important from the pharmaceutical and biomedical point of view. The evaluation of mechanical property is essential in various biomedical applications viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties of hydro gels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. Changing the degree of cross linking the desired mechanical property of the hydro gel could be achieved. Increasing the degree of cross linking a stronger hydro gel could be achieved though the higher degree of cross linking decreases the % elongation of the hydro gels creates a more brittle structure. Hence there is an optimum degree of cross linking to achieve a relatively strong and yet elastic hydro gel. Copolymerization with co-monomer, may result into hydrogen bonding within the hydro gel which has also been utilized by many researchers to achieve desired mechanical properties.

### 8.3 Biocompatible properties

It is important for the hydro gels to be biocompatible and nontoxic in order to make it applicable in biomedical field. Most polymers used for this purpose must pass cytotoxicity and *in-vivo* toxicity tests. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility consists basically of two elements: (a) bio-safety i.e. appropriate host response not only systemic but also local (the surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis and (b) bio-functionality i.e. the ability of material to perform the specific task for which it is intended. [30]

## 9. CONCLUSIONS

In Indian system of medicine majority of herbal products are made by using crude plant or portion of plant parts and their extracts. Natural remedies are more acceptable in the belief that they are safer with fewer side effects than the synthetic ones. There is a growing demand for herbal formulation in the world market and they are invaluable gift of nature Wound healing is a fundamental response to tissue injury that results in restoration of tissue integrity. This is mainly achieved by the synthesis of the connective tissue matrix. Collagen is a major protein of the extracellular matrix and is the major component that ultimately contributes to wound strength. Plants and their extracts have immense potential for the management and treatment of wounds. Herbal medications are considered safer than allopathic medicines which are associated with the side effects. One of the methods for its survival is preparation of extract and their formulations for better absorption and penetration of the active moiety into the systemic circulation. Among that Hydro gels are one of the most popular types of wound dressings. It will reduce the fluid loss from the wound surface and promote fibroblast proliferation which is essential for the rapid wound healing. After formulating the gel they should be subjected to animal and human studies to determine their effectiveness.

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