



# A Comprehensive Review On Herbs, Active Pharmaceutical Ingredients, Novel Drug Delivery Systems, And Advanced Technologies For Wound Healing And Antiseptic Activity

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**Abstract-** Wounds are the damage or breakage on skin surface which are the major causes of bacterial infection. Wounds can be recognized by their severity of infection during various phases. The main cause of bacterial infection is due to inflammation on the wound which causes continuation of various bacterial species on it. From last few years, 50% of the deaths and public health concerns are due to infections. Hence to overcome such health problems, wound healing is necessary. It not only heals the wound but also helps in termination of bacterial species causing severe infections. The healing action adapts various biological phases and rely on some factors like wound size, location, depth, age etc. The important mode of action of wound healing is the 'Anti-Bacterial'/'Anti-Microbial' activity which ruptures the structures of bacterial species leading to fasten the healing of wounds. Now-a-days wound healing has implied usage of various biodegradable and biocompatible materials which are FDA approved. Numerous technologies have come into existence for wound healing from which Dermal Patch Technology is the quickest, easiest and safest technique for wound healing. The paper reviews information mainly from peer-reviewed literature and other publicly available sources.

**Index terms– Haemostasis; Inflammation; Wound healing;**

## INTRODUCTION

Wound healing has been recognized as a topic of interest in both fundamental research and clinical medicine, posing an imminent threat to global socioeconomic development. Wounds are injuries which rupture the skin cell or other portions of the body tissues and are one of the most prevalent types of damage in both animals and humans.<sup>1</sup> Wounds are classified based on the severity of infection during surgery, which is a universally accepted standard nowadays, and include clean wounds that are non-infectious with no inflammation, clean but infected wounds, infected wounds that are open wounds, fresh or caused by accident, dirty and infected wounds that are old wounds caused by stroke, along with dead tissues or pierced organs.<sup>2</sup> The primary stage of wound healing is inflammation, which begins shortly after the injury when the ruptured blood vessels bleed transudate,

generating swelling. The primary purpose of inflammation is to promote the movement of white blood cell-derived monocytes and lymphocytes to the wound bed in order to prevent infections and control bleeding.<sup>3,4</sup> There are three stages of inflammation: acute, subacute, and proliferative. Each phase tends to reveal diverse clinical symptoms of the body. Bacterial infection may cause the progression of a chronic wound throughout the inflammatory phase.<sup>5</sup> Furthermore, increasing skin inflammation and the intrinsic causes of persistent wounds may lead to bacterial colonization, reducing the possibility of healing. Bacterial infection is the most significant factor in the development of a chronic wound damage.<sup>6</sup>

Microorganism-induced diseases are responsible for over 50% all deaths and remain a major public health concern, particularly in underdeveloped nations. Synthetic antimicrobial drugs are quite expensive and scarce in developing and underdeveloped countries. Bacteria, viruses, protozoa, fungi, and worms can all cause infection.<sup>7</sup> Despite the use of aseptic approaches and topical antimicrobial medications, the burn wound is a favorable environment for bacterial development and proliferation. The susceptibilities of different strains of bacteria vary significantly, and most antibiotics are resistant to pathogenic pathogens. A lot of research has been done in this field to find novel approaches to reduce infections. Because bacterial resistance is arising, it appears vital to seek out for medicinal plants and their healing properties. The indiscriminate use of antibiotics has resulted in the development of drug resistance in majority of bacteria. The safety of synthetic medications is an enormous concern because they have the potential to cause cancer and other fatal diseases when used over a prolonged period of time. Medicinal plants are regarded as valuable resources because they contain secondary metabolites with antimicrobial characteristics. Plant-derived compounds have been proven to be more active than well-established antibiotics. For these reasons, scientists are focusing their research on the development of plant-based antimicrobial medications. Medicinal plants have a huge potential for developing novel treatments that will help humanity and are a rich source of antibacterial compounds. They contain active constituents that are used in the treatment of many human diseases (Stary and Hans, 1998). The plant extracts have been developed and proposed for use as antimicrobial substances (Del Campo et al., 2000). Antimicrobial activity is affected by herb species, active ingredient concentration, microbe species and concentration, substrate composition, and treatment circumstances. It is critical to investigate the antimicrobial benefits of herbs and other plants in a variety of forms, such as extracts or essential oils, as a natural supply of antibacterial chemicals. A broad spectrum of medicinal parts are employed to create several rasayanas, each with unique medicinal qualities against certain microorganisms. Hundreds of plant species have been examined for antibacterial characteristics, however the majority have not been thoroughly investigated.<sup>8</sup>

Natural antimicrobial compounds are capable of improving antimicrobial activity against a wide spectrum of bacteria when used alone or in combination with antibiotics.

Antiseptics are biocides or products that destroy or inhibit the growth of microorganisms in or on living tissue. Whatever the type of microbial cell (or entity), it is probable that there is a common sequence of events. This can be envisaged as interaction of the antiseptic or disinfectant with the cell surface followed by penetration into the cell and action at the target site. The nature and composition of the surface vary from one cell type (or entity) to another but can also alter as a result of changes in the environment. Interaction at the cell surface can produce a significant effect on viability (e.g. with glutaraldehyde), but most antimicrobial agents appear to be active intracellularly. The outermost layers of microbial cells can thus have a significant effect on their susceptibility (or insusceptibility) to antiseptics.<sup>9,10</sup>

As a result, finding novel natural antibacterial wound healing patches with fewer side effects is critical. Many studies have been conducted in this domain, not only for infectious disorders, but also for other conditions used to control and cure infections and wounds. Dermal patch technology has proven to be the quickest, easiest, safest, and most cost-effective technique to aid wound healing. Nowadays, more attention is paid to pollution caused by non-biodegradable synthetic polymers which has resulted in worldwide concern on biodegradable substances such as polysaccharide, lipid, protein and other composite films (Karlsson and Albertsson, 1998). PVA (polyvinyl alcohol) is the most biodegradable of the vinyl polymers. Thus, incorporating biodegradability into the drug delivery system adds a new dimension to the usage of polymeric materials in or as drug delivery systems. However, a range of degradable polymers, both synthetic and natural, are potentially beneficial for

this purpose. Through this work, the use of intentionally degradable polymers in medicine has gained significance due to new advancements in drug delivery systems.<sup>11</sup>

## SKIN STRUCTURE

The human skin is a multi-layered structure composed of the epidermis, dermis, and subcutaneous tissue.<sup>12</sup> The epidermis is the skin's outermost layer, which is primarily made up of cuticles. It could withstand environmental stresses like ultraviolet radiation, pathogenic microorganisms, and unpredictable mechanical damage. It is able to reduce dehydration by controlling moisture levels.<sup>13</sup> The dermis is made up of thick, collagen-rich connective tissue. The dermis's extensive extracellular matrix (ECM), living cells, nerve endings, and blood vessels maintain the skin's structural integrity, elasticity, and nutrition.<sup>14</sup> The interaction of the epidermis and dermis has the potential to establish, maintain, and restore tissue homeostasis. Subcutaneous tissue is the deepest layer. It is primarily made up of vascularized loose peri-areolar connective tissue and adipose tissue, which serves as thermal isolation and mechanical barrier for the body.<sup>15</sup>

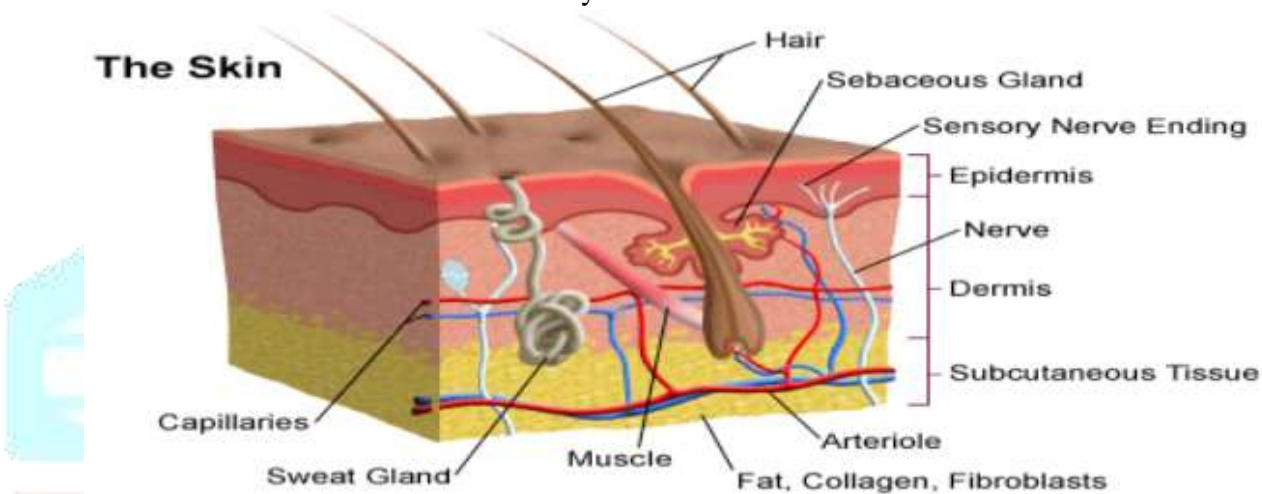


Fig1:Basic structure of skin

## WOUND HEALING

Wound healing is a complex process in which numerous cells work together to heal the tissue that has been damaged. Wound healing, also known as wound repair, is a complex process by which the skin, organ, or tissue recovers itself after injury. Wound healing progresses through a series of interdependent and overlapping stages in which a variety of cellular and matrix components act together to reestablish the integrity of damaged tissue and replacement of lost tissue.<sup>16</sup>

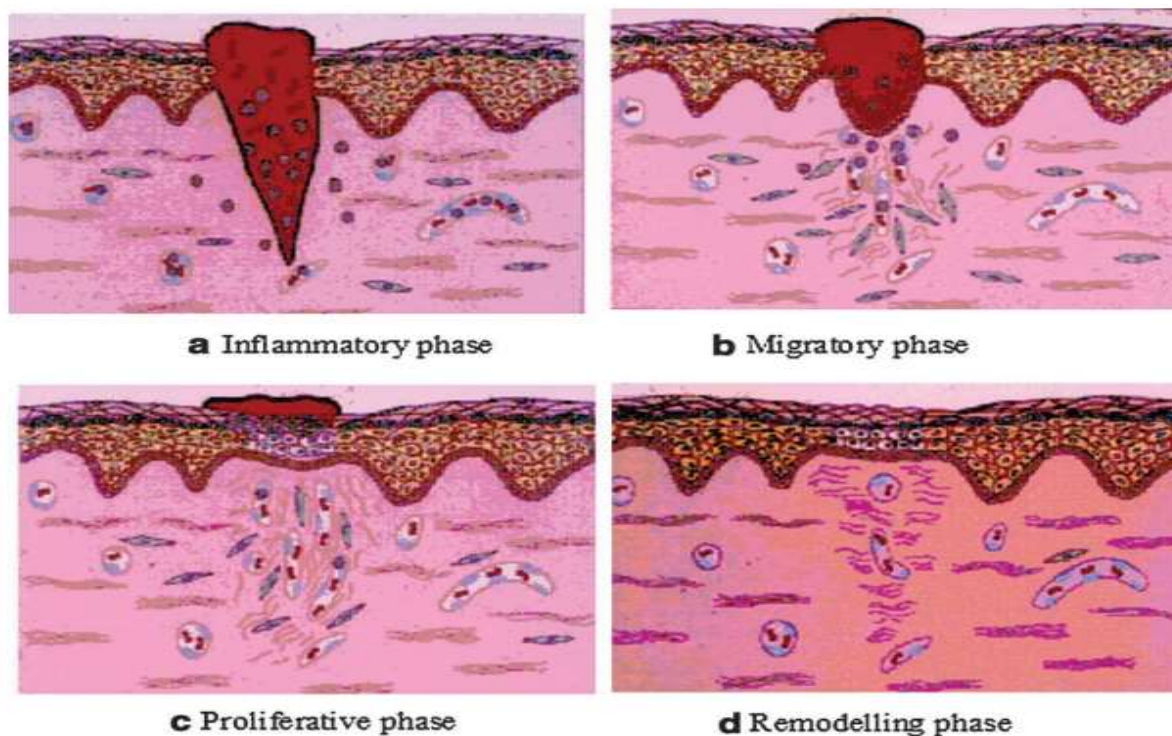


Fig2: Schematic representation of the phases of wound healing (a) infiltration of neutrophils into the wound area (b) invasion of wound area by epithelial cells (c) epithelium completely covers the wound (d) many of the capillaries and fibroblasts, formed at early stages have all disappeared (adopted from Gandour—unpublished)<sup>17</sup>

## HEMOSTASIS AND INFLAMMATION

Bleeding usually occurs when the skin is injured and serves to flush out bacteria and/or antigens from the wound. In addition, bleeding activates hemostasis which is initiated by exudate components such as clotting factors. Fibrinogen in the exudate elicits the clotting mechanism resulting in coagulation of the exudates (blood without cells and platelets) and, together with the formation of a fibrin network, produces a clot in the wound causing bleeding to stop. The clot dries to form a scab and provides strength and support to the injured tissue. Hemostasis therefore, plays a protective role as well as contributing to successful wound healing.<sup>18</sup> The inflammatory phase occurs almost simultaneously with hemostasis, sometimes from within a few minutes of injury to 24 h and lasts for about 3 days. It involves both cellular and vascular responses. The release of protein-rich exudate into the wound leads to vasodilation through release of histamine and serotonin, allows phagocytes to enter the wound and engulf dead cells (necrotic tissue). Necrotic tissue which is hard is liquefied by enzymatic action to produce a yellowish colored mass described as sloughy. Platelets liberated from damaged blood vessels become activated as they come into contact with mature collagen and form aggregates as part of the clotting mechanism.<sup>17</sup>

- **Migration-** The migration phase involves the movement of epithelial cells and fibroblasts to the injured area to replace damaged and lost tissue. These cells regenerate from the margins, rapidly growing over the wound under the dried scab (clot) accompanied by epithelial thickening.<sup>17</sup>
- **Proliferation-** The proliferative phase occurs almost simultaneously or just after the migration phase (Day 3 onwards) and basal cell proliferation, which lasts for between 2 and 3 days. Granulation tissue is formed by the in-growth of capillaries and lymphatic vessels into the wound and collagen is synthesised by fibroblasts giving the skin strength and form. By the fifth day, maximum formation of blood vessels and granulation tissue.<sup>17</sup>
- **Maturation-** This phase (also called the ‘remodelling phase’) involves the formation of cellular connective tissue and strengthening of the new epithelium which determines the nature of the final scar. Cellular granular tissue is changed to an acellular mass from several months up to about 2 years. Table 1 describes the appearance of wounds in relation to the stages of wound healing. These descriptions relate not only to

different types of wounds but also to the various stages through which a single wound may pass as it heals.<sup>19,20</sup>

## THE WOUND HEALING PROCESS

The skin, the body's largest organ, plays an important role in sensory processes, homeostasis, temperature regulation, and protection from viruses, toxins, and damage. The development of a wound is determined by an impairment of skin integrity, which can occur as a result of a disease or turn out accidental or intentional. Wounds can result from surgical intervention, an injury, or a combination of variables and situations such as pressure, shear, diabetes, or vascular disease.<sup>14</sup> They are divided into two types: acute wounds (such as surgical wounds and burns) and chronic wounds.<sup>21</sup> A chronic wound is described as a difficult-to-heal wound or ulcer that fails to attain anatomic and functional integrity within 3 months, despite an orderly and timely reparative process.<sup>22</sup> Wound healing comprises overlapping processes, including hemostasis/inflammation, proliferation, and remodeling, to restore tissue integrity and function. During a vascular inflammatory response, broken blood arteries contract and thrombocytes aggregate in a fibrin network, resulting in coagulation. During the proliferative stage, angiogenesis and re-epithelialization take place, resulting in wound healing. During the remodeling phase, the maximum tensile strength is attained by reorganizing, degrading, re-synthesizing the extracellular matrix, and remodeling the granulation tissue.<sup>23</sup>

Multiple growth factors and cytokines released at the wound site strictly control wound healing. Due to the complexity of the process, many factors may hinder delaying wound healing, boosting patient morbidity and mortality, and leading to a poor cosmetic outcome as well as significant discomfort and distress. From a macroscopic perspective, wound healing depends on several criteria, that include wound size, depth, location, patient age, and the presence of localized or systemic disease. Other factors that can influence wound healing include dietary and immunological state, stress, smoking, diabetes, obesity, and hypertension, as well as the older population's overall lifespan, which has raised the prevalence of non-healing ulcers. Aged skin's microcirculation, crucial for wound healing, exhibits decreased vaso-regulation, altered immune responses, and fewer progenitor cells. Chronic wounds are more common in older people, which has a significant influence on their quality of life. Chronic wounds have a substantial physical, mental, social, and economic impact on patients and the healthcare system, hence the problem of chronic wounds has been known as the 'Silent Epidemic'. An ideal dressing should imitate the extracellular matrix and be biologically stable, flexible, and capable of removing wound exudate while maintaining a moist environment at the wound site. It ought to safeguard the wound from external threats and bacterial infections, improve epidermal migration, and stimulate angiogenesis and connective tissue production. Several wound dressings have been created to prevent infection and promote healing. Current wound healing approaches include the use of autografts, allografts, cultured epithelial autografts, and wound dressings made from biocompatible and biodegradable polymers like collagen, chitosan, and hyaluronic acid, all of which have been approved by the Food and Drug Administration (FDA).

## CLASSIFICATION OF WOUNDS

Wounds can be classified as open or closed based on their origin, and as acute or chronic based on their healing process.

- 1) Open wounds:** Open wound allow blood to escape the body and cause noticeable bleeding. Open wounds are further divided into different categories (Schultz, 1999) based on the object that caused them.
- 2) Incised wounds:** This is an injury that causes no tissue loss and minimal destruction of tissue. It's caused by a sharp object, like a scalpel or knife. Bleeding in such circumstances can be profuse, thus fast action must be taken.
- 3) Laceration and tear wounds:** This is a nonsurgical injury combined with some form of trauma, which results in tissue loss and damage.

- 4) **Abrasions:** Abrasions are also known as superficial wounds, are the result of a sliding fall against a rough surface. During abrasions, the uppermost layer of skin, known as the epidermis, is scraped away, exposing nerve endings and causing a painful lesion. Serious abrasions can cause blood loss similar to that of a burn.
- 5) **Puncture wounds:** These are created when an item, such as a nail or a needle, punctures the skin. They are prone to infection because dirt can reach the depths of the wound.
- 6) **Penetration wounds:** These are formed when an item, such as a knife, enters and exits the skin.
- 7) **Gunshot wounds:** These wounds are produced by a bullet or similar object entering or passing through the body.
- 8) **Closed wounds:** When blood departs the circulatory system but stays in the body. This is evident as bruises. Closed wounds have fewer classifications but are equally hazardous as open wounds.
- 9) **Contusions or bruises:** Bruises are created by blunt force trauma, which damages tissue beneath the skin.
- 10) **Hematomas, or blood tumours:** These are created by injury to a blood vessel, causing blood to accumulate beneath the skin.
- 11) **Crush injury:** These occur when excessive force is applied to the skin over an extended period of time.
- 12) **Acute wounds:** According to Lazarus et al. (1994), an acute wound is a tissue lesion that often heals in a quick and orderly manner, restoring anatomical and functional integrity. Acute wounds typically occur by cuts or surgical incisions, and they recover within the specified time limit. However, a variety of physiologic and mechanical variables might hinder the healing process, causing the wound to not proceed through the typical stepwise healing process. It causes the formation of chronic wounds that take a considerable amount of time to cure.
- 13) **Chronic wounds:** Chronic wounds are those that do not heal normally, resulting in pathologic inflammation (Menke et al., 2007). Chronic wounds heal slowly, do not heal at all, or reoccur frequently (Krishnan, 2006). These wounds are a leading cause of physical impairment.<sup>24</sup>

Table1: Classification of wounds based on the appearance <sup>21</sup>

Wound Type	Appearance	Stage of Wound Healing Affected
Necrotic	Often black or olive green due to dead devitalised tissue, that is dry, thick and leathery to touch. Common with pressure sores	Under favourable conditions, dead tissue in a wound such as a pressure sore will usually separate spontaneously from the healthy tissue beneath. This occurs as a result of autolysis and presumably involves macrophage activity and the action of proteolytic enzymes which act at the interface of the necrotic and healthy tissue A dry environment prevents the autolytic and proteolytic actions of macrophages and enzymes
Sloughy	Fluid, moist, loose and stringy rehydrated necrotic tissue that is typically yellow in colour	Associated with excess exudates during inflammatory phase. Slough leads to wounds getting stuck in the late inflammatory stage leading resulting in delayed wound healing
Granulating	Significant quantities of granulation tissue, generally red or deep pink in colour. May produce excess exudate	Proliferative phase
Epithelialising	Pink in colour with formation of new epidermis	Involves both migratory and proliferative phases. Final stages of wound healing
Infected and malodorous	Red, hot inflamed tissue, pus present. Infection with anaerobic bacteria causes unpleasant odour	Inflammatory response, collagen synthesis, epithelisation. Infection prolongs the inflammatory process which delays wound healing

### FACTORS AFFECTING WOUND HEALING

The healing of wounds can be hampered by a number of reasons. Broadly speaking, there are two types of components that affect repair: systemic and local. Systemic factors are those that affect an individual's overall health or illness status and can affect their ability to heal, whereas local factors are those that directly affect the characteristics of the wound itself.

Table2: Factors affecting wound healing

Local Factors	Systemic Factors
Oxygenation	Age and gender
Infection	Sex hormones
Foreign body	Stress
Venous sufficiency	Ischemia
	Diseases: diabetes, keloids, fibrosis, hereditary healing disorders, jaundice, uremia
	Obesity
	Medications: glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapy
	Alcoholism and smoking
	Immunocompromised conditions: cancer, radiation therapy, AIDS
	Nutrition

#### A) LOCAL FACTORS

- **Oxygenation-** Oxygen is essential for the majority of wound healing processes and is crucial for cell metabolism, especially the ATP-based energy generation process. It restricts wounds from infection, triggers angiogenesis, improves keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and production of collagen, and promotes wound contraction (Bishop, 2008; Rodriguez et al., 2008). The ideal concentration of oxygen is essential for wound healing. The healing process requires oxygen for survival (Bishop, 2008).<sup>25</sup>
- **Infections-** Microorganisms that usually reside at the skin's outer layer become exposed to the underlying tissues when the skin is wounded. Whereas colonization is an accumulation of replicating bacteria on a wound that does not cause tissue damage, contamination is the presence of non-replicating organisms on a wound. A vital part of the wound-healing process, inflammation helps in the elimination of infected microorganisms. Both bacteria and endotoxins have the ability to prolong the period of inflammation by causing an extended elevation of pro-inflammatory cytokines including TNF- $\alpha$  and interleukin-1 (IL-1). Should this persist, the injury may turn chronic or fail to heal. Matrix metalloproteases (MMPs), a category of proteases that are capable of breaking down the extracellular matrix (ECM), also rise as a result of this chronic inflammation.

## B) SYSTEMIC FACTORS

- **Age-** Age is a major risk factor for poor wound healing, and elderly individuals (individuals over 60) is aging faster than any other age group (World Health Organization [WHO, [www.who.int/topics/ageing](http://www.who.int/topics/ageing)]). Associated with age delayed wound healing is linked to a changed inflammatory response.<sup>26</sup>
- **Stress-** Numerous research demonstrate that stress-associated disruption of neuroendocrine immune homeostasis is important to health (Glaser and Kiecolt-Glaser, 2005; Vileikyte, 2007). Investigations on humans and animals has revealed that psychological stress substantially slows down the rehabilitation of wounds. Any of these elements could have a detrimental impact on how the healing response is modulated.<sup>27</sup>

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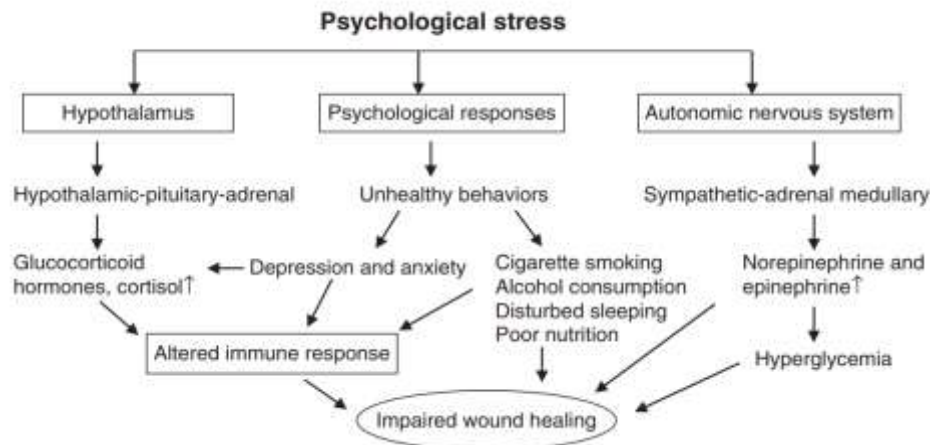


Fig3: The effects of stress on wound healing. Stress-impaired wound healing is mediated primarily through the hypothalamic-pituitary-adrenal, sympathetic-adrenal medullary axes, and psychological response-induced unhealthy behaviors.

- **Diabetes-** There is evidence suggesting that individuals who suffer from diabetes experience difficulties in recovering newly infected wounds. The decreased healing that occurs in patients with diabetes involves hypoxia, failure in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, elevated levels of metalloproteases, degradation from ROS and AGEs, reduced host immunological response, and neuropathy.<sup>29,30</sup>
- **Medications-** A variety of medications have a tendency to influence wound healing, especially those that restrict the functioning of platelets, the development of clots, response to inflammation, and cell proliferation. Evaluate just the frequently prescribed medications that are known to have a significant impact on healing, such as chemotherapy medications, non-steroidal anti-inflammatory drugs, and glucocorticoids.<sup>31</sup>
- **Glucocorticoid Steroids-** This is widely accepted that systemic glucocorticoids (GC), which frequently serve as anti-inflammatory medications, restrict wound repair by decreasing cellular wound actions, which includes the production of collagen and fibroblast proliferation, as well as through their global anti-inflammatory effects. According to Franz et al. (2007), systemic steroids result in insufficient granulation tissue and diminished contraction of wounds throughout the recovery process. The topical administration of corticosteroids has substantially various impacts than systemic application, which hinders wound repair<sup>31</sup>.
- **Non-steroidal Anti-inflammatory Drugs-** Ibuprofen serves as one of the numerous non-steroidal anti-inflammatory medicines (NSAIDs) that are frequently prescribed for the management of rheumatoid arthritis, inflammation, and discomfort. In accordance with clinical suggestions people should discontinue using NSAIDs for a duration of time that is comparable to four to five times the medication's half-life prior surgery in order to avoid anti-platelet effects. Hence, at the moment of wound healing, majority surgical patients fail to show substantial NSAID action. When it comes to using NSAIDs topically to chronic wounds, local ibuprofen-foam use stimulates moist wound healing, diminishes both acute and persistent wound pain, and aids in the healing of chronic venous leg ulcers (Price et al., 2007).<sup>32,33</sup>
- **Chemotherapeutic Drugs-** These drugs suppress the generation of proteins, RNA, or DNA, thereby decreasing wound fibroplasia and neovascularization. Chemotherapy promotes anaemia, thrombocytopenia,

and neutropenia, which raises the probability of infection, diminishes oxygen delivery to the wound, and enhances the chance of excessive blood loss at the location of the wound for patients.<sup>28,34</sup>

- **Alcohol Consumption**-Alcohol use impairs wound healing and enhances the possibility of infection, in accordance with clinical data and animal studies (Gentilello et al., 1993; Szabo and Mandrekar, 2009). Consuming alcohol reduces host resistance, and being intoxicated with ethanol at the location of an injury raises the chance that the wound will become infected.<sup>35</sup>
- **Smoking**-It is well-established that smoking has a detrimental effect on the final outcome of wound healing (Siana et al., 1989; Jensen et al., 1991; Ahn et al., 2008). People who smoke show post-operative delayed wound healing and increased risk of multiple complications, including infection, wound rupture, anastomotic leaking, necrosis of the wound and flap, epidermolysis, and reduced wound tensile strength (Chan et al., 2006; Ahn et al., 2008).<sup>36</sup> Additionally, there are about 4000 compounds in tobacco smoke, a few of which have been found to be hazardous to healing (Ahn et al., 2008). Smoking has an extensive pharmacological influence on the process of wound healing; its impact on wounds cannot be completely clarified by nicotine or any other single ingredient. A variety of variables, which fall under the categories of local and systemic factors, may delay wound healing by competing with one or more phases of the process. These elements' influence doesn't prevent one another. Any one or more of the individual phases may be modified by one or more events, which will ultimately determine how the healing process turns out.<sup>36,37</sup>

## SURGERIES FOR WOUND HEALING

For wound repair, there are several options for treatment available, such as:

- **Primary sutures**: The wounds are sealed using stitches.
- **Skin grafts**: The wounded region undergoes a transplant of healthy tissue that was taken from a different region of the body.
- **Tissue expansion**: Temporarily subcutaneously insertion of a small silicone balloon infused with salt water leads the skin to incrementally expand, thereby boosting the amount of skin available for reconstruction surgery.<sup>38</sup>

## HERBAL PLANTS EXHIBITING WOUND HEALING ACTIVITY

- **Morinda citrifolia**- It has been established that anthraquinones, flavonol glycosides, iridoid glycosides, lipid glycosides, and triterpenoids are the primary chemical constituents of this herb.<sup>39</sup>
- **Lycopodium serratum**- It has triterpenoids like oxolyococlavinol, oxoserratenetriol, tohogeninol, and tohogenol as well as the alkaloid serratidine.<sup>40</sup>
- **Sesamum indicum**- It has been suggested that sesame seeds are a good source of K and other minerals like (525.9 mg/100 g), P (516 mg/100 g), Mg (349.9 mg/100 g), Na (15.28 mg/100 g), Fe (11.39 mg/100 g), Zn (8.87 mg/100 g), and Mn (3.46 mg/100 g).<sup>41</sup>
- **Catharanthus roseus**- Vinblastin, vincristine tetrahydroalstonin, prinin, vindolin, catharanthin, vindolinin, ajmalicin, and vincoside—a glucoalkaloid precursor necessary for the formation of alkaloids—are the fundamental constituents.<sup>42</sup>
- **Cecropia pelata** - The main chemical components of *C. peltata* have been frequently reported to include chlorogenic acid and flavone C-glycosides (orientin, isoorientin, vitexin, and isovitexin).<sup>43</sup>
- **Euphorbia hirta**- Alkanes, triterpenes, phytosterols, tannins, polyphenols, and flavonoids have been reported to be present.<sup>44</sup>
- **Ginkgo biloba**- Terpene lactones, which primarily comprise ginkgolides and diterpenes, and ginkgo flavone glycosides, which primarily consist ginkgetin, bilobetin, and sciadopitysin, are the two main active components of *inkgo biloba*, though their amounts vary.<sup>45</sup>
- **Pterocarpus santalinus**- *Pterocarpus santalinus* extracts mostly comprise phenols, alcohols, ethers, ketones, polysaccharides, and fatty acids as their chemical constituents.<sup>46</sup>
- **Lawsonia alba**- The most commonly found phytochemicals include D-allose (17.61%), lawsone (12.87%), beta-D-glucopyranoside, methyl (12.74%), phytol (10.78%), 1-isobutoxy-1-methoxypropane (9.18%), n-hexadecanoic acid (6.33%), 9,12,15-octadecatrienoic acid (Z,Z,Z) (4.44%), squalene (4.06%), and vitamin E (3.60%).<sup>47</sup>

- **Achillea millefolium L-** In ethnopharmacology, yarrow (*Achillea*) species have been employed for an extended period of time. One of the most frequently utilized natural plant species for wounds, bleeding, stomachaches, gastrointestinal diseases, colds, flu, and stomach problems is *A. millefolium*.
- **Aloe vera-** Aloe vera has been recommended for the treatment of wounds from burns, wounds from surgery, damaged nipples, genital herpes, and psoriasis in addition to chronic wounds like pressure ulcers. With aloe vera hydrogel's advantageous impacts on fluid retention, angiogenesis, and wound contraction, the duration of healing have been shortened by 29%, and wounds have closed entirely in just 15 days.<sup>48</sup>
- **Curcuma longa-** Previous research suggested that mice's wounds recovered rapidly after dermal Curcumin treatment, generating robust granulation tissue composed mainly of deposited collagen and extending epithelium. In addition, by controlling the levels of different cytokines, curcumin administration significantly reduced matrix metalloproteinase-9 and tumor necrosis factor alpha and improved the healing process of wounds in mice. Yen Y.H. Curcumin improves the quicker recovery of cutaneous wounds involving an array of molecular mechanisms, involving the participation of collagen, TNF- $\alpha$ , MMP-9, and  $\alpha$ -SMA.<sup>49</sup> Integrating curcumin with ginger extract promotes skin function and healing at the same time in hairless rats whose skin has been harmed by corticosteroids, minimizing the possibility of non-healing wounds developing.<sup>50</sup>
- **Althaea officinalis-** *A. officinalis* hydroethanolic extract includes phytochemicals which function as antibiotics to eliminate gram-positive bacteria and may speed up wound healing through other mechanisms. The topical application of this remedy on a rat excision wound model was studied, and the wound healing percentage was much higher in the extract-treated wounds compared to the control.<sup>51</sup>
- **Calendula officinalis-** The beneficial effects of *calendula officinalis* on wounds from rat excision have been examined both topically and orally. Results demonstrated that the extract-treated group had a 90.0% wound closure rate on the eighth day after the wound was formed, compared to a 51.1% wound closure rate in the control group. Furthermore, the extract-treated group's hydroxyproline and hexosamine contents were significantly higher than those of the untreated group.<sup>52</sup> In addition, as calendula ointment greatly expedites the healing of cesarean punctures, it can be utilized to speed up the rehabilitation after cesarean sections.<sup>53</sup>
- **Matricaria chamomilla-** A chamomile-loaded mat's antimicrobial, antioxidant, biocompatible, and mechanical properties make it a good candidate for wound healing. Furthermore, mats loaded with 15, 20, and 30% chamomile exhibited excellent antibacterial performance, and the inhibitory zones spread as the chamomile content increased.<sup>54</sup>
- **Eucalyptus-** The ideal nanoemulsion of Eucalyptus essential oil (EEO) has been chosen for wound healing research, collagen estimate, and histopathological evaluation in rats as opposed to pure EEO and conventional gentamycin. In rats, the more effective EEO nanoemulsion revealed significant wound-healing efficacy.<sup>55</sup>
- **Jobba-** Jojoba oil is a renewable light-yellow oil that may be administered topically and has a tendency to strengthen skin barriers and heal wounds. In addition to 97% linear long-chain ethers, bioactive substances like polyphenols, flavonoids, and alkaloids make up jojoba oil. Jojoba oil dry nano-emulsion powders (JND) have been proven to be beneficial as natural oil-based anti-inflammatory and free radical scavengers for treatment acute lung injury (ALI) through decreasing bleeding and inflammatory cell infiltrations in ALI models.<sup>56</sup>
- **Plantago major-** *P. major* ointment is a secure and efficient herbal medicine for second-degree burn wounds. It serves as an analgesic and an antibacterial agent in addition to having wound-healing properties.<sup>57</sup>
- **Punicagranatum L.-** A previous study found that 10% of standard pomegranate extracts can speed up the healing of serious second-degree burn wounds, which are characterized by angiogenesis, a complete and mature epithelium, a low number of inflammatory cells, and a high density of collagen with good organization. Pomegranates are a promising medicinal plant for the recovery of skin burn wounds.<sup>58</sup>

## ACTIVE PHARMACEUTICAL INGREDIENTS USED IN WOUND HEALING

Wound care uses a variety of chemicals that facilitate the healing process. These compounds could have antibacterial, anti-inflammatory, or regenerative effects. The usage of these substances is dependent on the type of wound and must be done under the supervision of healthcare specialists.

- **Zinc oxide-** Topical zinc promotes the healing of minor and acute skin lesions while also stimulating re-epithelialization, reducing inflammation and bacterial development. Zinc oxide (ZnO) is distinguished by its photo-oxidizing catalytic and photo-oxidizing activity against chemical and biological species. ZnO nanoparticles have antifungal and antibacterial properties, making them efficient against Gram-positive as well as Gram-negative bacteria. Zinc is an essential trace element in the human body, and its importance in health and infection is recognised. Zinc deficiency, whether due to genetics or nutrition, can produce neurotic, pathologic, and physiological alterations, as well as delayed wound healing. Zinc (Zn) has recently gained substantial interest for wound consideration due to its different biophysiological characteristics.<sup>59</sup> Zinc is a vital trace mineral in the human body, and its role in both health and sickness is well understood. It acts as a cofactor in a variety of transcription factors and enzyme systems, including zinc-dependent matrix metalloproteinases, which promote auto debridement and keratinocyte migration during wound healing. Zinc offers resistance to epithelial apoptosis via cytoprotection against reactive oxygen species and bacterial toxins, which may be mediated by the cysteine-rich metallothionein antioxidant action. Zinc deficiency, whether hereditary or nutritional, may result in pathological alterations and delayed wound healing. Oral zinc supplementation may be effective in treating zinc-deficient leg ulcer patients, although its therapeutic role in surgical patients requires further investigation. Topical zinc administration appears to be superior to oral therapy because of its effectiveness in reducing superinfections and necrotic material through improved local defence systems and collagenolytic activity, and the sustained release of zinc ions that promotes epithelialization of wounds in normozincemic individuals.<sup>60</sup>
- **Povidone-iodine-** Povidone-iodine is a commercial antimicrobial agent utilised for skin disinfection, surgery, and local infection treatment. This chemical has a broad activity spectrum, including various species of Gram-positive and Gram-negative bacteria, mycobacteria, fungi, protozoa, and viruses. Povidone-iodine is indicated for acute wounds, lacerations, bruising, and deep wounds because of its excellent tissue penetration. PVPI is one of the most widely used topical antiseptics in wound care. . PVPI is a water-soluble iodine-polyvinylpyrrolidone compound that works as a broad-spectrum antiseptic against bacteria, viruses, fungi, protozoa, and yeasts. Despite its use as a topical antiseptic, PVPI solution was toxic to human skin fibroblasts, completely suppressing cell proliferation, implying a possible harm to cells involved in wound repair. These films have antibacterial and antifungal properties against *Escherichia coli* and *Candida albicans*, respectively.<sup>61</sup>
- **Gentamicin -** Gentamicin, an aminoglycoside antibiotic, is routinely used for the treatment of bone and soft tissue infections. Gentamicin can treat serious infections, particularly those caused by Gram-negative bacteria strains. The mechanism of action is to inhibit bacterial protein synthesis through electrostatic interaction with negatively charged phospholipid head groups. Gentamicin is bound to particular ribosomal proteins, forming non-functional complexes that cause mRNA misreading. Gentamicin is a common antibiotic known for its effectiveness against Gram-negative bacteria, particularly when combined with vancomycin or a penicillin.<sup>62,63</sup>
- **Chlorhexidine-** a synthetic molecule generated from bisbiguanide, has excellent antibacterial action and is not absorbed by the body, making it a promising material for fighting microbes. Its cationic structure, along with that of chitosan and the alcohol function contained in its structures, can precipitate proteins and denature lipids found in bacteria, and it is effective against both Gramme positive and Gramme negative strains. Chlorhexidine (CHX) was used to wounds following oral surgical procedures. This strategy is supported by CHX's broad-spectrum effects against Gram-positive and Gram-negative bacteria, which include bacteriostatic capabilities at low dosages and bactericidal qualities at high concentrations, in addition to an antifungal effect. Its mode of action involves increasing the permeability of target microorganisms' cell membranes, resulting in the precipitation of macromolecules in the cytoplasm and subsequent microbial death through cell lysis. As a result, CHX's action is primarily dependent on bacterial

load reduction, acting as an anti-infection agent that appears to be necessary in the early phases of wound healing. Nonetheless, the healing problem is more complex, with other elements at work.<sup>64,65</sup>

- **Anti-inflammatory** - Topical anti-inflammatory medicines used to treat inflammation following cataract extraction may also impair corneal wound healing. Corticosteroids have been the usual treatment for postoperative inflammation. However, topical nonsteroidal anti-inflammatory medications (NSAIDs) are also allowed to manage inflammation following cataract extraction.
  1. NSAID- Non-steroidal anti-inflammatory medicines (NSAIDs), which are often used to provide analgesic effects during the postoperative period, have an impact on wound healing. Antioxidants, that scavenge these reactive oxygen metabolites, have been shown to support the anti-inflammatory process, stimulate tissue repair, and aid in wound healing.
  2. Corticosteroid –Corticosteroids have a significant impact on almost all areas of wound healing. When corticosteroids are provided early after injury, elevated corticosteroid levels delay the formation of inflammatory cells and fibroblasts, the deposition of ground material and collagen, capillary regeneration, contraction, and epithelial migration.
- **Silver sulfadiazine** - For many years, silver sulfadiazine (SSD) has served as the standard topical antibacterial treatment burn wounds. Recently, nanometre-sized silver particles have been available, which have a high surface-to-volume ratio, stay effective even at low concentrations, and reduce the risk of silver toxicity to tissues. As a result, we conducted a randomised controlled experiment to examine the efficacy of topical SSD versus nano-crystalline silver (AgNP) hydrogel in burn wound treatment. it has some adverse effects such as argyria, leucopenia, hepatic, and renal toxicity.<sup>66</sup>
- **Iodine-Based Solutions-** Iodine, discovered in 1811, has been used for almost 150 years to treat wound infections due to its antibacterial qualities. A preparation of iodide was the first to be used for the treatment of wounds. The effectiveness of povidone-iodine for hand disinfection and skin preparation, as well as its usage as an antiseptic irrigant is proven. The three key applications of povidone-iodine are:
  - (i) Hand washing and disinfection.
  - (ii) Skin preparation for invasive procedures:
    - (a) Surgical procedures.
    - (a) Nonsurgical techniques include the insertion of urine catheters, intravascular catheters, epidurals, and venepuncture.
  - (iii) Use antiseptic irrigation.<sup>67</sup>
- **Hydrogen Peroxide-** Implications for Chronic Wound Treatment. chronic wounds are distinguished by persistent inflammation, which is also present in many chronic inflammatory disorders, including diabetes, rheumatoid arthritis, periodontal disease, cardiovascular disease, and inflammatory bowel disease. To avoid oxidative damage, it is necessary to maintain a suitable balance between H<sub>2</sub>O<sub>2</sub> production and detoxification. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is a topical antiseptic used in wound care that kills bacteria via oxidation burst and local oxygen generation. H<sub>2</sub>O<sub>2</sub> enhances oxidative stress while also resolving inflammation, making it a bidirectional inflammatory regulator. Uncontrolled H<sub>2</sub>O<sub>2</sub> production causes persistent inflammation, which contributes to delayed wound healing.<sup>68</sup>

## TECHNIQUES OF CONTROLLED WOUND HEALING DRUG DELIVERY

### A. Novel Drug Delivery System for wound healing

Numerous controlled release formulation technologies have been developed in recent years to deliver medications directly to the wound site and provide prolonged activity. Such delivery methods are extremely advantageous, particularly in the management of chronic wounds, because they minimise the need for frequent administration of medications in conventional dosage forms, hence boosting patient compliance. Topical antibiotic medication in the form of controlled release formulations is also more effective than systemic administration in the treatment of chronic or severely colonised wounds. Controlled release wound healing formulations are also extremely effective in enhancing the stability of vulnerable medications such as growth hormones. Various controlled release drug delivery methods, such as micro and nanoparticulate platforms, liposomes, solid lipid nanoparticles (SLNs), hydrogels, and others, have been used to create therapeutic agents that promote healing.

- **Polymeric, gold and silver nanoparticles:** Drug encapsulation into nanoparticles is an efficient approach to solve the issues of unbound medicines, such as poor water solubility, limited biodistribution, rapid degradation and clearance. The utilisation of nanoparticulate medication delivery vehicles for wound healing is expected to revolutionise the future of diabetic care. Nanoencapsulation has been proposed to improve the stability and solubility necessary for wound healing applications. Another intriguing finding is that gold nanoparticles (AuNPs) combined with antioxidants epigallocatechin gallate (EGCG) and  $\alpha$ -lipoic acid (ALA) improve wound healing. When administered topically, a mixture of AuNPs, EGCG, and ALA has been demonstrated to improve wound healing in vivo in mice by exhibiting anti-inflammatory and antioxidant effects within the wound. Silver-releasing nanoparticles have been historically employed as an antibacterial in wound care therapy. Other nanoparticle approaches studied for wound healing include TiO<sub>2</sub> nanoparticles for wounds in rats and Amphotericin B-encapsulated nanoparticles for topical therapy of burn wound models.<sup>69,70</sup>
- **Liposomes:** Liposomes are vesicular structures made up of hydrated lipid bilayers that resemble the lipid cell membrane seen in the human body. Because of their unique phospholipid complex, vesicular carriers like liposomes are extensively researched for use in topical medication administration. Vesicular carriers can play an important role in improving the solubility and bioavailability of hydrophilic and lipophilic medicines, as well as assisting with their prolonged release. In addition to providing stability and sustaining drug release, liposomes have been proven to enhance the membrane permeability of polar compounds with high molecular weight. Liposome-based formulations have been investigated for controlled administration of wound healing medicines such as plant extracts and growth hormones. Medication-entrapped liposomes can also be utilised to functionalize nonwoven gauzes to build a novel textile-based wound dressing. Such controlled release dressings result to increased medication release to control topical chronic inflammatory diseases and improving the wound healing process. Liposome formulation technology has also been used to encapsulate haemoglobin and expedite skin wound healing in the mice model.<sup>71-73</sup>
- **Nano and micro-emulsions:** Nano and micro-emulsions are popular delivery vehicles for wound healing medications because to their small droplet size, stability, long shelf-life, ease of formulation, high surface area, and increased solubilization efficiency. Indeed, their capacity to increase the solubility of both hydrophilic and hydrophobic medicines, together with continuous release of pharmaceuticals, has become more essential in the administration of plant-based wound healing preparations. In rats, the topically administered microemulsion formulation accelerated wound healing while also decreasing the inflammatory response to chemical-induced corneal alkali burns.<sup>74</sup>
- **Microspheres:** Applying relatively thin wrappings on tiny solid particles, liquid droplets, or dispersions is referred to as microencapsulation. Because of their tiny size (1–1000  $\mu$ m) and Additional characteristics associated with microparticles involve their ability for generating qualities that are environment-responsive, their capacity to swell and adhere, and their adaptability in terms of dose forms and product applications that help in wound healing preparations. Chronic wound treatment has been discovered to benefit considerably from the flexibility of microspheres as well as their capacity to modulate the pace of medication release. Micro- and nanoparticle systems with particulate materials in the formulations additionally deliver an additional occlusive effect to the skin that is advantageous for wound healing. In addition, as they comply to various instrumental preparation methods, such as spray drying, microspheres can be used to create microparticles with a rough surface that are thought to be a viable approach to the healing of burn wounds. More effectively penetrate burnt skin, enhancing the contact surface and facilitating a more efficient release of the formulation's ingredients in the wounded area. It is also possible to generate microspheres that will hold multiple medicines for transportation at once. Due to the difficulty of managing chronic wounds, administering numerous medications can frequently be necessary to promote wound healing while controlling infections.<sup>75-77</sup>
- **Solid lipid nanoparticles:** Designing a pharmaceutical formulation is crucial for healing severely damaged skin since the carrier substances in such formulations must not hinder the wound's healing process. As an effective and safe drug delivery method, SLNs and nanostructured lipid carriers have been attracting more attention throughout time. As a result of the non-toxic and non-irritating lipid nature of SLNs, they are

optimal for use as transporters for local therapeutic medication administration on skin that is injured or irritated. But because SLN dispersion lacks the viscosity necessary to be applied topically to skin, SLNs need to be frequently added to semi-solid systems, like gels, in order to enhance the uniformity of finished formulations and encourage the long-term viability of incorporated nanoparticles.<sup>78,79</sup>

- **Nanofiber mats:** Over the past few years, drug-releasing electrospun nanofibers have been attracting a lot of attention as a wound dressing mesh because of their unique architectural traits, which provided an environment that was favourable to enhancing wound healing. The high surface to volume ratio and porosity of nanofibers generated by the electrospinning technique allows gas permeation, promoting cell respiration, skin regeneration, moisture retention, exudate elimination, and haemostasis. Additionally, any type of wound surface could be covered by electrospun mats functionalized with antibacterial or therapeutic compounds.<sup>80</sup>
- **Hydrogels:** As especially absorbents in materials for wound dressings, hydrogels have drawn a lot of interest recently. In order to encourage effective wound healing, polymeric hydrogels are capable of absorbing tissue exudates and keep wounds from drying out while permitting oxygen to get through. In addition, the hydrogels' porosity, and the moist environment they generate allow the therapeutic compounds that are encapsulated to be administered into the wound throughout an extended period of time. As a wound dressing, the in-situ gel-forming hydrogel is particularly recommended since it penetrates the wound sites and is present in a sol condition prior to application before transforming into a gel system.<sup>81-84</sup>
- **Wafers and sponges:** Through freeze-drying polymer solutions and gels, solid porous structures that are efficiently applied to seeping surfaces of wounds are created, leading to the generation of lyophilized wafers and sponges. They are designed to be applied immediately to the surface of suppurating wounds with a minimum of human touch, containing both soluble and insoluble therapeutic agents with high drug-loading capability. Wafers for medication administration for promoting wound healing have several benefits, including the ability to absorb a significant volume of wound exudates due to their porosity and the maintenance of a moist environment. Lyophilized wafers can be applied to the wound surface; upon absorbing the amount of exudate, they modify into highly viscous fluids or resilient gels. If the equilibrium between fluid absorption and moisture loss remains intact, the wafers may stay in place indefinitely enabling sustained release of the drug. Additionally, lyophilized drug form are said to have improved drug stability in contrast with semisolid-based formulations. Wafers and sponges are attractive medication delivery methods for effective wound healing management because of each of these characteristics.<sup>85,86</sup>
- **Films:** It is well-established that free-standing films are biomaterials that can be utilized for tissue repair, medication delivery, wound healing, and even artificial organ regeneration. Hydrophilic bio adhesive polymers are employed to make these films, which are ideal for the wound healing process as they are biodegradable and easily absorbed into bodily fluids via the skin without causing any harmful implications. One advantage of topical drug delivery, as seen in wound healing films, is that it can concentrate medication at the site of injury for an extended period of time. In addition, modern dressings like films, sponges, hydrocolloids, gels, and pastes can create or maintain a moist environment that permits gaseous exchange (oxygen, water vapor), provide thermal insulation, remove excess exudates and blood, and be easily removed without triggering trauma to speed up the healing process of wounds.<sup>87</sup>

## B. Advanced Technology

Several advanced technologies for wound healing were being investigated and implemented in clinical practice. Here are some advanced technologies for wound healing:

- **Negative Pressure Wound Devices-** Negative pressure wound devices are relatively recent developments in wound care treatment, and their indications are constantly growing to include various elements of the wound. Advanced wound dressing materials can help to modify the wound environment to improve healing conditions. Acute wounds are increasingly being treated using NPWD closure. In patients with major comorbidities or other serious injuries, NPWDs can be used for large soft-tissue injuries, infected wounds, and wounds with damaged tissue.

- **Advanced Dressings-** Wound dressings and devices account for a significant portion of the global medical and pharmaceutical markets. The optimum dressing should promote quick healing at a fair cost, with minimal inconvenience to the patient. Traditional dressings for wound management included natural or synthetic bandages, cotton wool, lint, and gauzes, all of which had variable degrees of absorbency. Their major role was to keep the wound dry by allowing wound exudates to evaporate while preventing harmful microorganisms from entering the wound. These new dressings are based on the idea of creating an optimal environment for epithelial cells to migrate unhindered in the treatment of lesions.<sup>17</sup> Advanced therapeutic dressings that actively participate in wound healing to ensure speedy and full healing. The primary dressings are medicated moist dressings, tissue-engineered substitutes, biomaterials-based biological dressings, biological and naturally derived dressings, medicated sutures, and various combinations of the aforementioned classes. The modern dressings are mainly classified according to the materials from which they are produced include Hydrocolloid Dressings, Alginate Dressings, Hydrogel Dressings, Semi-Permeable Adhesive Film Dressings, Foam Dressings, Biological Dressings, Tissue Engineered Skin Substitutes.<sup>88</sup>
- **Hydrocolloid Dressings:** Hydrocolloid dressings are one of the most commonly utilised dressings.<sup>89,90</sup> Hydrocolloid dressings are beneficial clinically because, unlike other dressings, they adhere to both moist and dry areas. Hydrocolloid dressings are used to treat wounds that exude lightly to significantly, such as pressure sores, small burns, and traumatic injuries. They are also used to manage leg ulcers; they do not cause discomfort when removed, and they are particularly useful in paediatric wound care for managing both acute and chronic wounds. Hydrocolloid dressings typically feature an occlusive outer cover that restricts water vapour exchange between the wound and the surrounding environment. This can be detrimental for infected wounds that require a specific amount of oxygen to heal quickly.<sup>17</sup>
- **Alginate Dressings:** Alginate dressings are made from the calcium and sodium salts of alginic acid, a polysaccharide that contains mannuronic and guluronic acid units. Alginate dressings are available in two forms: freeze-dried porous sheets (foams) and flexible fibres, with the latter used to pack cavity wounds. When applied to wounds, ions in the alginate fibre are exchanged with those in exudate and blood to generate a gel-based protective coating.<sup>91</sup> Alginate dressings are effective for moderately to extensively leaking wounds. Alginate dressings in the form of fibres trapped in a wound are rapidly biodegradable.<sup>92</sup> Subsequent removal does not harm granulation tissue, making dressing changes nearly painless. The ease of biodegradation is used to make alginate sutures for surgical wound closures. A comparison of various brands of alginate dressings revealed significant differences in fluid retention, adhesion, and dressing residues.<sup>93</sup>
- **Hydrogel Dressings-** Hydrogels are insoluble, swellable hydrophilic materials composed of synthetic polymers such as poly(methacrylate) and polyvinylpyrrolidone. Hydrogels can be used as an amorphous gel, an elastic, solid sheet, or a film. When applied to the wound as a gel, hydrogel dressings typically require a secondary covering such as gauze and must be changed frequently. Hydrogel dressings contain a substantial volume of water (70-90%), hence they cannot absorb much exudate and are therefore only used for light to moderately oozing wounds. Hydrogels have minimal mechanical strength and are hence challenging to handle. and this has been noted to affect patient compliance. They are effective at cleansing dry, sloughy, or necrotic wounds by rehydrating dead tissues and enhancing autolytic debridement. Hydrogels also promote moist healing, are nonadherent, and cool the surface of the wound, which may contribute to a significant reduction in pain, and hence have excellent patient acceptability.<sup>94</sup>
- **Biological Dressings-**These dressings, also known as "bioactive dressings," are constructed of biomaterials that play an active role in the wound healing process. Bioactive wound healing dressings include tissue designed materials generated from natural tissues or artificial sources.<sup>95</sup> These technologies usually combine polymers such as collagen, hyaluronic acid, chitosan, alginates and elastin. Biomaterials have the advantage of constituting part of the natural tissue matrix, being biodegradable, and some playing an active role in normal wound healing and new tissue development.<sup>96</sup> Collagen is a natural component of connective tissue and a key structural protein in any organ. The structural, physical, chemical, biological, and immunological features have been extensively addressed in the scientific literature.<sup>97</sup>

- **Bioelectric devices**-Commercial ES (electrical stimulation) devices that generate direct current (DC), and mono and biphasic pulsed current waveforms are the main ES technologies that are reported to aid wound healing. Usually, ES is given with one electrode in the wound and the other opposite it, or with both electrodes placed around the incision. (Koel and Houghton, 2014). ES is an evidence-based application with established efficacy, boosting wound area reduction by 40% in 4 weeks of treatment, thereby doubling the healing pace. Unidirectional ES provided better outcomes than bidirectional ES. ( Koel and Houghton, 2014) ES technologies have a solid research foundation(Harding, 2013), with the potential to become the mainstream intervention in the treatment of chronic and complex wounds.
- **3D wound imaging**- Three-dimensional wound measurements were performed utilising a unique 3D-WAM camera, allowing wound assessment from a volume perspective. The 3D-WAM camera is an accurate and dependable technology that may be used for a variety of wounds. However, volume measurements were most effective for large, deep wounds. Furthermore, the 3D photos are based on digital technology, which allows them to be used remotely. 3D imaging offers the ability to provide more precise data on which to make treatment decisions. In practice, the device was found to be comparatively easy to use and sturdy enough to meet the demands of clinical practice.<sup>98</sup>
- **Wound tracking and monitoring devices**- Multispectral and hyperspectral imaging (HSI) are new imaging techniques that have the potential to change the way people treat wounds. Hyperspectral photos contain enough spectral information to detect and discriminate spectrally distinct items.<sup>99</sup> A three-camera vision system is designed to measure the shape and volume of lesions, particularly pressure sores. This approach can help clinicians monitor the healing process for these wounds. The vision system is made up of three progressive scan video cameras installed on a triangular frame that includes a light source and optional texture projection in the centre. The cameras are not intended for high accuracy measurement applications.<sup>100</sup> Remote patient monitoring, often known as telemonitoring, strives to improve patient care by digitally transmitting health-related data. This enables early identification and intervention for illness decompensation, patient education, and an improvement in the patient-physician interaction. Telemonitoring appears to improve patient care and treatment outcomes. The quantity of publications demonstrates the increasing interest in the subject. Telemonitoring is yet to be assessed in the context of postoperative care and surgical pathology.<sup>101</sup>
- **Electronic skin patches**-A single-electrode TENG-based E-skin patch that senses motion and promotes wound healing by combining electrical stimulation and photothermal heating capability is produced by using conductive and photothermal polypyrrole/Pluronic F127 hydrogels as electrolytes. The E-skin patches are biocompatible, stretchable, and shape adaptive.<sup>101</sup>
- **Cold plasma tech**- The kINPen, an atmospheric pressure argon plasma jet, is one of the most promising sources in plasma medicine. It is electrically safe (CE-marked), certified as a medical device class IIa, and antiseptically effective. It mostly promotes wound healing. According to the existing literature, its utilisation does not offer any health hazards in people in terms of UV exposure, heat damage, and tissue toxicity. Old plasmas are found in a number of applications.<sup>102</sup>
- **Hyperbaric oxygen therapy** - When paired with traditional wound management methods, hyperbaric oxygen therapy can help heal difficult acute wounds. However, it is not recommended in standard wound care. Adjunctive hyperbaric oxygen therapy is a safe and effective way to boost tissue oxygenation and help heal tough wounds. The majority of the research on hyperbaric oxygen therapy supports its use in chronic wounds, although its use in acute wounds, flaps, and grafts is less well established.<sup>103</sup>
- **Extracorporeal shock-wave therapy**- Extracorporeal shock-wave therapy (ESWT) significantly improves chronic wound healing. Blood perfusion increased considerably after ESWT compared to the controls. Treatment with an ideal session of ESWT dramatically improved diabetic wound healing, which was associated with increased neo-angiogenesis, tissue regeneration, and topical anti-inflammatory response. Extracorporeal shock-wave therapy improved wound healing by enhancing topical blood flow and tissue regeneration.<sup>104</sup>
- **Electrical stimulation device**- Human investigations have indicated that electrical stimulation accelerates wound healing and increases cutaneous perfusion. Electrical stimulation is an adjuvant therapy that is underutilised in plastic surgery and may increase flap and graft survival, speed up postoperative recovery.

Several applications of electrical stimulation have been identified in medical literature to speed up wound healing and increase cutaneous perfusion. This is a straightforward procedure that could be used as an adjuvant therapy in plastic surgery.<sup>105</sup>

➤ **Wound healing patches:**

Transdermal patches are a long-used drug delivery system (DDS) for wound healing. The transdermal drug delivery method has numerous advantages over traditional methods of drug delivery, including a regulated rate of medicament release, avoidance of hepatic metabolism, simplicity of termination, and a prolonged duration of effect. Transdermal drug delivery system (TDDS) refers to topically delivered medications in the form of patches or semisolids (gels) that distribute pharmaceuticals for systemic effects at a predetermined and controlled rate. The process of drug transdermal permeation begins with stratum corneum sorption, followed by drug penetration through the viable epidermis, and lastly drug uptake in the dermal capillaries. Transdermal drug delivery systems are classified into four types: membrane permeation control, matrix diffusion control, adhesive dispersion control, and micro reservoir/micro sealed dissolution control. Transdermal route has gained popularity in drug delivery due to its flexibility and convenience when compared to other routes of administration, and it is one of the most acceptable, practical, safe, and cost-effective ways to deliver drugs. A drug is injected inside a patch that is worn on the skin for a considerable amount of time in a relatively large dose. The medicine reaches the bloodstream directly through the skin via diffusion. Because the medicament has a high level of concentration on the patch but a low concentration in the blood, it will continue to diffuse into the blood for an extended period of time, maintaining a constant drug concentration in the blood flow.<sup>106</sup>

### Conclusion

In conclusion, our exploration into the realms of wound healing and antiseptic activity has unveiled a rich tapestry of potential remedies and groundbreaking technologies. From the time-tested efficacy of herbs to the precision of active pharmaceutical ingredients, the integration of novel drug delivery systems and advanced technologies has ushered in a new era of healing possibilities. The inclusion of active pharmaceutical ingredients underscored the importance of scientific precision and targeted intervention in modern healthcare. The emergence of novel drug delivery systems has revolutionized the way we administer treatments, ensuring optimized efficacy and patient compliance. These systems offer tailored solutions, addressing the unique challenges posed by wound healing and antiseptic applications. Moreover, advanced technologies have played a pivotal role in augmenting traditional approaches. From smart dressings that monitor healing progress to nanotechnology-enabled treatments, the convergence of science and innovation has opened up new frontiers in the quest for efficient wound care solutions. It is evident that the amalgamation of herbs, active pharmaceutical ingredients, novel drug delivery systems, and advanced technologies holds immense promise for the future of healthcare. The journey to effective wound healing and robust antiseptic interventions is an ongoing exploration

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