Popular Medicinal Plants Used For the Healing Of Wound-Review

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Abstract- **The treatment of chronic wounds significantly affects global social and economic conditions. Chronic wound conditions made it impossible to regenerate the functioning epidermis, which delayed the predicted completion of the wound opening. Non-healing wounds are on the rise in the entire world. Delay in wound healing is associated with chronic inflammation, excessive expression of cytokines that cause inflammation, oxidative stress, and bacterial infection. The use of many traditional medicines in the treatment of cutaneous wounds has been investigated. Several phytochemicals, including alkaloids, tannins, phenolic acids, and flavonoids are known to have potential wound-healing characteristics. However, the cutting-edge nanotechnology platform may be able to enhance the delivery of drug based on plant therapeutics. Therefore, the goals of novel delivery strategies of the main biologically active from plant-based sources are to hasten the healing of wounds, prevent complications from wounds, and improve compliance among patients. Phenols and Terpenes are two examples of bioactive chemicals called plant secondary metabolic products that are abundant in natural extracts. These compounds' anti-inflammatory, antioxidant, and antibacterial activity properties may aid in the healing of wounds. The management of wounds effectively is a significant difficulty because wound healing is a challenging process. Due to the negative side effects of modern medicine and the lower cost of herbal products, natural herbal therapies have now become essential for the management of skin problems and the management of skin-related infections.**

The current study aims to provide an overview of the most recent research on medicinal herbs used in the healing of wounds. Through a variety of processes, involving cell proliferation, angiogenic effects, and collagen synthesis-stimulating, phytochemicals can act at various phases of the process. The efficiency of wound therapies may be significantly increased by the use of natural substances in nanotechnology systems. To expand the therapeutic usage of these medicines, safety evaluation in research studies would be necessary..

Materials and methods

Multiple databases, including Web of Science, Science Direct, Scopus, Google Scholar, and PubMed, were searched.

Result

Hemostasis, inflammation, proliferation, and remodeling are the four phases that make up the four stages of the wound healing process. Wound healing frequently involves the use of medicinal herbs. The results showed that medicinal plants had their ability to heal wounds in this area assessed.

Conclusion

Finally, medicinal plants and their chemicals offer medicinal proof for the creation of novel medications in the discipline of wound healing.

Keywords: **Medicinal plants, herbs, wound healing, secondary metabolites, wound dressings, drugs**

1. INTRODUCTION

To protect the body from the outside environment, the skin is essential. Wounds are defined as harm to the skin's structural integrity brought on by burns, scalds, incisions, and human lesions like pressure sores, diabetic foot, venous ulcers, etc [1]. In both the prevention and therapy of infections caused by microbes and wounds, phytochemicals have shown a great deal of promise. Wounds are linked to high morbidity, which greatly raises the expense of medical care while also representing a growing health and financial burden [2]. Phytochemicals that are antioxidant and wound-healing promote blood clotting, and anti-microbial, quicken wound healing, and combat infection. Polyphenol-rich medicinal plants are said to have amazing wound-healing properties. Because they are astringent, phenolics aid in wound healing. Microbial infections would also impede the healing process, eventually resulting in chronic wound infection and repetition problems [3]. Infants and the elderly, who represent the two opposing extremities of the age spectrum, are particularly susceptible to traumatic wounds [4].

A wound is defined as the actual splitting of working tissues. On the other hand, healing entails four different phases that start soon after an injury. These phases overlap and last for a long time. Hemostasis, inflammation, proliferation, and tissue remodeling are the four sequential and coordinated phases of the complicated biochemical and cellular process of wound healing. When physical tissue is damaged, repair is required. The success of the repair depends on the extent of the damage, the ability of the tissue to regenerate, the amount of necrotic tissue, and the presence of foreign bodies [5]. The recovery process is not linear; depending on both intrinsic and extrinsic elements, such as cytokines and growth hormones, among others, it may advance through phase reverses or ahead. From a macroscopic standpoint, wound healing is influenced by several factors, including patient age, wound size, depth, location, and the presence of local or systemic illness [6]. Figure 1 shows the relationship between phytochemical components and wound healing.

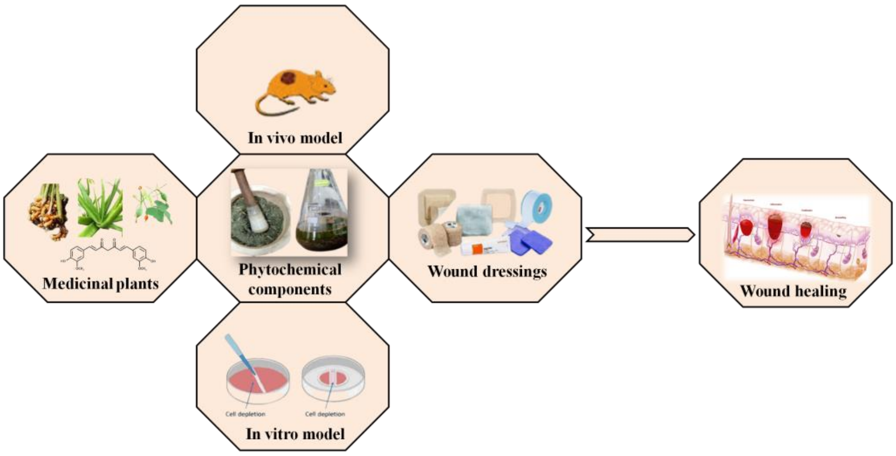

Figure.1 the relation between phytochemical components and wound healing

Wounds can lessen the physiological function of the human skin, which acts as a physical shield against stimuli from the outside. Wounds are viewed in the medical sciences as a serious issue requiring immediate attention. The countries have employed plant medicine for several uses over the years, including treating wounds [7]. According to the seriousness of the wound and the absence of infections that can delay healing, a healthy person's wound can heal in a few days. In contrast to chronic wounds, where the healing process is disrupted, acute wounds are typically treated throughout the healing process. This ineffectiveness results in prolonged healing duration and chronic inflammation brought on by increased neutrophil infiltration [8].

Hemostasis, inflammation, proliferation, and tissue remodeling are the four sequential and coordinated phases of the complicated biochemical and cellular process of wound healing. When a physical tissue disruption occurs, repair is required. The success of the repair depends on the severity of the injury, the capacity of the tissue to regenerate, the presence of necrotic tissue, and the presence of a foreign body infection [9]. The physiological and molecular processes involved in the physiology of wound healing help wounded tissues regain their normal structure and functioning. This process comprises numerous stages, including inflammation, which involves tissue equilibrium and inflammation, followed by proliferation, where the key steps involve angiogenesis and the creation of an extracellular matrix with the help of various cellular mediators. The wound finally closed, and during the remodeling phase, the healthy tissue was restored [10].

Therefore, the ideal wound dressing should include characteristics of flexibility, permeability, moisture retention, and water absorption to establish a microenvironment favorable to wound repair. This dressing will operate as a temporary barrier to the wound. The ability of the dressing to promote cell migration, proliferation, and differentiation as well as antibacterial characteristics, biocompatibility, and these other biological functions are what matter most for improving wound healing [11].

To cover and heal the wound, various biomedical textile materials made using various manufacturing processes are used. The fundamental qualities of a perfect wound dressing should be biocompatibility, non-toxicity, protection against infection, absorbency, permeability, and rapid drug administration. The majority of wound dressings are built using textiles, such as fibres, yarns, nonwoven, woven, crochet, knitted, and braided fabrics, composites, and electrospun nanofibrous materials. There are also uses for foams, films, hydrogels, matrices, and hydrocolloids. Since the beginning of time, dressings for wounds have undergone constant development. In addition to absorbing exudate and holding onto moisture, wound dressings might decrease microbial infection and supply healing chemicals to the wound environment. Wound dressings come in a wide variety of diverse forms, such as foams, alginates, hydrogels, films,hydro-fibers, tissue-engineered skin, and hydrocolloids amongst others [12].

One of the core tenets of conventional medicine is the use of natural medicine and principles for healing. Some of them have successfully achieved clinical utility after attaining relevance in various phases of research for inflammation, cancer, and other chronic diseases, even though the bulk of them are not in the mainstream due to a lack of proof. Although the medical benefits that conventional wet and dry dressings are widely recognized, their efficacy in promoting wound healing, preventing infections, and creating physical barriers is limited. Additionally, adhesion to these dressings may cause additional tissue damage during deletion. To hasten wound healing, prevent wound complications, and improve patient compliance, multiple therapeutic techniques are therefore used concurrently in the therapy of chronic wounds. Utilizing phytochemicals with nanoscale or encasing active ingredients in a nanostructure are two of these tactics. As nanocarriers have a large surface area /volume ratio and alter physiochemical properties, this is one of the most promising strategies to increase the wound healing effectiveness of natural compounds [13].

The purpose of this review is to explain the significance of medicinal plants used for wound healing and to examine the published studies in this area. In this study, we aim to gather information about phytochemicals utilized in wound healing and explore their mode of action. Additionally, this review aims to give a general overview of the skin, the healing process, and some details on the most recent treatments for wound healing.

The role of different traditional medicines has been explored for use in the healing of cutaneous wounds, where several phytochemicals, such as flavonoids, alkaloids, phenolic acids, and tannins are known to provide potential wound-healing properties. However, the delivery of plant-based therapeutics could be improved by the novel platform of nanotechnology.

Numerous studies on the therapeutic effects of medicinal plants and their herbal preparations are currently being conducted. It has been demonstrated in vivo and in vitro investigations, as well as excisional and incisional experimental models, that specific plants speed up the renewal of damaged tissues. In the ethnobotanical literature, therapeutic substances derived from medicinal plants were extensively studied. By bolstering the immune system, these natural compounds act as a barrier to wound infection and promote tissue regeneration. Therefore, it is important to focus on wound healing mechanisms and new developments in novel natural product delivery systems, which indicate their potential as efficient and safe methods of treatment for chronic wound healing conditions.

REVIEW OF LITERATURE

It is pertinent to concentrate on research journals not yet covered in prior review articles to offer a unique contribution to the discipline in this piece. To achieve this, specific plants, chemicals, and effects on wound healing investigated in the last five years have been emphasized and covered in great detail. Therefore, this review summarizes the most recent data on the potential advantages of utilizing natural medicines as well as the root causes.

Methodology

In this review, the therapeutic abilities of phytochemicals are also covered. First, a few fundamental facts regarding wounds and the anatomy of the skin are given. The process of wound healing and its various stages are then briefly discussed. This article provides a broad summary of current developments in conventional treatments for skin wound healing with a special emphasis on the medicinal activity, mechanism of action, and clinical studies of the most frequently used substances that are natural. Figure 2 represents the flow of the review study.

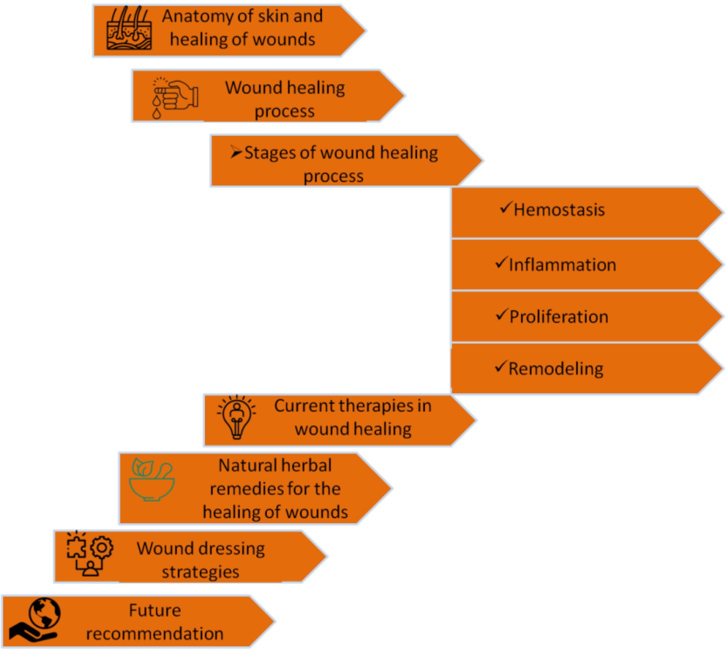

Figure.2 flow of the review study

2. ANATOMY OF SKIN AND HEALING OF WOUNDS

The epidermis, dermis, and hypodermis are the three layers that make up the skin, with more sub-layers present [14]. Figure 3 represents the factors affecting wound healing shown below,

Figure.3 the factors affecting the wound healing

A biological and physical barrier, the epidermis is made up of keratinocytes (95%) and other cells that are primarily descended from Keratinocytes [15].

3.1 Wound healing process

The hemostasis phase, the inflammatory phase, the proliferation phase, and the remodeling phase are each of the four overlapped phases of the wound healing process. The three concurrent stages, namely hemostasis/inflammation, proliferation, and remodeling/maturation, characterize normal wound healing. A variety of different variables and mediators control these stages. Hemostasis is initiated in the first step by the restriction of blood vessels to stop blood loss. To create a fibrin network or clot, platelets assemble. Numerous cell types, including monocytes, fibroblasts, neutrophils, and keratinocytes migrate to the site of the wound. The four chronological phases of the wound healing procedure, that are known, are highly interconnected [16].

3.2 Stages of the wound healing process

A carefully organized series of processes that are eventually intended to restore the barrier role and structural quality of the skin define wound healing. The four influenced-by-time stages of the healing process—coagulation and hemostasis, inflammation, proliferation, and wound remodeling—are triggered by damage to tissues.

a. Hemostasis

Coagulation and hemostasis occur right away after damage (Figure A) to stop bleeding. Vasoconstriction, the creation of a platelet plug, and platelet degranulation are all components of hemostasis. Platelets emit pro-inflammatory substances during the first two to three days following injury, which promotes the growth and expansion of inflammatory cells. To protect the blood vessel and create a matrix that enables the penetration of cells required in the later stages of healing, these processes necessitate numerous interconnected steps. Extrinsic and intrinsic routes stimulate the coagulation cascade, causing the accumulation of platelets and clot formation [17]. Figure 4 represents the stages of wound healing.

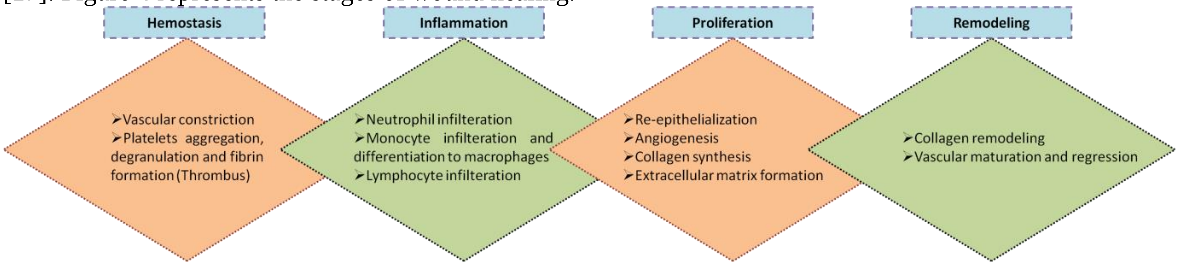

Figure.4 the stages of wound healing

Hemostasis involves three processes that happen quickly one after another. Blood vessels contract as a first response to stop bleeding, causing vascular spasms. In the second stage, platelets cling to one another to create a temporary seal over the ruptured blood vessel wall within seconds of the blood vessel's epithelial wall being damaged. Platelets are encouraged to attach to the damaged site by exposed collagen [18].

b. Inflammatory Phase

The early inflammatory phase and the late inflammatory phase are the two distinct steps that make up this stage. Neutrophils, whose primary job is to ward against infection, infiltrate the wound site as a result of molecular reactions that are triggered by the initial inflammatory phase. Within a period of 24 to 36 hours of damage, several chemoattractive chemicals start to draw neutrophils to the wound site [19]. By producing proteolytic enzymes and oxygen-derived free radical species after they have reached the wound surroundings, neutrophils eliminate germs, foreign particles, and injured tissue. Once the assignment is finished, the neutrophils are removed from the wound. Before moving on to the next stage of healing, macrophages enter the site during the late inflammatory phase and continue the phagocytosis process [20].

c. Proliferative Phase

This stage, which starts on the 3rd day after wounding and endures for about two weeks, includes the main healing mechanisms. Transforming growth factors (TGF-) and platelet-derived growth factors (PDGF), which are discharged by inflammatory cells and platelets, are elements that bring in fibroblasts and myofibroblasts to the area immediately following an injury for the first three days [21]. Once inside the wound, fibroblasts multiply rapidly and move on to deposit the freshly made extracellular matrix by creating matrix proteins such as hyaluronan, fibronectin, proteoglycans, and type 1 and type 3 procollagen. A critical process is the creation of collagen. Collagen plays a crucial role in every stage of wound healing because it helps maintain strength [22].

d. Remodeling Phase

Scar tissue production happens during wound remodeling and is finished in about twelve months or longer. Capillary development slows, apoptosis reduces the abundance of fibroblasts and macrophages, and blood flow and metabolic activity fall as the lesion heals. A completely developed scar with fewer cells and blood vessels and great tensile strength is the result [23]. Whereas simple traumas account for the majority of wounds, systemic and local factors may change and slow down the delicately balanced repair process. As a result, wounds may develop that do not heal in a timely and ordered fashion and eventually become chronic, non-healing wounds [24].

3.3 Current therapies in wound healing

The difficulties in managing refractory wounds are frequently linked to microbial contamination and infections. For rapid wound healing, these must be eliminated. The usage of nanoparticle-based anti-microbial treatments has increased as a result of the emergence of multi-drug-resistant diseases [25].

Although wound care is a difficult problem, there are several well-researched, highly effective methods. Several different types of wound dressing are currently being used as functional therapy for managing wounds. The infections caused by microorganisms cause the wound-healing process to be delayed, which results in non-healing wounds that demand extended hospitalization and significant medical costs [26].

3. NATURAL HERBAL REMEDIES FOR THE HEALING OF WOUNDS

Since the beginning, traditional medicine has used herbal remedies to quicken the healing of wounds. Due to their enormous potential to influence wound healing, several plants and different versions of them have historically been employed concerning wound care [27]. Through several processes, plant-based extractions as well as isolates assist tissue regeneration, which frequently combine to enhance the entire healing process. Nowadays, the effectiveness of a variety of these particular herbs and their ways of action are extensively documented. A new source of alternative pharmaceutical compounds for handling numerous diseases, including wound healing, is therefore natural products and their pure components. The care of wounds through substantial research has been conducted in the last few years [28]. The following table 1 indicates the list of medicinal plants and their properties along with the mechanism action used for wound healing.

- **Table 1. indicates the list of medicinal plants and their properties along with the mechanism action used for the wound healing**

Plant	Main bioactive components	ABP	AI	RP	AO	AV	Mechanism of Action	Ref
Salvia officinalis	Terpenes, Sesquiterpenes	○	+	○	○	-	1. 1. Reduces pro-inflammatory cytokines. 2. 2. Downregulates mRNA expression levels of IL-6, IL-1 β, and TNF-α augment fibroblast proliferation via enhancing cyclin-D1 expression.	[29-31]
Achillea millefolium	Flavonoids	✓	+	✓	-	-	1. 1. Reduces inflammatory mediators NO and PGE_2. 2. 2. modulates the inflammatory cytokine and growth factor. 3. 3. Stimulates keratinocyte differentiation and motility. 4. Stimulates collagen expression.	[32-35]
Bletilla striata	Flavonoids, Polysaccharides, Triterpenoids, Stilbenoids	✓	✓	✓	✓	✓	1. 1. Increases the NO and promotes, 2. 2. Promotes epithelial cell growth and fibroblast proliferation. 3. 3. Promotes the expression of mediators of the inflammatory response. 4. 4. Promotes the expression of mediators of the neutrophils, monocytes, and macrophages chemotaxis.	[36-39]
Aloe vera	Flavonoids, Polysaccharides	✓	+	+	-	-	1. 1. Modulates signaling proteins phosphorylation. 2 2. Moderately stimulates keratinocyte migration. 3 3. Strongly promotes fibroblast proliferation. 4 4. Modulates the inflammatory response.	[40-41]
Calendula officinalis	Triterpenoids, Flavonoids, Coumarins, Quinones	-	✓	+	-	-	1. 1. Increases keratinocytes and fibroblast proliferation. 2. 2. Promotes expression of mediators of the inflammatory response. 3. 3. Stimulates collagen production and angiogenesis. 4. 4. Promotes expression of mediators of the inflammatory response. 5. 5. Reduced glutathione levels. 6. Inhibits lipoxygenase activity.	[42-43]
Curcuma longa	Curcuminoids	-	✓	✓	✓	-	1. 1. Enhances fibroblast migration. 2. 2. Enhance the granulation tissue formation.	[44-46]

							3. 3. Enhance the collagen deposition. 4. Regulates many genes implicated in the initiation of inflammatory responses (NF-(κ) B, AKT, PI3K, IKK). 5. 4. Increases TGF-β production. 6. 5. Increases fibroblast Proliferation.	
Crocus sativus	Carotenoids, Monoterpenoids , Flavonoids, Phenolic acids	-	✓	✓	✓	-	1. 1. Increases fibroblast proliferation. 2. 2. Increases the level of anti-inflammatory cytokines (IL-4 and IL-10). 3. 3. Reduces the level of pro-inflammatory cytokines (TNF-α and IL-6). 4. 4. Enhances vascularization. 5. 5. Inhibits lipid peroxidation.	[47-48]
Casearia sylvestris	Triterpenoids, Phenolic acid	✓	-	-	-	-	1. 1. Reduces myeloperoxidase activity. 2. 2. Reduces early and late edema.	[49-50]
Malva sylvestris	Polysaccharides, Flavonoids	✓	✓	+	✓	-	1. 1. Increases the wound healing rate. 2. 2. Increases collagen deposition. 3. 3. Enhances vascularization. 4. 4. Modulates the inflammatory response.	[51-52]
Glycyrrhiaglabra	Flavonoids, Terpenoids	✓	✓	✓	✓	-	1. 1. Reduces superoxide anion. 2. 2. Increases the wound healing rate. 3. 3. Increases fibroblast proliferation. 4. 4. Inhibits NO production. 5. 5. Increases collagen deposition.	[53-54]
Plantago L.	Monoterpenoids	✓	+	✓	✓	-	1. 1. Reduces pro-inflammatory cytokine level (PGE2, TNF-α). 2. 2. Reduces superoxide anion. 3. 3. Inhibits NO production. 4. 4. Decreases fibroblast's hydrogen peroxide cytotoxicity.	[57-58]
Rosmarinus officinalis	Flavonoids	✓	✓	✓	✓	-	1. 1. Reduces inflammatory cytokines expression (IL-1β, IL-6, TNF-α). 2. 2. Reduces the expression of iNOS, COX-2, P-IκB, and NF-κB/p65. 3. 3. Inhibits NO production.	[57-58]
Reynoutria japonica	Polyphenols, Tannins	✓	✓	✓	✓	✓	1. 1. Increased synthesis of collagen III.	[59-62]

							2. 2. Strongly stimulated fibroblast proliferation and migration.	
Datura innoxia	Alkaloids, phenols, carbohydrates, flavonoids, saponins, Terpenoids	✓	✓	✓	✓	✓	1. It significantly inhibited the markers of inflammation. **1.** 2. Potent in vivo anti-inflammatory, antinociceptive, and antidepressant effects.	[63-65]

In the table ABP- has antimicrobial properties, AI- has anti-inflammatory properties, RP- re epithelization properties, AO- has antioxidant properties and AV is anti-virulent, TNF- Tumor necrosis factor alpha, IKK-IkappaB Kinase, Akt-Protein Kinase B, PI3K-Phosphoinositide 3-kinase, PIB-Phosphorylated Inhibitor kappa B, IL-Interleukin, PGE 2- Prostaglandin E, COX-2-Cyclooxygenase-2, iNOS-Inducible Nitric Oxide Synthase, NO-Nitric Oxide, NF-B- Nuclear Factor Kappa B.

4.1 **wound dressing strategies**

Anti-microbial agents, absorbents, occlusive dressings, adhesion materials, and graded debridement dressings are some of the wound dressing techniques used today. According to clinical outcomes, dressing material can be physically manufactured from a variety of materials, including synthetic, herbal, and animal sources. In the past, bandages made of cotton, natural, or synthetic fibers have been used to dress wounds. The gauze dressing that follows has a little formulation difference from the bandage dressing. However, none of the aforementioned methods succeed in keeping the wound moist, and they make the removal process more painful. To keep the damaged skin region moisturized, speed up the healing process, and prevent microbial infection, bandage dressings now often contain both moisturizers and medicinal medicines like antibiotics.

Conclusion

The severity of wounds has a detrimental effect on individual standards of life all over the world. The relationship between the components of the extracellular matrix, the right cell types, and cell surface receptors with the therapeutic substances determines how effectively wounds are treated. The intricate composition of skin tissue makes it difficult to produce a medicine that can promote a quick and efficient healing process. We have acquired a greater understanding of the impact of herbal medicines on wound healing and the underlying molecular mechanisms thanks to scientific research amassed over the previous five years. All of the plants included in this review have antioxidant, anti-inflammatory, and antibacterial effects. By recent studies, the main cause of herbal medicines' ability to speed up wound healing.

In wound dressings, carotenoids, flavonoids, and triterpenoids encourage antioxidant activity and reduce oxidative stress. Reactive oxygen species (ROS) are involved in the healing process, the recruitment of lymphoid cells, angiogenesis, and the eradication of pathogens at the wound site by functioning as secondary messengers to immunocytes and non-lymphoid cells. Increased ROS have been found in vivo and have been linked to sluggish wound healing. In addition to encouraging the release of pro-inflammatory cytokines and activating matrix metalloproteases, high keratinocytes, and dermal fibroblasts can suffer deleterious consequences from ROS-induced modification and/or degradation of extracellular matrix proteins.

The association of various extracts with unique phytoconstituents has attracted growing interest. Establishing appropriate doses and administration methods are important considerations in using phytochemicals in wound healing. Research should be carried out to determine the best phytochemical composition, plant origin, and delivery method.

Natural medicines prepared from herbal plants provide protection in wound healing; incorporating the use of herbal agents for healing with contemporary products and practices to develop new wound care therapies is an ongoing method of wound care. Based on these findings, it is recommended that various methods of therapy be employed concurrently in the care of wounds, particularly chronic wounds, to hasten the healing process and prevent wound complications. In addition, there are many issues in improving the effectiveness and use of natural products in wound care, and efforts should be made to address them. To prove the products' safety, Multidisciplinary efforts are needed to demonstrate the safety of products, monitor their adverse effects, and conduct double-blind controlled clinical trials. Good manufacturing practices and regulatory norms are equally important to increase the use of medicinal plants by physicians and encourage their incorporation into national health systems. In this review, we focused on several related ingredients and medicinal plants commonly used for wound healing.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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