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COMMON INDIAN MEDICINAL PLANTS AS EMERGING WOUND HEALING AGENTS: DEEP INSIGHTS INTO APPLICATIONS AND MECHANISMS

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ABSTRACT: Any bodily harm, such as damage to the skin's epidermis and disruption of its normal architecture and function, is referred to as a wound. The significance of wound healing has been known since ancient times. Several attempts have been made to design innovative wound dressings composed of the finest materials for speedy and successful wound healing. Medicinal herbs greatly aid the wound healing process. Many researchers have concentrated in recent decades on creating innovative wound dressings that combine medicinal plant extracts or their purified active components, which might be utilized instead of standard wound dressings. Several researchers have looked at the mechanisms of action of different herbal medicines in the wound healing process. This work aims to emphasize and examine the mechanical viewpoint of wound healing mediated by natural compounds. Some herbal medications stimulate re-epithelialization, angiogenesis, granulation tissue development, and collagen fiber deposition by increasing the production of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF-α). Other wound dressings containing herbal medicines decrease the production of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and inducible nitric oxide synthase (iNOS), resulting in anti-oxidant and antiinflammatory characteristics at different stages of the wound healing process. Aside from the growing public interest in traditional and alternative medicine, using herbal medicine and natural products for wound healing has a number of advantages over using conventional medicines, including greater effectiveness due to multiple mechanisms of action, anti-bacterial activity, and long-term wound dressing safety.

INTRODUCTION: It is a worldwide problem to design and produce an adequate wound dressing for treating acute and chronic wounds.

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Because wound healing is such a complicated process, an ideal wound dressing should have the following qualities: retaining moisture around the wound, allowing gaseous transmission, biocompatibility, biodegradability, non-toxicity, stimulation of growth factors, ease of changing and removing wound dressings, ability to transfer bioactive compounds to wound sites and wound protection from infections and microbial growth. Infection is one of the most common causes of

wound complications, and it arises as a result of the suitable environment for microorganism development. The emergence of multidrug-resistant diseases adds to the difficulty of developing sophisticated wound dressings that have both anti-bacterial and wound-healing characteristics. Anti-microbial activity of natural chemicals and medicinal plant extracts against common bacteria present in wounds, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* has been studied in many researches. Anti-bacterial and antifungal bioactive chemicals in medicinal plants may help heal wounds quicker and more effectively. As a result, in recent years, the mechanism of herbal medications and purely natural products in wound healing has gotten much attention. Some herbal remedies seem to have diverse modes of action and demonstrate therapeutic qualities at different phases of the wound healing process [1].

Many herbal extracts exhibit strong anti-oxidant capabilities, according to the results of different *in-vitro* and *in-vivo* tests. Anti-oxidants may help wounds heal faster and protect tissues from oxidative stress. Anti-oxidant action is found in flavonoids, anthraquinons, and naphthoquinones. Shikonin, alkanin, lawsone, emodin, epigallocatechin-3-gallate, ellagic acid and some herbal extracts have potent anti-oxidant activity, scavenging reactive oxygen species (ROS), inhibiting lipid peroxidation and increasing intracellular anti-oxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px).

Angiogenesis, fibroblast cell proliferation, and the creation of provisional extracellular matrix are all aided by herbal medication (ECM). Herbal extracts and natural products have immunomodulatory and anti-inflammatory properties that help wounds heal faster. By reducing the production of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and inducible nitric oxide synthase, for example, α-mangostin possesses anti-inflammatory properties (iNOS). Nuclear factor-κB (NF-κB) translocation is inhibited by both curcumin and α-mangostin. Curcumin also serves as a ROS scavenger in the inflammatory phase, enhances granulation tissue production and collagen deposition in the proliferation phase, and boosts TGF-α level in the re-modelling phase [2]. One of the main mechanisms involved in wound healing is the extracellular signal-regulated kinase (ERK)/AMP-activated protein kinase (AMPK) signalling pathway, which emodin activates by raising phosphorylation of ERK1/2 and AMPK. Thymol and carvacrol stimulate re-epithelialization, angiogenesis, granulation tissue development, and collagen fibre deposition in the proliferation phase by increasing the production of vascular endothelial growth factor (VEGF) and TGF-α. Carvacrol, on the other hand, efficiently inhibits COX-2, while thymol mostly inhibits COX-1. For example, gauze and cotton wool dressings did not play an active part in the wound healing process. Novel wound dressings that stimulate biological activity by releasing bioactive substances included in the dressing have recently been created. Many researchers have also studied the in-vitro and in-vivo wound healing effects of wound dressings containing herbal extracts or natural products. This article focuses on medicinal plants' wound-healing qualities and the mechanism of action of certain purified active natural compounds in the wound-healing process [3].

1. Understanding Wound:

1.1. Skin Histology: Skin is the biggest organ in the body, accounting for 8-20 percent of total body mass. It is divided into three layers: the epidermis (superficial layer), dermis (deep layer), and hypodermis (deepest layer), as well as sub-layers. According to compelling data, various layers of the skin play a significant part in the wound healing process.

Keratinocytes make up around 95 percent of the epidermis, and all proliferating keratinocytes originate in the basal layer. These keratinocytes in the basal layer are mostly responsible for the epidermal response in wound healing. This is the epidermis' lowest layer, including basal cells that divide constantly. Old cells are pushed to the skin's surface, where they finally shed. Collagen fibres are typically used as connective tissue in the dermis layer. Type-I and type-III collagens are the most frequent fibres that give tenacity, but type IV collagen envelops Schwann cells and vascular endothelium at the dermo-epidermal interface. Furthermore, the dermis layer includes elastic fibres that play an important role in facilitating skin recoil. The hypodermis is a layer of fat and connective tissue underneath the epidermis [4].

1.2. Wound: Any injury to the body, often damage to the skin's epidermis (e.g., cut, blow, or other impacts), that disrupts its normal architecture and function is referred to as a wound. Wounds are classified as open or closed and acute or chronic, depending on the underlying cause of wound development and wound healing physiology. Acute wounds, which are divided into surgical (incisions, excisions and surgically debrided wounds) and accidental (burn wounds, chemical, electrical and thermal traumas) categories, go through normal inflammation, tissue growth, and re-modelling processes. All of these steps take place in a timely way. Chronic wounds require a long time to heal because the healing phases do not advance normally, and there is a local infection. Chronic wounds are caused by a variety of conditions, including diabetes, autoimmune illnesses, hypoxia, trauma, and insufficient wound care in the early stages. Impaired wound healing is a frequent and important problem in diabetic patients since it may develop into foot, venous, and pressure ulcers. As a result, a diabetic wound has a higher chance of serious consequences, including infection and amputation. Infection, poor glucose metabolism, and the risk of neurovascular problems are all factors that impede wound healing in diabetes individuals. Chronic wounds get infected because they are often exposed to germs due to delayed wound healing. The proliferation of common bacteria such as *S. aureus*, *P. aeruginosa*, and *Enterococcus faecalis*, as well as common fungus such as *Candida albicans*, *Candida parapsilosis*, *Malasezzia restricta*, and *Curvularia lunata*, is the major cause of chronic wound infections [5].

1.3. Physiological Process of Wound Healing: Based on the conventional classification, wound healing is divided into four stages: hemostasis, inflammation, proliferation, and maturation or remodeling [6].

1.3.1. Hemostasis Phase: Hemostasis, the earliest stage of wound healing, starts within minutes following an injury and lasts for 1 hrs to 3 hrs. Vasoconstriction is the initial phase in the hemostasis process, which decreases blood flow and causes platelets to clump together and form platelet plugs. Consequently, during the coagulation cascade, a fibrin mesh forms around the platelet plugs, assisting in creating a stable clot. Platelets also start secreting cytokines and growth factors, which aid in the healing of wounds.

1.3.2. Inflammation Phase: Inflammation happens shortly after a blood vessel is injured, and it is the second step of the wound healing process. As a consequence, their contents leak, and the area swells. The inflammatory stage lasts between 24 hrs and 48 hrs and may last up to a week. Controlling bleeding, preventing bacterial infection, and removing cell debris from the wound are all important aspects of this stage. The most significant cells in the phagocytosis process are phagocytic cells such as neutrophils and macrophages. It starts with neutrophils entering the wound site and continues as monocytes from the circulation are drawn in and differentiate into macrophages. Through phagocytosis, this stage removes germs and injured tissues and produces a slew of growth hormones that promote fibroplasia and angiogenesis. As a result, this step lays the groundwork for creating the provisional extracellular matrix (ECM).

1.3.3. Proliferation phase: The proliferation phase starts on the 2-day after damage and may extend up to 20-days in acute wounds, depending on the wound size. This phase is characterized by tissue granulation and the development of new blood vessels from pre-existing vessels (angiogenesis).

The presence and multiplication of fibroblasts, keratinocytes, endothelial cells, and thin-walled capillaries are all histological evidence of the formation of granulation tissue. In granulation tissue, fibroblasts are responsible for forming and altering the extracellular matrix (ECM). ECM produces a network of type-III collagen, which is a weaker version of the structural protein, quickly at first. Transforming growth factor (TGF) is produced by both fibroblasts and keratinocytes, which causes granulation tissue development and myofibroblast differentiation. Myofibroblasts and grasping the wound's margins control the contractile mechanism in wound closure.

1.3.4. Remodeling phase: Epithelialization is the last phase in the proliferative process, forming a cellular barrier over the granulation tissue. When the wound is appropriately moisturized and hydrated within 48 hrs after damage, epithelialization happens more rapidly. The

maturation stage, also known as the re-modelling stage, is the last stage of wound healing, lasting anywhere from 21-days to a year following the injury. In this procedure, wound closure and scar formation were achieved by replacing collagen type-III with collagen type-I.

2. Wound Healing Activity of Some Medicinal Plants and Their Application:

2.1. *Alkanna tinctoria, Arnebia Euchroma* and *Lithospermum erythrorhizon*: Shikonin and its stereoisomer, alkanin, are water-insoluble pigments and naturally occurring isohexenylnaphthazarins that may be found in abundance in the roots of Boraginaceae plants such as *Alkanna tinctoria* (Alkanet, Alkanna), *Arnebia euchroma* and *Lithospermum erythrorhizon* (Lithospermum) [7].

2.1.1. Mechanisms of Wound Healing:

2.1.1.1. Anti-bacterial Mechanisms: Shikonin is anti-bacterial and anti-inflammatory, and it can help with wound healing. In general, Shikonin and its stereoisomer alkanin have anti-bacterial action against Gram-positive bacteria like *S. aureus*, *E. faecium*, and *B. subtilis*, with MIC values ranging from 0.30 μg/mL to 6.25 μg/mL. At a concentration of 200 μM, Shikonin prevented the production of biofilms by *P. aeruginosa* and *S. maltophilia*. With MIC values of 6.25 μg/mL, 50 μg/mL, and 25 μg/mL, shikonin and alkanin showed anti-bacterial activity against MRSA, vancomycin-resistant *Enterococcus faecium*, and vancomycin-resistant *Enterococcus faecalis*, respectively.

Shikonin's anti-bacterial mechanism against MRSA was examined by researchers. Shikonin's MICs against seven MRSA strains ranged from 7.8 μg/mL to 31.2 μg/mL, while ampicillin and oxacillin showed significantly lower anti-bacterial activity, with MICs of 31.2 μg/mL to 250 μg/mL and >250 μg/mL, respectively. Shikonin's anti-bacterial activity has been linked to its direct binding effect on peptidoglycans, cytoplasmic membrane permeability, and ATPase activity suppression [8].

2.1.1.2. Anti-oxidant mechanisms: The anti-oxidant properties of shikonin and its derivatives, as well as the structure-activity connection, have been studied in a number of researches. The radical scavenging activity of alkannin and shikonin against the DPPH radical was strong, with EC_{50} values of 19 ppm and 17 ppm, respectively. The naphthoquinone moiety seems to be required for anti-oxidant action, with the side chains of alkannin and shikonin perhaps playing a small role.

Esterification of the side chain hydroxyl group did not affect the radical scavenging activities of alkannin and shikonin. Shikonin may also react directly with free radicals, with IC_{50} values of 27 μM and 17 μM, respectively, being more reactive than ascorbic acid or α-tocopherol. Furthermore, shikonin had a remarkable anti-lipid peroxidative activity in microsomal lipid peroxidation, with an IC_{50} value of 9 μM, while tocopherol only inhibited 11 percent at 50 μM [9].

2.1.2. Effect on different stages of wound healing: Shikonin and alkanin's capacity to scavenge reactive oxygen species (ROS) might be a significant mechanism for lowering oxidative stress and inflammatory processes. Shikonin, for example, is a known superoxide anion radical scavenger that forms semiquinone radicals in the presence of superoxide anion radicals through a reduction reaction. In terms of superoxide anion radical scavenging activity, there was no difference between shikonin and its isomer alkannin. Furthermore, the production of the shikonin semiquinone radical may be responsible for shikonin's anti-tumor and anti-bacterial activities.

Shikonin and alkanin promote wound neovascularization and speed up the wound-healing proliferation phase. The effects of shikonin and alkannin on granulation tissue growth were studied *in vivo*. The proliferation of granulation tissue is aided by the multiplication of fibroblasts, macrophages, and angiogenesis. Many leukocytes, including monocytes, neutrophils, macrophages, and granulocytes, have CD11b+ on their surfaces. Cell adhesion, migration, chemotaxis, and phagocytosis are just a few biological functions it plays in innate immune cells. According to the results, higher expression of CD11b+ cells in the granulation tissue increased the number of macrophages, monocytes, and granulocytes in the granulation tissue. Despite this, there was no evidence of shikonin or alkannin inducing CD3+ cells in the granulation tissue. Shakonin and alkanin hastened the growth in subcutaneous tissue

thickness and, as a result, the proliferation of granulation tissue, according to histopathological data. The subcutaneous skin tissue included infiltrating cells such as macrophages, lymphocytes, and histiocytes, as well as new blood vessels. In the granulation tissue, fibroblasts and collagen fibre growth were also seen. The effects of shikonin in human gingival fibroblasts were studied, and it was shown that activation of the ERK-1/2 signalling pathway boosted the production of VEGF and fibronectin, promoting proliferation, migration, and type I collagen formation. The effects of shikonin analogues on wound healing have been studied extensively.

Arnebin-1 (β,β-dimethylacryl shikonin) isolated from *Arnebia* species was used topically to increase cell proliferation, motility, angiogenesis, and wound re-epithelialization. Arnebin-1 likewise boosted TGF-1 expression at both the translational and transcriptional levels. Arnebin-1's pro-angiogenic activities on human umbilical vein endothelial cells and its favourable benefits on diabetic wound healing were also investigated. Arnebin-1 increased the expression of eNOS, VEGF, and HIF-1β (hypoxia-inducible factor 1-β), as well as CD31 expression, according to the findings.

The PI3K-dependent signalling pathway also aided in the healing of diabetic lesions. The benefits of alkanin, shikonin, and their analogues in wound healing have led to the creation of many FDA-approved pharmaceutical formulations, including Histoplastin Red®, Epouloderm®, and Helixderm®. The effectiveness of these pharmaceutical formulations was tested in several clinical studies. 72 individuals with leg ulcers caused by varicose veins on the lower half of their legs were treated with Histoplastin Red® ointment over three years in a clinical study. All of the patients had previously been treated with a range of commercially available conventional drugs.

The wounds were resistant to standard therapy due to toughening of the connective tissue surrounding the ulcers and insufficient blood circulation. During the first or second week of therapy, the ulcer's base was cleansed, and the necrotic tissue deteriorated simultaneously. Proliferous granulation tissue development and epithelialization were detected at the ulcer borders during the following two weeks. Following that, the ulcer started to clean up and soften. In most cases, 5-6 weeks of therapy resulted in full healing or a considerable decrease in ulcer size.

Furthermore, throughout therapy, there was no sign of skin irritation. The efficiency was set at 80 percent. In patients with partial-thickness burn injuries, the efficacy and safety of Helixderm® were assessed and compared to standard conservative therapy (Fucidin gauze and Betadine solution). Helixderm® recipients enjoyed quicker and more pleasant recovery and smoother and less brittle surface tissue, according to the results [10].

2.1.3. Methods of application: The inclusion of shikonin extracted from the *Lithospermum erythrorhizon* was carried out using electrospun poly(ε-caprolactone) (PCL)/poly(trimethylene carbonate) (PTMC) fibre mats. The fibre mats were shown to have anti-bacterial action against *Escherichia coli* and *Staphylococcus aureus*, two pathogens often seen on burn sites. Furthermore, *in-vitro* drug release experiments demonstrated that shikonin was quickly released initially, then plateaued after 11 hrs.

The wound healing efficiency of *Arnebia euchroma* cream (10 percent and 20 percent) in second-degree burn wounds was tested in a rat model. The 10 percent cream showed a better reaction to inflammation than the 20 percent cream, according to the data. Furthermore, wound closure and re-epithelialization rates in cream containing 20 percent extract were significantly lower than in cream containing 10 percent extract and silver sulfadiazine. A solution of *Alkanna tinctoria* extract (16 percent) in medicinal olive oil hastened partial thickness burn wound healing in rabbits in another *in vivo* investigation but had no significant impact on severe burns between the control and treatment groups.

In patients with second-degree burns, the impact of *Alkanna tinctoria* extracts combined with beeswax and olive oil as a wound dressing was examined. When compared to the control group (6.90 ± 1.77 days) with regular therapy, the treated group had earlier epithelization (3.00 ± 0.85 days) (the mixture of nitrofurazone and rifamycin) [11].

2.2. *Aloe barbadensis*: The Liliaceae family's Aloe vera (*Aloe barbadensis*) is one of the oldest therapeutic plants having wound healing activities for a number of skin problems, including burns, infections, and diabetic dermal wounds. Wounds are often treated using *A. barbadensis* leaves and gel. Vitamins (vitamin-A, vitamin-C, vitamin-E, and vitamin-B_{12}), enzymes (Bradykinase, which helps to reduce excessive inflammation), minerals, sugars, anthraquinones (aloin and emodin), lignin, saponins, phenolic compounds, hormones (auxins and gibberellins that aid wound healing), salicylic acid (anti-inflammatory and anti-bacterial properties), and amino acids are among the active components of *A. barbadensis* [12].

2.2.1. Mechanisms of Wound Healing:

3.2.1.1. Anti-bacterial Mechanisms: A. *barbadensis*'s antifungal and anti-bacterial activities have been proved in many researches. Scientists compared the anti-bacterial efficacy of *A. barbadensis* leaf extracts and gel to that of traditional antibiotics against Gram-positive (*S. aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*) and Gram-negative (*P. aeruginosa*) bacteria isolated from human skin wounds, burns, and acne (methicillin, bacitracin, vancomycin, novobiocin and erythromycin). Their results revealed that *A. barbadensis* had 100percent effectiveness against Gram-negative bacteria and 75.3 percent activity against all tested Gram-positive isolates, while vancomycin had 80.5 percent and 72.2 percent efficiency against Gram-positive and Gram-negative isolates, respectively. At a MIC of 400 μg/mL, *A. barbadensis* gel showed anti-bacterial efficacy against multidrug-resistant *P. aeruginosa* isolated from individuals with burn wound infections [13].

2.2.1.2. Anti-oxidant mechanisms: The anti-oxidant capacity of *A. barbadensis* leaf gel is rather high. Vitamin-A, vitamin-C, vitamin-E, phenolic compounds, ascorbate and anthraquinones are among the chemical ingredients of *A. barbadensis* that have a strong anti-oxidant effect. *A. barbadensis* is an effective and safe natural anti-oxidant that lowers lipid oxidation as a result of their combined impact. *A. barbadensis* gel inhibits iron oxidation by acting as a free radical scavenger. The anti-oxidant potential of *A. barbadensis* gel was evaluated in a variety of competent and deficient *Saccharomyces cerevisiae* strains. The findings showed that the gel protected all of the cultures tested, including mutant strains, against hydrogen peroxide (H_2O_2)-induced oxidative stress damage [14].

2.2.2. Effect on different stages of wound healing: Proliferation and migration of fibroblast cells are considerably increased by *A. barbadensis* gel. It promotes the production of ECM components such as fibronectin, proteoglycans, and collagen, resulting in an earlier proliferative phase and quicker wound healing. According to researchers, A. barbadensis gel was recently discovered to have diverse angiogenic and migratory effects on fibroblasts and endothelial cells.

According to the results, *A. barbadensis* stimulated fibroblast migration and had a larger proliferative impact on fibroblasts than on endothelial cells. *A. barbadensis*-treated fibroblasts expressed considerably more integrin-1 and CD31 genes than endothelial cells. Integrins are mediators for ECM binding and are involved in cell migration, angiogenesis, wound re-epithelialization, and re-modelling. Because of the increased lymphocyte numbers, topical use of *A. barbadensis* cream raises the ratio of CD4+/CD8+ lymphocytes in the wound region, which speeds wound healing. CD4+ lymphocytes drive keratinocytes to produce IL-1 in the wound region during the proliferation phase, and IL-1 then encourages endothelial cells to enhance angiogenesis, fibroblast cell proliferation, and ECM formation. The anti-inflammatory impact of *A. barbadensis* on wound healing has been studied extensively. The impact of *A. barbadensis* on leukocyte adhesion, TNF-α, and IL-6 levels was studied in a burn wound model.

When compared to the control group, the treated group showed a considerable reduction in leukocyte adhesion. Compared to the control group, pro-inflammatory cytokines such as TNF-α and IL-6 were significantly lower in the *A. barbadensis*-treated group. *A. barbadensis* also affect inflammatory responses in Raw 264.7 cells by downregulating MCP-1 (monocyte chemoattractant protein-1) chemokine expression in a dose-dependent manner. By activating growth factor-α (TGF-α), *A. barbadensis* speeds up wound healing.

TGF-expression was measured using RT-PCR in a rat incision wound model, and the findings showed a substantial increase in TGF-gene expression in the *A. barbadensis* gel-treated group as compared to the control group. Increased TGF-expression promotes epithelialization and angiogenesis, resulting in quicker granulation tissue development in wound beds treated with *A. barbadensis*. *A. barbadensis* enhances the production of bFGF (basic fibroblast growth factor) in fibroblast cells in a dose-dependent way and time-dependent way, in addition to TGF-α.

The expression of these genes diminishes with time, preventing the overproduction and buildup of matrix proteins that cause hypertrophic scarring. An effective wound healing agent reduces inflammation, speeds up fibroplasia, and improves healing tissue re-modelling in the shortest amount of time with the fewest negative effects. To be clinically desirable, the healed wound should have a minimal scar tissue size and optimum biomechanical function. According to histopathological findings, the number of fibrocytes in the A. barbadensis therapy group was considerably higher than in the control group.

It also raised collagen mass density in a more structured fashion than the control group at the same stage of wound healing. Blood vessel number and diameter were increased in *A. barbadensis*-treated wounds than in untreated ones. At 10-days after damage, *A. barbadensis* significantly decreased the number of lymphocytes and macrophages in the treated group when compared to the control group, but the untreated group had a large number of lymphocytes and macrophages on day-20. Numerous researches have been conducted on the treatment of chronic ulcers and diabetic wounds. Diabetic wounds take longer to heal owing to a number of connective tissue abnormalities, and they also have a greater risk of infection and other consequences. Collagen levels drop in diabetic wounds due to unbalanced collagen production and breakdown of freshly generated collagen. As *A. barbadensis* was applied topically or orally to diabetic wounds in an animal model, collagen levels in the granulation tissue rose by up to 89 percent and 83 percent, respectively, compared to the control group. Treatment with *A. barbadensis* gel also accelerates the healing of diabetic wounds, resulting in a shorter epithelialization time and quicker recovery. According to immunohistochemical data, the expression of both TGF-β1 and VEGF increased in type-2 diabetic rats treated with A. vera compared to the control group, resulting in quicker wound healing. The provisional matrix is made up of glycosaminoglycans and proteoglycans, which are produced by fibroblasts in the wound region. *In vivo* investigations revealed that oral and topical *A. barbadensis* gel treatments successfully enhanced glycosaminoglycans, hyaluronic acid, and dermatan sulphate levels [15].

2.2.3. Evidence from Clinical Trials: Several clinical investigations have looked into the impact of *A. barbadensis* on wound healing. For example, in an interventional comparison research, patients with second-degree burns were treated with silver sulfadiazine (SSD) 1 percent ointment and A. barbadensis gel. Although the SSD 1 percent ointment is one of the most often used topical anti-microbial agents, it has several adverse effects, including renal toxicity, leukopenia, and delayed wound healing.

The study's results demonstrated that Aloe vera's cell proliferation and anti-inflammatory characteristics produced early wound epithelialization with a pain-relieving effect that was superior to SSD. In contrast, a double-blind, randomized, and controlled clinical research in patients with split-thickness skin transplant donor-sites found that topical *A. barbadensis* gel had a substantial and quicker healing effect, but no significant pain alleviation. According to scientific investigations, *A. barbadensis* is more effective in first-degree and second-degree burn wounds than in the other degrees, and it may reduce healing time to as few as 9-days. *A. barbadensis*'s therapeutic properties have also been studied in the treatment of skin ulcers, surgical wounds, and chronic wounds. According to the results, *A. barbadensis* helps to prevent skin ulcers. In reality, *A. barbadensis*'s bioactive components, such as mucopolysaccharides, amino acids, and zinc, are responsible for improving skin integrity, reducing erythema, retaining moisture, and thereby preventing skin lesions [16].

2.2.4. Methods of Application: Chitin and chitosan-based nanocomposite are biocompatible

materials that have been used in medication delivery systems for a long time. A novel wound dressing scaffold made of collagen (0.5 percent)/chitosan-glucan complex hollow fibres encapsulated with *A. barbadensis* (1 percent dry powder) was recently developed and its mechanical properties, such as swelling percentage and scaffold stability, were significantly improved when compared to native collagen in the presence of *A. barbadensis*. In the presence of *A. barbadensis*, however, pore size and fibre porosity decreased marginally. A novel herbal biodegradable nanofiber consisting of poly (ε-caprolactone) (PCL)/gum tragacanth (GT) and *A. barbadensis* gel was also developed using the electrospinning process (5 percent). The diameter of nanofibers shrank in the presence of *A. barbadensis*, while mechanical parameters including tensile strength and strain increased. By adding *A. barbadensis* gel into PCL/GT nanofibers, the hydrophilic nature of the nanofibers was enhanced, and the original structure of the nanofibers was conserved after the biodegradation test. The *in-vitro* morphology of fibroblast cells cultivated on *A. barbadensis* loaded-PCL/GT nanofibers revealed increased cell proliferation, good adhesion, and a well-spread morphology of cells [17].

2.3. *Camellia sinensis*: Green tea, commonly known as *Camellia sinensis*, is a popular beverage drunk all over the globe. Green tea is a good source of anti-oxidant chemicals because of its high polyphenol concentration. Green tea's main ingredient, epigallocatechin-3-gallate (EGCG), has a diverse range of pharmacological and biological properties [18].

2.3.1. Mechanisms of Wound Healing:

2.3.1.1. Anti-bacterial Mechanisms: With modest potency, EGCG inhibits the growth of a broad spectrum of Gram-positive and Gram-negative bacteria. The direct binding of EGCG to the peptidoglycan layers of bacteria, causing cell wall breakdown, is thought to be the anti-bacterial mechanism against Gram-positive bacteria. EGCG, on the other hand, is unable to attach to the peptidoglycan layers of Gram-negative bacteria because these bacteria's outer membranes may prevent such binding. By producing H_2O_2, EGCG causes oxidative stress in Gram-negative bacteria cells. Using atomic force microscopy (AFM), researchers discovered that EGCG had anti-bacterial properties against *S. aureus* and *E. coli*. They discovered that EGCG binds directly to the peptidoglycan layer of *S. aureus*, while H_2O_2 production mostly damages Gram-negative *E. coli* cell walls [19].

2.3.1.2. Anti-oxidant Mechanisms: The three hydroxyl groups on the Bring, as well as the gallate group at the carbon-3 position, both contribute to free radical scavenging action, according to the structure-activity connection of EGCG. EGCG's anti-oxidant effect is mediated by various pathways, including hydrogen atom transfer, lipid oxidation prevention, electron transfer, and chelating redox-active metal ions. EGCG may also protect cells and tissues from oxidative damage by blocking pro-oxidant enzymes such as lipoxygenase, xanthine oxidase, COX-2, and iNOS and boosting anti-oxidant enzymes, including glutathione S-transferases (GST) and SOD [20].

2.3.2. Effect on Different Stages of Wound Healing: By lowering the amount and activity of the AP1 transcription factor, EGCG suppresses epidermal cancer cell growth. EGCG, on the other hand, seems to prevent normal keratinocytes from changing by boosting AP1 factor-dependent involucrin gene expression via the MAPK pathway, which activates the Ras, MEKK1, MEK3, and p38 cascades. Because AP1 proteins are homodimers of Jun proteins and heterodimers of Jun and Fo's factors, EGCG therapy increases the levels of Fra-1, Fra-2, FosB, JunB, JunD, c-Jun, and c-Fos in normal keratinocytes as a consequence of increased AP1 expression. These findings revealed that EGCG has diverse functions in normal and altered cells. The inhibitory effect of EGCG on the contraction of a floating collagen gel by fibroblasts was investigated, and the results revealed that a binding interaction mediates the inhibition process between EGCG and platelet-derived growth factor (PDGF), a triggering factor in collagen gel contraction. Furthermore, since EGCG interacts with a range of proteins, including fibronectin, fibrinogen, and histidine-rich glycoprotein, it may cause collagen gel contraction in response to various serum variables. In human dermal fibroblasts cells, the anti-inflammatory effects of EGCG (50 μM)-loaded nanoscale and microscale

particles were studied. The findings indicated that EGCG inhibited TNF-α, IL-1, and IL-6 expression after 24 hrs. Because of the anti-oxidant qualities of green tea, researchers discovered that chitosan green tea polyphenols complex increases transglutaminase (TGM) activation and the formation of mouse skin tissues. TGM1 (keratinocyte transglutaminase) expression reached its highest level after 24 hrs in the excision wound model, whereas TGM2 (tissue transglutaminase) and TGM3 (epidermal transglutaminase) expression reached their maximum levels after 72 and 168 hours, respectively. After the peak period, all TGM (1-3) levels in the control group declined and were normalised after 10-days. In the excision wound model treated with chitosan green tea polyphenols complex, there was a significant rise in TGM1 and TGM2 expression that remained stable after 10-days. TGM3 expression was also comparable to that of the control group.

This data points to chitosan green tea polyphenols' beneficial effects on wound healing, which may be linked to their anti-oxidant characteristics and stimulation of TGM expression. Green tea has the ability to speed up the re-epithelialization and re-modelling of granulation tissues during wound healing. On day-4, the green tea-treated group had regained more epithelial tissue than the control group, according to histological testing. On day-10, the green tea-treated group had achieved epithelialization, which resulted in considerable wound closure and the creation of a wound scar. The wound region in the control group was surrounded by fibrosis, which contained persistent inflammatory debris and caused sluggish re-epithelialization.

EGCG inhibits macrophage accumulation, LPS-induced inflammation, and notch signalling in diabetic wounds in mice, enhancing wound healing. Another research studied green tea extract's potential in diabetic and nondiabetic rat models. Green tea extract increased the modulation of circulating hypoxia-responsive microRNAs (HRMs) in diabetic and nondiabetic rat models by significantly up-regulating miR-199a and miR-21 and significantly lowering the expression of miR-424 and miR-210, resulting in quicker wound healing. On full-thickness wounds generated in type 2 diabetic mice, the effectiveness of an EGCG (10 ppm) loaded-collagen sponge was tested. EGCG boosted granulation tissue production and hastened re-epithelialization, resulting in a well-regenerated and differentiated epidermis. Immuno-histochemistry demonstrated a significant increase in Ki-67 immunoreactivity, showing that EGCG improved wound re-epithelialization by enhancing basal epidermal keratinocyte proliferation. EGCG increased CD31, indicating more newly created blood vessels. EGCG also increased the expression of α-smooth muscle actin (α-SMA), a protein that suggests the activation of myofibroblasts in the dermis. EGCG promotes diabetic wound healing by speeding up angiogenesis and reepithelialization and improving granulation tissue production by activating myofibroblast activity [21].

2.3.3. Evidence from Clinical Trials: The direct application of topical EGCG (topical treatment on the fully epithelialized wound and formed scar) was compared to zonal priming (early intervention with topical EGCG to control inflammation immediately after injury) in the modulation of cutaneous scarring in human skin in a double-blind, randomized trial. In the presence of EGCG, gene and protein studies revealed a reduction in mast cell counts. Boosted M2 macrophage levels increased the anti-inflammatory response in the presence of EGCG. At week 1, zoning with EGCG therapy dramatically decreased the expression of vascular endothelial growth factor A (VEGFA) and CD31. In contrast, at 1-2 weeks following direct application, considerable down-regulation of VEGFA and CD31 was detected. Furthermore, direct EGCG treatment decreased scar thickness and improved scar flexibility [22].

2.3.4. Methods of Application: The electrospinning process was used to create a wound dressing made of chitosan/polyethylene oxide nanofiber infused with green tea, which had significant anti-bacterial action against *E. coli* and *S. aureus*. These nanofibers may retain moisture in their structure due to their high swelling property, preventing them from adhering to the wound surface. Furthermore, between the wound and the dressing, oxygen may readily diffuse [23].

2. 4. *Centella asiatica*: Scleroderma, eczema, psoriasis, leprosy, and other chronic inflammatory problems, as well as skin wounds, have all been

treated with *Centella asiatica* in both traditional and contemporary health systems. The presence of a saponin termed asiaticoside and to a lesser degree madecassoside, which triggers type-I collagen production in human dermal fibroblast cells, is at least largely responsible for *C. asiatica*'s broad spectrum of biological activities [24].

2.4.1. Mechanisms of Wound Healing:

3.4.1.1. Anti-bacterial Mechanisms: The leaf and callus extracts of *C. asiatica* were tested against four diseases. The extracts had dose-dependent anti-bacterial properties, with the highest growth inhibition against *P. aeruginosa*, *E. coli*, and *S. aureus* at 100 µg/mL. Anti-bacterial activity was also seen at concentrations less than 100 µg/mL. In addition, at 125 µg/mL, the aqueous extract of *C. asiatica* had anti-bacterial activity against *S. aureus* and *E. coli* [25].

2.4.1.2. Anti-oxidant Mechanisms: Asiaticoside's anti-oxidant action is important in the wound healing. The impact of topical application of asiaticoside (0.2 percent) on anti-oxidant levels in rat excision wounds was studied. On the 7-day following treatment, Asiaticoside dramatically reduced lipid peroxide levels while increasing enzymatic and nonenzymatic anti-oxidants such as SOD, CAT, GSH, vitamin E, and ascorbic acid in newly created tissues. However, as compared to the control group, there was no significant change in anti-oxidant levels after 14-days of therapy (normal saline). Asiaticosides were thought to have a role in the induction of anti-oxidant levels during the early stages of wound healing [26].

2.4.2. Effect on Different Stages of Wound Healing: Asiaticoside's mode of action has been studied, and it seems that it works via many pathways, including increasing MCP-1 synthesis, increasing anti-oxidant capacity of wound cells through increased SOD, CAT and GSH levels, and inhibiting COX-1, COX-2, and PGE_2 production. At modest concentrations, asiaticoside increases collagen formation, glycosaminoglycan synthesis, and ECM buildup. Furthermore, the expression of genes involved in angiogenesis, ECM re-modelling and a number of growth factor genes is influenced by *C. asiatica* extract. In cultures of human skin fibroblasts, the triterpenoid fraction of *C. asiatica* extract (25 µg/mL) dramatically boosted collagen production and the amount of cell layer fibronectin. ECM protein deposition has been demonstrated to be influenced by *C. asiatica* extract. It stimulates fibroblast proliferation, activates the Smads pathway, and reduces the action of metalloproteinases, all of which help to increase collagen deposition.

In a burn wound model, scientists looked at the effects of a low dosage of asiaticoside (10 pg, 1 ng, or 100 ng/wound area). MCP-1, VEGF, and IL1 levels in burn wound exudates were shown to be enhanced by asiaticoside. The enhancement of VEGF production and the elevation of MCP-1 expression in keratinocytes by a low dosage of asiaticoside hastened burn wound healing through enhancing angiogenesis.

Collagen production is stimulated by *C. asiatica* extract, which also promotes fibroblast proliferation and migration, resulting in quicker re-epithelization and wound closure. It also improves scar development by improving the type-I/III collagen ratio by increasing the quantity of type-I collagen. The ethanolic extract of *C. asiatica* enhanced wound healing in normal and dexamethasone-suppressed wounds by enhancing wound breaking strength in incision wounds and quicker epithelization and wound contraction. On day-10, histopathological examinations indicated that wounds treated with *C. asiatica* had a well-developed matrix, well-organized collagen pattern, formed bundles between cells, and increased neovascularization. When compared to the dexamethasone group, wounds treated with *C. asiatica* extract displayed moderate cell populations, some matrix development, and neovascularization.

As a consequence, *C. asiatica* extract may successfully counteract dexamethasone's suppressive effects on wound healing [27].

2.4.3. Evidence from clinical trials: Two clinical investigations on *C. asiatica*'s wound healing potential have been done due to its favourable safety profile. On second-degree burns, a polyester wound dressing was compared to commercially available wound dressings in research. The trial group reported much-decreased pain and improved wound epithelialization, with no major side effects

or adverse clinical signs. The clinical experiment revealed a *Pseudomonas aeruginosa* infection on day 7. The research, however, had significant flaws, including the lack of blinding and a lack of clarity in the randomization technique. In addition to topical benefits, an oral formulation of *C. asiatica* extract containing 50 mg asiaticoside /capsule enhanced wound healing and reduced scar and keloid development in diabetic wound patients when compared to placebo. Furthermore, no notable negative effects have been recorded as a result of using *C. asiatica* extract [28].

2.4.4. Methods of Application: Several new wound dressings using asiaticoside as the pharmacologically active component have been described in the literature. The toxicity of Asiaticoside-loaded alginate films made by a solvent-casting technique against normal human dermal fibroblasts was not substantial (NHDF). With varied concentrations of asiaticoside, a nano-composite including polyvinyl alcohol /asiaticoside/chitosan was created using electrospinning technology. The formulation with the greatest concentration demonstrated the best wound contraction activity after 5-days in rabbits [29].

2.5. *Chamomilla recutita* and *Matricaria chamomilla*: Chamomile, also known as *Chamomilla recutita* and *Matricaria chamomilla*, is a prominent medicinal herb belonging to the Asteraceae family with a variety of therapeutic characteristics. Flavonoids (apigenin, luteolin, quercetin, patuletin, *etc*.) and terpenoids (α-bisabolol and chamazulene) are active components in chamomile. Apigenin, a multifunctional flavonoid, is the most prevalent flavonoid in chamomile flowers in terms of quantity [30].

2.5.1. Mechanisms of Wound Healing:

2.5.1.1. Anti-bacterial Mechanisms: Anti-bacterial properties of chamomile extract and essential oil were shown against Gram-positive and Gram-negative microorganisms. Apigenin is effective against a broad spectrum of germs, although *S. aureus* strains were resistant to it. Apigenin is more active against Gram-negative bacteria like *E. coli* and *P. aeruginosa* than Gram-positive bacteria like *E. coli* and *P. aeruginosa*. Apigenin's anti-bacterial mechanism against *E. coli* was explored by scientists. Apigenin induces bacterial death by activating cellular oxidative pathways that rely on the formation and buildup of reactive nitrogen and oxygen species, according to researchers [31].

2.5.1.2. Anti-oxidant mechanisms: DPPH radical, ferric reducing anti-oxidant power (FRAP), ABTS radical cation, and chelating of ferrous ions were used to assess the anti-oxidant impact of chamomile extract. According to the results, the presence of phenolic chemicals in chamomile resulted in strong anti-oxidant activity. With an EC_{50} value of 2.07 μg/mL, chamomile essential oil was also shown to have a strong anti-oxidant action against the DPPH radical [32].

2.5.2. Effect on Different Stages of Wound Healing: Apigenin has anti-inflammatory and analgesic properties. Apigenin increased the mRNA expression of collagen type-I, alpha 2 (Col12) and collagen type III, alpha 1 (Col31) in NIH/3T3 and human dermal fibroblast (HDF) cells, according to the researchers. Apigenin, on the other hand, activates the smad2/3 signalling pathway and enhances dermal collagen production by increasing the expression of phosphorylated smad2 and smad3 proteins in a dose-dependent manner.

Two flavonoids, apigenin and luteolin, were studied for their ability to protect human HaCaT cells (immortalized keratinocytes) against UV irradiation damage. UV irradiation causes collagen degradation, which is mediated by cellular matrix metalloproteinases (MMPs). Apigenin and luteolin reduced irradiation-induced damage and UV-induced collagenolytic MMP-1 production via reducing UV-induced phosphorylation of Ca^{2+}/calmodulin-dependent protein kinases (CaMKI and CaMKII), which are upstream modulators of MAPK pathways, according to the results of this research. In cultivated HaCaT cells, they also reduced UV-induced phosphorylation and expression of cJun, c-Fos expression, and activation of activator protein 1 (AP-1) signalling. The efficiency of chamomile and corticosteroids in wound healing was examined. According to the results, animals given chamomile had a substantially faster wound healing time than those given corticosteroids, with only the chamomile group having entirely healed wounds after 5-days.

Chamomile extract ointment stimulated re-epithelialization and collagen production for oral wound healing in an animal model.

According to the study's author, chamomile extract ointment had no impact on inflammation or fibroblast count in rats euthanized 7-days and 10-days after therapy. In albino rats, the effects of topical *M. chamomilla* extract on burn wound healing were investigated and the results suggested that chamomile extract has a lot of promise for accelerating burn wound healing. The impact of chamomile ointment on the healing of coronary artery bypass graft operation wounds in diabetic individuals was studied in a randomised clinical study. From the 2-day after surgery, the intervention group's wound was treated with chamomile ointment, whereas the control group's wound was cleansed with betadine and wrapped for 14-days. On 7-days and 14-days following the intervention, the findings demonstrated a substantial difference between the two groups.

The findings also showed that chamomile ointment benefited the wound in diabetic individuals at least one week after coronary artery bypass graft surgery. The effectiveness of an apigenin-loaded hydrogel was tested in a diabetic wound model. The SOD, GSH, and CAT levels in the granuloma tissue of the apigenin-treated group were considerably higher. Apigenin also raised granuloma weight, collagen, and protein content, stimulating cellular proliferation and expediting wound healing. Histopathological data demonstrated the proliferation of epithelial tissue surrounding the wound region and an increase in blood vessels, fibroblast cells, and collagen fibers in the apigenin-loaded hydrogel group. The control group's granulation tissue showed less epithelialization, fibrosis, and macrophage aggregation and fewer collagen fibres, suggesting that the wounds had not healed fully [33].

2.5.3. Methods of Application: The electrospinning process demonstrated an active wound dressing made of poly (ε-caprolactone) / polystyrene nanofibrous with chamomile (15 percent) anti-bacterial and antifungal activity against *S. aureus* and Candida albicans. Chamomile-loaded nanofibers mats enhanced epithelialization and collagen fibre production in the dermis, resulting in a quicker rate of granulation tissue development, according to the results of the *in vivo* research [34].

2.6. *Curcuma longa*: Curcumin is a well-known bioactive component found in the rhizomes of *Curcuma longa*. It has a variety of biological activities, including anti-inflammatory, protective, and anti-oxidant capabilities, making it an excellent candidate for wound healing research. Curcumin and its nano-formulations have recently been the subject of a detailed analysis of their potential involvement and diverse cellular pathways in treating various malignancies. However, due to its limited solubility, stability, and bioavailability, it has been difficult to use as a bioactive ingredient in traditional wound healing formulations [35].

2.6.1. Mechanisms of Wound Healing:

2.6.1.1. Anti-bacterial Mechanisms: Curcumin's anti-microbial action aids in the speeding up of the wound healing process. Curcumin's anti-bacterial mechanisms have recently been the subject of a detailed review paper. Through the bacterial quorum sensing regulatory system, curcumin may limit the production of bacterial biofilms and bacterial adherence to host receptors. Bacterial virulence factors are also inhibited.

Curcumin may also stop bacteria from multiplying by damaging cell membranes, DNA, proteins, cell walls, and other components. Curcumin may also affect the permeability of the cytoplasmic membrane and the ATP-binding cassette transporters found in Gram-negative and Gram-positive bacterial cells' cytoplasm. Curcumin revealed a significant anti-bacterial effect against MRSA [36].

2.6.1.2. Anti-oxidant Mechanisms: Several researches have looked at dietary curcumin's anti-oxidant activity as well as its possible health effects. Cucumin exhibits DPPH, ABTS, and DMPD radical scavenging properties, as well as hydrogen peroxide scavenging, ferrous ion chelating, and ferric ion reduction. Curcumin reduced 97.3 percent lipid peroxidation at 15 μg/mL, but tocopherol only inhibited 84.6.3 percent at 45 μg/mL. According to numerous experimental and theoretical studies, Curcumin's anti-oxidant activity and free radical kinetics depend on H atom donation from the phenolic OH group. Curcumin

boosted the activity of anti-oxidant enzymes including SOD, CAT, and GSH in rats when given orally. Compared to the control group, topical curcumin treatment on excised wounds of rats increased the activity of these anti-oxidant enzymes [37].

2.6.2. Effect on Different Stages of Wound Healing: Curcumin demonstrated its positive benefits through many pathways in the different phases of the wound healing process, according to the published research. The topical use of curcumin on a burn site dramatically boosted angiogenesis and resulted in quicker wound healing in animal research. Curcumin incorporation into collagen films also had encouraging outcomes, as shown by a higher wound healing rate and an increase in fibroblast and macrophage proliferation. The film significantly reduced oxidative stress in the wound region, as shown by a considerable drop in SOD and increased catalase expression. Curcumin-loaded chitosan/poly (lactic acid) (PLA) nanofibers were investigated for their healing potential.

When compared to the control group, there was a significant difference in wound area reduction on day 18, and the therapy enhanced the rate of epithelialization and wound closure. Furthermore, wound healing effects of curcumin and CMC formulation pretreatment in mice subjected to different doses of radiation demonstrated that this formulation may boost the rate of wound contraction as well as collagen, DNA, and nitric oxide production while lowering the mean wound healing time. In another trial, the outcomes were almost the same even when curcumin was applied directly to the wound region. Curcumin seems to have wound-healing capabilities through several pathways and at various stages. Inhibition of the NF-B transcription factor and scavenging ROS in the inflammatory phase increased granulation tissue development and collagen deposition in the proliferation phase, and increased TGF- levels in the remodelling phase are among the potential processes. TGF levels were higher in curcumin-treated wounds than in the control group, which promoted fibroblast proliferation and granulation tissue development. Other pathways have been hypothesized, such as stimulation of the Wnt signalling pathway and reduction of MCP-1 expression. Curumin can speed up wound healing and re-epithelialization. During the 12-days following damage, treatment with curcumin-loaded chitosan/alginate sponge increased wound contraction by 90 percent, while this parameter was determined to be 74 percent in the control group.

On day-8, histological results in an animal research indicated that the curcumin-treated group had increased fibroblast proliferation and thick collagen deposition, leading to quicker epithelialization. On the other hand, the control group showed uneven fibrous scarring and inadequate epithelialization. The time it took for treated wounds to fully epithelialize was cut in half, from 23-days to 11-days. Using gum tragacanth/poly(ε-caprolactone) electrospun nanofibers, the wound healing abilities of curcumin on diabetic wounds were also examined. The nanofibers demonstrated good anti-bacterial activity against MRSA and ESBL bacteria. A 15-day *in-vivo* research on diabetic rats revealed that the formulation dramatically improves wound closure and collagen levels.

Another research employed poly(ε-Caprolactone) nanofiber as a vehicle for curcumin treatment wounds in diabetic rats. The findings showed that the formulation may decrease inflammation, with a substantial drop in IL-6. The wound closure rate in the treated group was considerably greater after 10-days. Furthermore, topical curcumin enhanced diabetic wound healing by increasing neovasculogenesis via increased production of VEGF, TGF-1, and HIF-1α [38].

2.6.3. Methods of Application: Due to curcumin's limited bioavailability and water solubility, a study team employed chitosan nanoparticles to boost curcumin bioavailability while simultaneously improving the biological stability of collagen-based scaffolds. In streptozotocin-induced diabetic rats, the constructed scaffold greatly enhanced wound contraction rate.

Histological studies validated the results, as full epithelialization with thick granulation tissue development was seen in H&E staining. Curcumin was included into guar gum/polyhydroxyalkanoates films, and the findings revealed that the film had adequate anti-bacterial action against Gram-positive bacteria. A nearly 90 percent wound contraction was reported after 7-days of therapy in

an animal model, with a statistically significant difference between the control and treatment groups [39].

2.7. *Embelia ribes*: False black pepper is the popular name for *Embelia ribes*, which belongs to the Myrsinaceae family. The bitter fruit of *E. ribes* is used to cure a range of ailments, including gastrointestinal problems, fever, and inflammatory illnesses. Embelin is a naturally occurring alkyl-substituted hydroxy benzoquinone that is the main ingredient in the fruits of *E. ribes*. Embelin exhibited anti-diabetic, chemopreventive, anti-cancer, anti-inflammatory, analgesic, anti-bacterial, and anti-oxidant properties, among other biological actions [40].

2.7.1. Mechanisms of Wound Healing:

2.7.1.1. Anti-bacterial Mechanisms: Embelin, a compound isolated from *E. ribes*, has anti-bacterial activity against Gram-positive bacteria (*B. subtilis* and *S. aureus*) as well as Gram-negative bacteria (*E. coli* and *P. aeruginosa*), with MIC and MBC values ranging from 20 µg/mL to 50 µg/mL and 75 µg/mL to 400 µg/mL, respectively. Scientists discovered that embelin has bactericidal and bacteriostatic action against Gram-positive and Gram-negative microorganisms. The greater quantity of emblin (100 µg/mL) was shown to have strong anti-bacterial action against a variety of microorganisms [41].

3.7.1.2. Anti-oxidant Mechanisms: Emblin reduces oxidative stress indicators like malondialdehyde and increases anti-oxidant enzymes like SOD, CAT, and GSH peroxidase, making it a potential anti-oxidant. In an *in-vitro* investigation employing THP1 human leukemic monocytes and BV-2 mouse microglia, embelin's anti-oxidant activity was assessed, and the findings showed that it had strong anti-oxidant capabilities after 24 hrs. Embelin's long alkyl C10 tail may have a role in cell membrane insertion, which increases anti-oxidant defence and cytoprotection in microglia. According to computational calculations, two forms of embelin scavenging actions may be implicated: the first through the interaction of the quinone moiety and the second by proton capture in the cell. In an H_2O_2-induced senescence model of human dermal fibroblasts, Embelin prevented cell senescence by lowering p21 and MMP1 gene expression while raising COL1A1 gene expression in a dose-dependent manner [42].

3.7.2. Effect on Different Stages of Wound Healing: The anti-inflammatory activities of embelin have been linked to a decrease in TNF-α level in various studies. TNF-α receptors are found in almost every cell type and play a role in a variety of physiological processes. TNF-α produces secondary cytokines which drive a wide range of inflammatory responses. TNF-α converting enzyme (TACE) is a protease that helps release the soluble part of pro-TNF-α into the extracellular space, and embelin has been found to be a powerful TACE inhibitor *in-vitro* tests.

The anti-inflammatory effects of embelin in both acute and chronic irritating contact dermatitis were investigated using an animal model. According to the findings, embelin lowers skin edoema in both acute and chronic skin inflammation by suppressing IL-1β and TNF-α and so preventing leukocyte buildup. Embelin effectively suppressed LPS-induced TNF-α production in mice in a dose-dependent manner, according to the findings. TNF-α production by human keratinocytes was similarly suppressed. Moreover, embelin inhibits myeloperoxidase (MPO) activity in the chronic inflammation model.

Myeloperoxidase, a peroxidase present in neutrophil azurophilic granules and other myeloid cells, is released into the extracellular environment after degranulation. As a consequence, embelin's anti-inflammatory effect is shown by its inhibition of MPO expression in a chronic inflammation paradigm. In an animal model with excision, incision and dead space wound, the crude extract of *E. ribes* leaves and embelin extracted from the extract were examined. The wound healing characteristics of both treated groups were remarkable. The embelin-treated mice took less time to complete epithelialization of the excision site than the ethanol-treated animals. The group given embelin had a quicker epithelialization of the incision site, followed by a high rate of contraction. The embelin-treated group had significantly stronger incision wound tensile strength than the ethanol extract group. The existence of additional chemical elements that restrict the action of embelin might explain the crude ethanol extract's

lower wound healing effectiveness, according to the author. The wound tissue of the ethanol extract-treated group showed fibrosis, moderate epithelialization, and collagen production, whereas the embelin-treated group had complete healing, with more fibroblasts and a significant increase in collagen tissue and blood vessels, according to histopathological evidence.

On a cutaneous wound in diabetic rats, the wound healing efficacy of topical ointment (5 percent) and oral (25 mg/kg and 50 mg/kg) embelin administration was evaluated. In an excision diabetic wound model, topical embelin ointment increased the proportion of wound contraction, suggesting rapid epithelium and collagenization. When compared to the control group, topical and oral embelin therapy significantly improved the breaking strength of diabetic incision wounds. In embelin-treated granulation tissues, the levels of hydroxyproline, hexosamine, DNA, and total protein increased, and stimulating cell proliferation. The embelin-treated groups had much greater epithelialization, less inflammatory components, and less neovascularization, according to the histological findings [43].

2.7.3. Methods of application: In a rat excision wound model, the wound healing efficiency of a hydrogel film based on polyvinyl alcohol and PEG combined with embelin (0.2 percent) was investigated. In a 12 hr *in vitro* release trial, more than 80 percent of the embelin was released. The animal treated with embelin loaded hydrogel exhibited symptoms of thin epidermis development at the end of the 6-day following treatment, according to the results, without any scar infection. This impact was only seen in the hydrogel group, perhaps owing to the hydrogel's capacity to maintain a moist environment in the wound region [44].

2.8. *Garcinia mangostana*: Traditional medicine has employed mangosteen (*Garcinia mangostana*), a tropical tree with edible fruit, to treat skin illnesses, wound infection, and chronic ulcers. Active ingredients in *G. mangostana* include xanthones, flavonoids, saponins, and tannins. The principal active components discovered in mangosteen peel and fruit extract are xanthones, which include -mangostin, which has a wide range of biological activities including anti-oxidant, anti-bacterial, anti-inflammatory, analgesic, anticancer, and cytotoxic effects [45].

2.8.1. Mechanisms of Wound Healing:

2.8.1.1. Anti-bacterial Mechanisms: Mangosteen extracts have anti-bacterial properties against a broad spectrum of Gram-positive and Gram-negative bacteria. Mangosteen pericarp showed considerable growth inhibition against *S. aureus*, *S. typhi*, and *E. coli* at low concentrations, such as 5 μM, 10 μM, and 15 μM. Anti-bacterial activity of mangosteen extract loaded-alginate gauze was shown to be substantial against Gram-positive bacteria (*S. epidermidis*, *S. aureus*, and MRSA) and moderate against Gram-negative bacteria (*E. coli* and *Acinetobacter baumannii*).

The biocompatibility and non-toxicity of alginate gauze dressing integrated with 0.01 percent w/w and 0.02 percent w/w mangosteen extract were also shown *in-vitro* on keratinocyte HaCaT cells and human dermal fibroblasts (HDF). α-Mangostin showed anti-bacterial efficacy against vancomycin-resistant Enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), with MIC values ranging from 6.25 μg/mL to 12.5 μg/mL, respectively. Mangostin and commercially available antibiotics such as gentamicin and vancomycin hydrochloride, which may be used to treat VRE and MRSA infections, were shown to have synergistic effects. Within 5 mins - 10 mins, mangostin compromises the integrity of the cytoplasmic membrane, resulting in intracellular content leakage and water molecule diffusion across the membrane. The isoprenyl group of mangostin, which is a short lipid tail, is the driving factor behind α-mangostin's rapid penetration into the membrane's hydrophobic area. The isoprenyl group increases α-mangostin's hydrophobicity and lowers the free energy barrier to entry [46].

2.8.1.2. Anti-oxidant mechanisms: The pericarp of the mangosteen is high in xanthones. Using a supercritical carbon dioxide extraction technique, scientists evaluated the anti-oxidant activity of xanthones extracted from *G. mangostana*. The high anti-oxidant capacity of mangosteen was revealed by the results of anti-oxidant assays including DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals (IC_{50} = 41.8 μg/mL), lipid peroxidation (IC_{50} =

21.5 µg/mL), hydroxyl radicals non-site specific (IC_{50} = 23.1 µg/mL), and hydroxyl radicals site-specific (IC_{50} = 30.0 µg/mL). The results of the cytochrome-c experiment demonstrated that xanthones converted ferric cytochrome-c to ferrocytochrome-c in a time-dependent manner similar to ascorbate. Mangosteen has a significant number of phenolic acids from the hydroxybenzoic acid and hydroxycinnamic acid families, in addition to xanthones. In the DPPH and lipid peroxidation systems, base-hydrolyzed phenolic acids and free phenolic acid from mangosteen demonstrated high anti-oxidant activity [47].

2.8.2. Effect on different stages of wound healing: *In-vivo* investigations revealed that mangosteen extract, particularly α-mangostin, had wound-healing properties. Growth factors promote fibroblast proliferation and play an important role in wound healing. On human gingival fibroblasts, the effects of mangosteen peel pericarp on TGF-1, VEGF-A, basic fibroblast growth factor (bFGF), and platelet-derived growth factor subunit B (PDGF-B) expression were recently explored. These growth factors work as chemotactic macrophages in the wound healing process. According to the findings, mangosteen peel pericarp boosted TGF-1, VEGF-A, and bFGF expression while decreasing PDGF-B expression. As a gel containing mangosteen peel extract was applied to a burnt wound model, epidermal growth factors' expression rose significantly compared to the control group, resulting in enhanced fibroblast and keratinocyte proliferation. MRSA-induced superficial skin infection was also treated with *G. mangostana* extract and α-mangostin, which had an anti-inflammatory effect. The expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8, as well as toll-like receptor-2 (TLR-2) mRNAs, was dramatically decreased by *G. mangostana* extract.

MRSA-infected lesions treated with *G. mangostana* extract healed completely 10-days later, and the number of MRSA colonies decreased significantly from the 1-day of therapy. Despite the fact that α-mangostin reduced mast cell formation and downregulated the expression of pro-inflammatory cytokines and TLR-2, the wounds did not heal within 10-days, and *G. mangostana* extract had a stronger anti-inflammatory impact. This might be owing to the presence of additional anti-inflammatory components in the *G. mangostana* pericarp. The capacity of α-mangostin to decrease prostaglandin E_2 (PGE_2) production as well as its anti-oxidant action, both of which contribute to the wound healing process' proliferation phase, is the second mechanism. Furthermore, α-mangostin inhibited the production of TNF-α, IL-6, and iNOS, indicating that it has anti-inflammatory properties. The findings of the *in vivo* investigation demonstrated that α-mangostin may reduce total leukocyte migration, particularly neutrophil migration.

At greater dosages of α-mangostin, NF-κB translocation and the cyclooxygenase-2 (COX-2) enzyme activity were also reduced. *G. mangostana*'s anti-inflammatory and anti-oxidant qualities help the epidermis reepithelize more quickly. *G. mangostana* promotes EGF expression, which might speed up re-epithelialization, wound contraction, and collagen deposition when applied topically. Topical application of *G. mangostana* to burn wounds resulted in a significant proportion of epithelization compared to the control group. The dermal-epidermal junction in the treatment group was clearly defined 14-days after treatment, according to histological data [48].

2.8.3. Methods of Application: Because of its poor solubility in aqueous environments, α-mangostin's usage in wound healing processes is limited, and its bioavailability in skin ulcers is reduced. Researchers boosted the water solubility of α-mangostin by forming a compound with 2-hydroxypropyl-cyclodextrin and integrating it into a sodium carboxymethylcellulose hydrogel, which raised the solubility by 11.7-fold over α-mangostin alone. Mangosteen extract was also carried *via* novel wound dressings made of synthetic polymers such as poly (vinyl acetate) scaffold, PVA fibre mats, and cast PVA films. The PVA fibre mats released mangosteen extract more quickly than the film. The fibre mats' extremely porous nature led to a higher degree of swelling in the medium. Up to 3 percent w/v of mangosteen extract, a poly (vinyl acetate) spray-on dressing integrated with mangosteen extract demonstrated no toxicity against L929 mice fibroblasts, normal human fibroblasts (NHF), and keratinocyte (HaCat) cells [49].

2.9. *Hypericum perforatum*: Hypericaceae flowering plant *Hypericum perforatum* contains a broad range of biological and pharmacological effects, including anti-depressant, anti-oxidant, anti-bacterial, anti-inflammatory, and pain relief. Naphtodianthrones (hypericin, pseudohypericin, and protohypericin), prenylated acylphloroglucinols (hyperforin and adhyperforin), and flavonoids are among the physiologically active chemicals discovered in *H. perforatum* (epigallocatechin, rutin, quercetin and hyperoside). Xanthones and sesquiterpenes are abundant in *H. perforatum* essential oil. The most frequent chemicals discovered in *H. perforatum* are hypericin and hyperphorin [50].

2.9.1. Mechanisms of Wound Healing:

2.9.1.1. Anti-bacterial Mechanisms: A number of studies on *H. perforatum* extract's anti-bacterial activity have been reported in the literature, demonstrating that it is used in traditional medicine to treat wounds, skin infections, and other infectious disorders. Gram-positive bacteria are more resistant to *H. perforatum* extract than Gram-negative bacteria. With a MIC of 50 µg/mL, the methanolic extract of *H. perforatum* was the most effective against Gram-positive bacteria. With MICs ranging from 1 µg/mL to 100 µg/mL, hyperforin suppressed the development of Gram-positive bacteria as well as methicillin-resistant *S. aureus* and penicillin-resistant *S. aureus*. It was also shown to have a significant anti-bacterial action against MRSA, with a MIC of 1 µg/mL [51].

2.9.1.2. Anti-oxidant Mechanisms: Several studies have looked into *H. perforatum*'s anti-oxidant and free radical scavenging abilities.

The presence of flavonoids and phenolic acids in *H. perforatum* may explain its anti-oxidant action. The anti-oxidant activity of main components of *H. perforatum* was found to be substantial, but phloroglucinols and naphthodianthrones had no impact. The anti-oxidant ability of *H. perforatum* was indicated by the results of anti-oxidant tests involving DPPH radicals (the lowest IC_{50} = 0.52 µg/mL), lipid peroxidation (IC_{50} = 0.0079 µg/mL), NO scavenging (IC_{50} = 6.11 µg/mL), and superoxide scavenging (IC_{50} = 1.86 µg/mL). *H. perforatum* exhibited a maximal reduction capacity of 104 mg Fe equivalents/g, according to the ferric reducing ability of plasma (FRAP) test. *H. perforatum* oil-loaded chitosan cryogel was recently created by explorers as a wound dressing. The free radical scavenging activity of chitosan cryogel combined with *H. perforatum* oil showed the maximum DPPH scavenging activity at a concentration of 100 µg/mL (69.9 percent). It has excellent anti-bacterial action against *E. coli* and *Legionella pneumophila* [52].

2.9.2. Effect on Different Stages of Wound Healing: On lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, the anti-inflammatory effects of hyperforin and hypericin were investigated, and the results indicated that both substances suppressed iNOS and COX-2 gene expression in a dose-dependent manner. Hyperforin and hypericin suppress iNOS and COX-2, which reduces the synthesis of nitric oxide (NO) and progesterone (PGE_2) and hence the inflammatory response.

These pathways give a rationale for treating inflammatory skin conditions with *H. perforatum*. *H. perforatum* impacts the wound healing process' proliferative phase by enhancing fibroblast proliferation, maturation, and collagen deposition. The wound healing efficacy of *H. perforatum* oil emulsion in an animal model's excision wounds was investigated. The results showed that mice treated with *H. perforatum* oil had a 97 percent reduction in wound area compared to those treated with mupirocin (68 percent) and vaselin (3 percent). When comparing the *H. perforatum* oil-treated group to the other treatment groups, X-ray examination of animal skin indicated a substantial increase in angiogenesis in the *H. perforatum* oil-treated group.

When compared to the control group, the *H. perforatum* oil-treated group exhibited dense bundles of collagen fibres, more fibroblast cells, and new blood vessels, according to a histological inspection of granulation tissue. The wound healing effects of an ointment based on a complete extract of *H. perforatum* were tested *in vivo* incision, excision, and thermal burn wound models. *According to histological results, H. perforatum produced rapid epithelium regeneration and normal collagen fibre disposal*. In addition, *H. perforatum* ointment reduced edoema in the

epidermis and dermis and the degree of hypodermis congestion. Even on the 6-day of therapy, the *H. perforatum* ointment showed positive results.

On day-9, the *H. perforatum* ointment-treated group (96.56 percent) had significantly more wound closure than the control group treated with the ointment base (33.79 percent) and the non-treated group (14.85 percent). The excision wound model's re-epithelialization was accomplished on day-12. On day-21, granulation tissue had matured in virtually all of the dermis' depth. H. perforatum gel may improve tissue regeneration in diabetic wounds by enhancing fibroblast proliferation, collagen production, and revascularization. Topical and systemic *H. perforatum* on a diabetic wound model were studied. Compared to the diabetic control group, oral and topical treatment of H. perforatum resulted in greater hydroxyproline and collagen density and increased tensile strength. The rate of contraction and angiogenesis in the *H. perforatum*-treated group was considerably greater than in the diabetic control group. In general, oral *H. perforatum* treatment was more effective than topical *H. perforatum* treatment [53].

2.9.3. Methods of application: *H. perforatum* oil was created using the solvent casting technique at different quantities, and chitosan sheets were utilized as a carrier for it. Because of its capacity to regulate water loss from wounds and maintain a moist environment throughout the wound healing process, water vapour permeability is regarded as one of the most important aspects in wound dressing. The addition of *H. perforatum* oil to chitosan films created a porous structure, which enhanced the wound dressing's water vapour permeability. On NIH3T3 fibroblasts, *H. perforatum* oil-loaded chitosan films demonstrated great biocompatibility, no cytotoxic effects, and a proliferative impact. A two-layer wound dressing was created, with the top layer consisting of electrospun poly(ε-caprolactone) nanofibers and the bottom layer consisting of opposite-direction electrospraying and electrospinning of polyethylene glycol/*H. perforatum* oil and poly(ε-caprolactone) polymer solutions. *H. perforatum* oil packed in polyethylene glycol (PEG) capsules may be released into the medium by dissolving them. The wound dressing substance's non-adhesivity on the wound surface is an essential feature in the wound healing process because it permits it to be removed without deforming.

There were no cells adhering to or growing on the surface of this membrane when it was incubated with L929 fibroblast cells. This demonstrates the wound dressing's ability to stay non-adhesive to the wound surface. Both *H. perforatum* oil and wound dressings containing *H. perforatum* oil were biocompatible and enhanced cell survival by increasing metabolic activity. Membrane biocompatibility improved as *H. perforatum* oil concentration increased, and the impact of apoptosis/necrosis reduced [54].

2.10. *Lawsonia inermis*: The henna tree, *Lawsonia inermis*, is a valuable medicinal plant for the treatment of burn injuries, skin infections, wounds, and ulcer healing. Its anti-microbial and anti-inflammatory capabilities are responsible for this. Carbohydrates, phenolic compounds (lalioside, lawsoniaside, and syringinoside), flavonoids (luteolin, apigenin, quercetin, kampferol, and catechin), saponins, proteins, alkaloids (harmaline and harmine), terpenoids, quinones (juglone, arbutin, alizarin, lawsone, anthraquinone, and emodin). The primary ingredient in the extract of *L. inermis* flowers, leaves (approximately 0.5 percent - 1.5 percent in dried powdered leaves), and branches is lawsone (2-hydroxy-1,4-naphthoquinone). It is the source of henna's red–orange color [55].

2.10.1. Mechanisms of Wound Healing:

2.10.1.1. Anti-bacterial Mechanisms: *S. aureus*, *B. subtilis*, *E. coli*, *S. paratyphi*, *S. dysenteriae* and *C. albicans* are among the multi-drug resistant strains that *L. inermis* leaves extract has anti-bacterial action against. Henna leaf extract has also been shown to suppress the development of bacteria that cause infections in burn wounds. *L. inermis* leaf extract has anti-bacterial action that is concentration dependant, with Gram-negative bacteria being more susceptible than Gram-positive bacteria. With MICs equivalent to Lawsone, DMSO and ethanolic extract of henna leaves had the strongest activity against Gram-positive and Gram-negative bacteria. With MIC values of 2.30 mg/mL and 2.030 mg/mL for extract and 1.02 mg/mL and 0.51 mg/mL for Lawsone, respectively, the ethanolic extract of *L. inermis* and Lawsone is

more active against *E. coli* and *S. aureus* than the other bacteria. The presence of Lawsone is primarily responsible for the anti-bacterial action of henna leaves crude extracts [56].

2.10.1.2. Anti-oxidant Mechanisms: The presence of various active components, including flavonoids and naphthoquinones, contributes to the high anti-oxidant activity of *L. inermis* leaves. Lawsone, apigenin, luteolin, cosmosiin, *p*-coumaric acid, 2-methoxy-3-methyl-1,4-naphthoquinone, and apiin have significant free radical scavenging activity and are comparable to the anti-oxidant activity of ascorbic acid, were found to be abundant in *L. inermis* leaves, according to researchers. The active chemicals in henna leaves operate as free radical scavengers and their immunomodulatory effects are thought to be due to their ability to inhibit phospholipid membrane peroxidation, which protects immunocompromised cells from free radical damage. The anti-oxidant properties and *in-vivo* wound healing capacity of cuttlefish skin gelatin and aqueous *L. inermis* extract gel and film were investigated. By enhancing the activity of anti-oxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH) peroxidase, the addition of *L. inermis* extract to gelatin gels and films increased anti-oxidant activity in wound tissues, resulting in quicker wound healing. During the fibroplasia stage of wound healing, anti-oxidants also encourage cell growth. The anti-oxidant capabilities of *L. inermis* leaves seem to be important in the wound healing process's proliferation phase [57].

2.10.2. Effect on Different Stages of Wound Healing: Henna and lawsone alter skin homeostasis by activating keratinocytes' aryl hydrocarbon receptor (AhR) pathway. The AhR is critical for protecting the skin's integrity against long-term environmental assaults. By interfering with natural skin reconstruction processes and regulating epidermal cell proliferation and differentiation in the skin, Lawsone has an effect on wound healing. Exposure to lawsone increased the expression of AhR-dependent genes in human primary keratinocytes and keratinocytic cell lines. Several researchers have looked at different uses of the drug delivery method using nanoparticles in recent years. Nanofibers containing *L. inermis* leaves extract was utilized to treat second-degree burn wounds in animal models, with the findings showing that wound healing was hastened.

The CD68 immunohistochemical stained wound pictures demonstrated that treating the burn wound sites with *L. inermis*-loaded-nanofibers significantly decreased macrophage populations, reducing inflammation. Clear re-epithelialization, angiogenesis, sebaceous glands, hair follicles, and a well-organized pattern of collagens were seen histopathologically. The expression of growth factors is influenced by the henna extract. Following treatment of fibroblast cells with an ethanolic extract of *L. inermis* for 48 hrs, the expression of TGF-1 and VEGF-A genes increased significantly. According to the results of an *in-vitro* scratch test, the ethanolic extract of henna considerably increased the migration of mouse fibroblast cells after 24 hrs of treatment when compared to the control group.

Lawsone also influences TGF-β1 expression. In comparison to the control scaffolds, electrospun polycaprolactone/gelatin nanofibers containing lawsone (0.5 percent and 1 percent) dramatically elevated the gene expression of COL1 and TGF-1. Another research looked at glucose transporter-1 (Glut-1) gene expression and insulin-like growth factor I (Igf-1) in Wistar rats given *L. inermis* extract ointment. According to the findings, the levels of Igf-1 and Glut-1 in the L. inermis-treated group were considerably greater than in the control group. Upregulation of Glut-1 expression, which increases cell proliferation and migration through epidermal growth factor receptor regulation, results in increased glucose transport and absorption in the presence of *L. inermis* extract. By upregulating Igf-1 expression, *L. inermis* extract also influences fibroblast and keratinocyte growth. *L. inermis* shortens the length of the inflammatory process and primarily stimulates keratinocyte re-epithelialization. On 3-days and 7-days after wound formation, topical treatment of *L. inermis* (3 percent and 6 percent) increased revascularization, collagen deposition, and re-epithelialization rates while reducing inflammatory cell infiltration to histopathological results. Lowsone is involved in the production of granulation tissue and the early stages of tissue restoration. Compared to the control group (21.6 ± 0.50 days), topical Lawsone

gel enhanced wound contraction and decreased epithelialization time (13.4 ± 0.45 days). One week following treatment with lawsone-loaded nanofibers, the histological features of newly formed granulation tissue revealed the beginning of re-epithelialization and greater fibroblast and collagen content than the control group. 14-days after treatment, organized connective tissue was densely formed, and angiogenesis was inhibited, while the control group showed partial re-epithelialization with many lymphocytes, macrophages, inflammatory cells, and exudates. Patients confined to bed or in the Intensive Care Unit (ICU), as well as those who sit in a wheelchair for extended periods, are at risk of developing pressure ulcers or bed sores, which are caused by constant pressure on the skin.

The impact of a topical combination of *L. inermis* and distilled water on pressure ulcer grade one in ICU patients was studied in a clinical experiment. Both the control and intervention groups received a regular skin care regimen. The average area of a pressure ulcer was reduced (3.54 ± 33.91) in the intervention group but grew (29.9 ± 37.93) in the control group, according to the findings. According to the Pressure Ulcer Scale for Healing (PUSH) test, henna lowered the intervention group's PUSH score (5.36 ± 3.12), whereas the control group's PUSH score (1.91± 1.53) was higher. In both groups, there was a substantial difference in PUSH score before and after the intervention [58].

2.10.3. Methods of application: In a wound dressing made of hydroxyethylcellulose (HEC)/polyvinylpyrrolidone (PVP), the impact of Henna incorporation on hydrogel characteristics was investigated, and Henna extract was cross-linked by irradiation. The porosity, fluid absorption capacity, water retention, and hydrogel adhesivity all increased in the presence of *L. inermis* extract, but the gelation degree of the hydrogel reduced marginally. This hydrogel was biocompatible and had anti-bacterial properties against *S. aureus* and *E. coli*. Using high shear as a cross-linking technique, polyvinyl alcohol (PVA)/chitosan hydrogel sheets, including *L. inermis* extract, were created. Hydroxyproline and hexosamine are indicators of collagen manufacturing at the wound site, and *L. inermis* extract in hydrogel films significantly raised their concentration, resulting in early tissue reconstruction and wound healing promotion. Wound dressings made from *L. inermis*-loaded nanofibrous scaffolds based on gelatin have been described. Nanofibrous mats including *L. inermis*, poly-L-lactic-acid (PLLA), and gelatin showed anti-bacterial efficacy against *E. coli* and *S. aureus*. *In vitro* biological tests on *L. inermis*-loaded PLLA-Gelatin nanofibrous mats revealed that they were biocompatible with 3T3-L1 fibroblasts. Topical use of *L. inermis* ethanolic extract in an excision wound model and oral administration of L. inermis ethanolic extract in incision and dead space wound models increased wound contraction and tensile strength, and collagen turnover, resulting in improved wound healing [59].

2.11. *Nigella sativa, Thymus vulgaris* and *Zataria multiflora:* *Thymus vulgaris* and *Zataria multiflora* are Lamiaceae plants with significant levels of thymol and carvacrol, two important natural monoterpenoid phenols. Camphor, 1,8-cineole, α-pinene, and camphene are also found in *T. vulgaris* essential oil. Alkaloids, phenolic compounds, flavonoids, essential oils, tannins, triterpenoids, steroids, and saponins are among the active components found in the methanolic extract of *T. vulgaris* leaves [60].

2.11.1. Mechanisms of wound healing

2.11.1.1. Anti-bacterial Mechanisms: The essential oil of *T. vulgaris* and its primary components have anti-bacterial and anti-fungal properties. *T. vulgaris* essential oil was tested for anti-bacterial activity against Gram-negative and Gram-positive bacteria, and it was shown to have bacteriostatic activities against all test species. Another research used the microdilution broth technique to assess the anti-bacterial activity of *T. vulgaris* essential oil and its primary components and the interactions between chosen compounds against a range of microorganisms. Thymol and carvacrol, two powerful monoterpene phenols found in *T. vulgaris* essential oil, were the most active ingredients, with MIC values ranging from 0.125 µg/mL – 1 µg/mL, while linalool was moderately active and *p*-cymene, borneol, α-terpinene, and α-terpinene were inactive. Synergistic interactions between thymol and *p* cymene were detected against four pathogens, but no synergistic interactions were observed between

the highly active ingredients. *E. coli* was used to test the anti-bacterial mechanism of carvacrol and thymol. Carvacrol and thymol at 200 µg/L suppressed *E. coli* growth, according to the results of the time-kill curve.

This work's anti-bacterial activity of carvacrol and thymol is proven by permeability and depolarization of the cytoplasmic membrane. Scientists also believe that thymol's anti-bacterial impact is due to disruption of the lipid component of the bacterial plasma membrane, which causes changes in membrane permeability and intracellular material leakage. Furthermore, delocalized electrons in thymol and carvacrol enable proton exchange from the hydroxyl group, resulting in a pH gradient across the cytoplasmic membrane [61].

2.11.1.2. Anti-oxidant Mechanisms: Anti-oxidant activity is found in *T. vulgaris* and *Z. multiflora*, as well as their active components thymol and carvacrol. The anti-oxidant activity of *T. vulgaris* essential oil was tested using two distinct extraction methods: steam distillation and organic solvent extraction (a mixture of essential oil and other non-polar compounds).

The findings revealed that the anti-oxidant capacity of steam-distilled essential oil was marginally greater than that of the lipophilic fraction produced by solvent extraction. The anti-oxidant activity of *Z. multiflora* essential oil was tested *in vivo* at dosages of 100 µL/ kg, 200 µL/ kg, and 400 µL/ kg. In a dose-dependent manner, *Z. multiflora* showed high DPPH scavenging action, notably at dosages of 200 µL/ kg and 400 µL/kg. It also reduced thiobarbituric acid reactive compounds and prevented lipid peroxidation in a dose-dependent manner. Thymol is a free radical scavenger with an IC_{50} value of 0.538 ± 0.02 µg/mL for anti-oxidant activity against DPPH [62].

2.11.2. Effect on Different Stages of Wound Healing: Inflammatory cytokines and oxidative stress are modulated by thymol and carvacrol, which also have anti-bacterial properties. Several studies on the anti-inflammatory effects of thymol and carvacrol revealed that these natural isomers could reduce the expression of pro-inflammatory cytokines like TNF-α, IL-1, IL-6, IL-8, IL-17, IL-25, and IL-33 while increasing the expression of anti-inflammatory cytokines like IFN-γ and Forkhead box protein P3 (FOXP3).

Thymol and carvacrol influence the synthesis of nitric oxide and TGF-1 as well. Carvacrol efficiently inhibits COX-2, but thymol has an IC_{50} value of 0.2 µM and is a powerful COX-1 inhibitor. In addition, with IC_{50} values of 0.1 µM and 0.3 µM, thymohydroquinone and thymoquinone from *N. sativa* seeds showed an inhibitory impact on COX-2. Thymol and carvacrol induce re-epithelialization, angiogenesis, granulation tissue development, and collagen fibre deposition in the proliferation phase via increasing vascular endothelial growth factor (VEGF) and TGF- expression. These natural substances influence fibroblast metabolism as well as collagen formation, resulting in the full replacement of type-III collagen with type-I collagen.

Thymoquinone, thymohydroquinone, thymol, and *p*-cymene are some of the active ingredients found in *N. sativa* seeds. The wound healing properties of *N. sativa* and thymoquinone in animal models have been documented in a thorough study. The immuno-modulatory and anti-inflammatory properties of thymoquinone have been studied in a number of investigations. The anti-inflammatory activities of thymoquinone are linked to its suppression of the manufacture of key mediators in inflammatory processes such iNOS, COX-2, prostaglandin-E_1 (PGE_1), PGE_2 and LPS-induced pro-inflammatory cytokines (IL-1β, IL-5, IL-13, and TNF-α). Thymol and carvacrol are engaged in the wound healing process at all stages. Thymol and carvacrol's anti-bacterial action and their modulatory influence on inflammatory cytokines and oxidative stress help with wound healing hemostasis and inflammation. In the proliferation phase, they also speed up re-epithelialization, angiogenesis, fibroblast proliferation, and granulation tissue formation. Thymol and carvacrol promote collagen deposition, speed wound closure, and alter the proliferation of fibroblasts and keratinocytes in the final stage. *In vitro* and *in vivo* tests were used to evaluate the anti-bacterial effectiveness and wound healing activity of electrospun thymol-loaded polycaprolactone mats. Wounds treated with thymol-loaded polycaprolactone mats showed no inflammatory

response and just a few layers of coagulative necrosis on the surface of the exposed part of the wounds, according to immunohistochemical and histological findings.

Thymol-rich carpets also helped to prevent infection and speed wound healing. The control group, which was just treated with polycaprolactone mats, had significant widespread necrotizing dermatitis in the wound region and huge infiltrations of inflammatory cells (macrophages and lymphocytes). In the wound region, there was also severe tissue necrosis. The inflammatory reaction impacted all layers of the skin, even reaching the adipose tissue, and bacteria colonies were seen on the surface. Compared to the thymol wound dressing group, chlorhexidine as positive control showed no inflammatory response but a much thicker layer of coagulative necrosis on the exposed surface of the wound.

Chlorhexidine effectively eliminates microbial contamination on the wound bed, but its effect is short-lived, and repeated doses may delay wound healing. Thymol-loaded carpets gently release thymol at the wound site, preventing local toxicity from recurrent chlorhexidine exposure. In diabetic male rats, the effects of *N. sativa* were studied. The length of wound healing for the non-diabetic untreated group, non-diabetic phenytoin (1 percent)-treated group, and *N. sativa* (20 percent and 40 percent)-treated groups was 23-days, 21-days, 18-days, and 15-days, respectively, according to the data. Diabetic lesions treated with *N. sativa* extract exhibited a very minimal amount of inflammatory multinuclear cells, according to histological data (neutrophils). As a result, the inflammatory phase of wound healing was lower in diabetics who were not treated and diabetics who were treated with phenytoin. In diabetic rats, *N. sativa* extracts enhanced wound healing [63].

2.11.3. Methods of application: As a wound dressing, nanofibrous cellulose acetate/gelatin loaded with *Z. multiflora*-nanoemulsion significantly increased L929 fibroblast cell adhesion and proliferation as well as anti-bacterial activity against *S. aureus* and *E. coli*. The capacity of this wound dressing to significantly speed the wound healing process was shown in an *in-vivo* investigation on a full-thickness burn wound model. The zein/thyme essential oil nanofibers were electrospun in situ onto the wound site of mice lately, and the results showed that the wound healed completely after 11-days.

Furthermore, nanofibrous membranes made of zein/poly (ethylene oxide) and thyme essential oil showed extreme hydrophilicity and efficiently absorbed wound exudate. Another wound dressing with a nanofibrous scaffold was made using chitosan and poly(ethylene oxide) as a co-spinning agent. Then thyme extract (3 percent) was electrospun into the scaffold to aid wound healing. The anti-bacterial activities of this nanofiber were also proven against *E. coli*, *S. aureus*, and *P. aeruginosa*. The inhibitory effect of these monoterpenoid phenols may be described as interactions with the cell membrane of microorganisms, which is also linked to their hydrophobicity.

It was also discovered that a wound dressing made up of chitosan film and 1.2 percent thyme essential oil had a very strong anti-oxidant effect, owing to the presence of carvacrol in thyme oil. *In-vitro*, *ex-vivo* and *in-vivo* tests were used to evaluate the anti-bacterial activity of thymoquinone-loaded polyvinyl pyrrolidone (PVP) film and hydrogel against *S. aureus*. In an *in-vitro* test, *S. aureus* was fully inhibited and no germs grew in the presence of thymoquinone film and hydrogel. Gentamicin, on the other hand, suppressed *S. aureus* growth in a dose-dependent manner. Furthermore, an *ex-vivo* experiment on human cadaver skin indicated full eradication of microorganisms in the presence of thymoquinone film. Thymoquinone film showed a significant decrease in S. aureus infection in mice in a full-thickness wound infection model. In an *in-vitro* wound closure experiment, when human keratinocyte monolayers were scratched, the thymoquinone treatment group (100 ng/mL thymoquinone) showed 85 percent wound closure on day-6 compared to the control group (50 percent wound closure). Using an electropining apparatus, many nanofiber scaffolds of PVA-*N. sativa* extract were produced, and they showed outstanding anti-bacterial activity against *S. aureus* and *E. coli* [64].

2.12. *Punica granatum*: The Punicaceae family includes *Punica granatum*, often known as pomegranate, and its different sections have been

exploited as sources of bioactive chemicals with potential biological activity. Phenolic acids, hydrolysable tannins, ellagitannins (punicalagin and punicalin), flavonoids (flavonols, flavones, and anthocyanidins), ellagic acid, epicatechin, epigallocatechin, and their derivatives are abundant in *P. granatum*. Ellagic acid, found in numerous regions of the pomegranate and possesses anti-oxidant, anti-bacterial, and anti-inflammatory activities, is the key active component [65].

2.12.1. Mechanisms of Wound Healing:

2.12.1.1. Anti-bacterial Mechanisms: Several researches have looked at the anti-bacterial action of pomegranate extracts. The findings indicate that Gram-positive bacteria are more susceptible to them than Gram-negative bacteria. Against a wide range of bacteria and fungi, the hydroalcoholic extract of pomegranate peel showed high anti-bacterial and antifungal activity. Purified pomegranate juice byproduct fractions have significant anti-bacterial activity against MRSA and *E. coli*, with an IC_{50} of 50 μg/mL. *P. granatum* has a lot of phenolic compounds.

The interaction of phenolic components with sulfhydryl groups of proteins seems to be the fundamental mechanism of phenolic component toxicity to microbes, rendering substrates unavailable to bacteria. *S. aureus* growth and the formation of enterotoxins were both suppressed by *P. granatum* extracts [66].

2.12.1.2. Anti-oxidant Mechanisms: Pomegranate arils, juice, and peel extracts all showed high anti-oxidant activity. At 50 ppm, a methanolic extract of pomegranate peel demonstrated strong DPPH scavenging action. With IC_{50} values ranging from 0.33 μg/mL to 11 μg/mL, total tannins and isolated components (*e.g.*, ellagic acid and punicalagins) from pomegranate fruit displayed significant anti-oxidant activity and decreased ROS generation [67].

2.12.2. Effect on Different Stages of Wound Healing: In an animal model, the wound healing ability of *P. granatum* peel extract was investigated as a topical gel (2.5 percent and 5 percent) against an excision wound. Estimation of collagen levels in terms of hydroxyproline content revealed that the 5 percent topical gel-treated group had around twice as much hydroxyproline as the control group, resulting in a wound healing period (10-days) that was faster than the control group (16 days - 18 days). In an animal model of profound second-degree burns, pomegranate peel extract showed a significant reduction in inflammatory cells, quicker creation of granulation tissue, and avoidance of infection. The efficacy of topical ointments containing ellagic acid (2.5 percent) and pomegranate extract standardized to 40 percent ellagic acid (2.5 percent, 5 percent, and 7.5 percent) on albino rat incision wounds were evaluated in two different experiments by the same authors.

Both investigations found that ellagic acid ointments reduced polymorphonuclear neutrophil (PMN) cell infiltration while increasing collagen production and angiogenesis, resulting in a faster wound healing process. Better outcomes were found when the amounts utilised were comparable to the ideal dosage of pure ellagic acid (100 percent).

This suggests that the numerous components contained in pomegranate extract standardized to 40 percent ellagic acid may have a synergistic or additive impact. An investigation of the wound healing efficiency of pomegranate whole fruit extract standardized with 40 percent ellagic acid in the form of ointment (10 percent) found a high density of collagen with a reasonable arrangement in a deep second-degree burn lesion in another research.

The major ingredients of pomegranate peel extract, punicalagin-A, and punicalagin-B, include 16 dissociable hydroxyl groups, which are responsible for the peel extract's free radical scavenging and anti-oxidant properties. The researchers created a pomegranate peel extract hydrogel and tested its long-term and accelerated stability. Punicalagin is stable under stressful storage circumstances, according to the results. Punicalagin-loaded polyvinyl alcohol nanofibers were used as wound dressings. The treatment group had a higher mean level of total anti-oxidant capacity (372.05 μM) than the control group (303.1 μM), suggesting that it may help with wound healing's inflammatory stage. Pomegranate peel extract efficiently avoided infection and hastened the healing of a deep second-degree burn lesion in an animal model, preventing the development of hypertrophic scars.

In the pomegranate peel extract-treated group, histological data indicated that many new collagen fibres were generated, inflammatory cells were greatly decreased, and a considerable number of fibroblast and granulation tissues developed on day-14. On day-21, rats given pomegranate peel extract developed fleshy buds with blood vessels and fibroblasts, while inflammatory cells were removed and replaced with new granulation tissue, resulting in quicker epithelialization and wound healing.

On day-15, microscopic examination of a severe second-degree burns model treated with standardised pomegranate extract containing 40 percent ellagic acid revealed minimal inflammatory cells, moderate collagen bundles, and mature re-epithelialization. The efficacy of pomegranate peel extract based-gel on excision wounds in alloxan-induced diabetic rats was examined in two different experiments. The pomegranate peel extract gel increased the expression of growth factors such TGF-β1, EGF, and VEGF, according to the results. When compared to the control group, pomegranate peel gel therapy boosted fibroblast proliferation and collagen regeneration in diabetic rats' wound tissues, according to histological testing. The diabetic group that received pomegranate peel gel exhibited higher hydroxyproline levels in wound tissues than the diabetes group. Compared to the control group, pomegranate peel extract dramatically accelerated epithelialization and boosted neovascularization in diabetic wound tissues [68].

2.12.3. Methods of Application: Researchers created a polymeric film using pomegranate peel extract (1.25 percent w/v and 2.5 percent w/v) that included polyvinyl alcohol, starch, and polyacrylic acid. Films containing the lower concentration (1.25 percent) of pomegranate peel extract had anti-bacterial activities against *S. aureus* and *S. epidermidis*, but the difference was not statistically significant when compared to films having a greater concentration (2.5 percent). In the lower concentrations of peel extract, it was also non-hemolytic, non-toxic, and biocompatible. With an IC_{50} value of 1.715 μg/mL, the standard extracts of *P. granatum* placed on biointeractive gelatin-based membrane included 32.24 mg/g gallic acid and 41.67 mg/g ellagic acid, providing strong anti-oxidant effectiveness. In an animal model, this membrane significantly improved wound contraction rates on day-3, day-7, and day-14 compared to the control group [69].

2.13. *Rheum officinale* and *Polygonum cuspidatum*: Polygonaceae plants like *Rheum officinale* and *Polygonum cuspidatum* are high in anthraquinones such emodin, aloe emodin, rein, and chrysophanol. Wound healing and skin problems are treated with *R. officinale* root and *P. cuspidatum* entire plant [70].

2.13.1. Mechanisms of Wound Healing:

2.13.1.1. Anti-bacterial Mechanisms: Emodin's ability to impair cellular metabolism has given it anti-bacterial effectiveness against a wide range of infections. Emodin was shown to have anti-bacterial properties against *E. coli*, *P. aeruginosa*, and several MRSA strains. Scientists looked into emodin's anti-bacterial mechanism against *S. aureus*. They discovered that *S. aureus* had a lower total protein concentration. Emodin's anti-bacterial properties against *S. aureus* are mediated via bacterial membrane rupture, protein synthesis inhibition, and reduced succinate dehydrogenase and malate dehydrogenase actions on oxidative respiratory control [71].

2.13.1.2. Anti-oxidant Mechanisms: Emodin's anti-oxidant action is mediated by a variety of pathways, including the inhibition of radical production, radical scavenging activity, and anti-oxidant defence strengthening. Emodin also reduces lipid peroxidation, and its mechanism is assumed to be based on inhibiting lipid peroxyl radical propagation in the mitochondrial membrane. Emodin has a stronger inhibitory effect against lipid peroxidation than α-tocopherol. For inhibiting oxygen consumption and malondialdehyde formation, emodin had IC_{50} values of 12.5 μM and 16.8 μM, respectively, whereas α-tocopherol had IC_{50} values of 102 μM and 94.7 μM [72].

2.13.2. Effect on Different Stages of Wound Healing: Collagen expression is regulated by many signalling pathways, including the focal adhesion kinase (FAK), p38 MAPKs, ERK pathway, AKT pathway, and AMPK. Emodin stimulates the ERK1/2 and AMPK pathways in Hs27 fibroblasts

by causing a 2.5-fold increase in phosphorylation of ERK1/2 and AMPK 3 hours after treatment. The role of each route in collagen production was determined using standard chemical inhibitors. The results showed that blocking the AMPK pathway lowered emodin-induced collagen levels, showing that emodin-induced AMPK activation was responsible for collagen production. Inhibition of the ERK1/2 pathway, on the other hand, had no impact on emodin-induced collagen expression.

Emodin boosts type I collagen expression while leaving the collagen breakdown pathway (cellular matrix metalloproteinase-1 (MMP-1) expression) and cellular viability untouched. TGF-β signalling is a multifunctional cytokine that plays a vital role in collagen expression regulation. Fibroblasts produce TGF-β1 and it aids wound healing by increasing the development of granulation tissue and collagen. Because Smad2 phosphorylation was equal in both the vehicle and emodin treatments in Hs27 fibroblasts, the researchers concluded that TGF-β signalling is not involved in emodin-induced collagen formation. On the other hand, researchers discovered that treating excisional wounds with emodin (derived from the roots of *Rheum officinale*) for 7-days increased TGF-β1, Smad2, and 3 protein expression as well as collagen levels. The efficacy of *P. cuspidatum* extract on wound healing was investigated in an animal model and immunohistochemical findings revealed that the number of TGF-β1 positive cells in the extract group was significantly higher than in the control group. In contrast to the control group, mice treated with *P. cuspidatum* extract exhibited quicker epithelialization and angiogenesis, a higher rate of fibroblast cell proliferation, better-ordered collagen bands, and less inflammatory cells in their granulation tissue. The impact of emodin gel on hypertrophic scars was studied.

The stimulation of fibroblast proliferation leads to the accumulation of a substantial number of improperly produced ECM proteins as well as the secretion of a range of cytokines and substances, resulting in hypertrophic scarring. According to the results, emodin slowed the proliferation of fibroblasts in the immediate region and reduced the hardness of hypertrophic scars. The PI3K/Akt signalling pathway was dramatically suppressed by emodin, which lowered the expression of TNF-α, IL-6, and MCP-1 in hypertrophic scar tissue. Emodin also reduced TGF-α and IL-1 expression in hypertrophic scar tissue. When compared to the control group, emodin therapy substantially modified the histology condition and histopathological scores on day-14. During the early proliferative phase, the adhesion and interaction of inflammatory cells with topical fibroblasts results in an extensive and continuous inflammatory response, leading to hypertrophic scars. Emodin decreased the cell-cell contact between inflammatory cells and hypertrophic scarring fibroblasts, which lowered the inflammatory response in hypertrophic scars [73].

2.13.3. Methods of Application: Emodin (derived from *P. cuspidatum*) was encapsulated in ultra-fine cellulose acetate fibre mats using an electrospinning process. The behaviour of emodin release is regulated by the quantity of loaded herb, according to the release study of these fibre mats. The maximal release of emodin from fibre mats containing 0.01 percent, 0.05 percent, and 0.1 percent was around 41 percent, 76 percent, and 88 percent, respectively. The cytotoxicity results revealed that cellulose acetate fibre mats containing emodin were not harmful to human dermal fibroblast-adult cells. However, with an increase in emodin concentration from 0.005 percent to 0.1 percent, cell viability reduced marginally from 96.8 percent to 87.2 percent. The fibre mats with 1.0 percent emodin, on the other hand, exhibited the highest reduction in cell viability (31.6 percent) [74].

2.14. *Zingiber officinale*: Ginger (*Zingiber officinale*) includes various physiologically active chemicals such as gingerols, shogaols, flavonoids, diterpenoids and sesquiterpenoids in its rhizome, which is widely used as a spice and condiment. The main pungent chemicals are zingerone, shogaols, and gingerols. The anti-inflammatory properties of ginger are attributed to gingerols and shogaols [75].

2.14.1. Mechanisms of Wound Healing:

2.14.1.1. Anti-bacterial Mechanisms: With MICs of 1 mg/mL and 2 mg/mL and minimal bactericide concentrations (MBCs) of 2 mg/mL and 4 mg/mL, ginger essential oil showed anti-bacterial activity against *S. aureus* and *E. coli*, respectively. Using the SDS-PAGE technique, researchers looked into the underlying anti-bacterial mechanism of ginger.

Adding ginger essential oil caused the bacterial cell protein bands to vanish, resulting in a significant increase in the nucleic acid content of the bacterial solution. Some genes involved in bacterial energy metabolism, the tricarboxylic acid cycle, DNA metabolism, and cell membrane-related proteins may be suppressed by ginger essential oil. Ginger's main pharmacologically active component is 6-gingerol. Its anti-bacterial activity was tested against *P. aeruginosa*, and its mechanism was investigated. 6-Gingerol inhibited quorum sensing receptors, which decreased biofilm formation and numerous virulence factors in *P. aeruginosa*. 6-gingerol interacts to the quorum sensing receptor LasR through hydrophobic contacts and hydrogen bonding, according to in silico research. The aromatic ring of 6-gingerol contributes to its antagonistic characteristics, while the lengthy alkyl chain and carbonyl group serve to give specificity for the LasR receptor [76].

2.14.1.2. Anti-oxidant Mechanisms: With IC_{50} values of 0.4 mg/mL and 4.25 mg/mL, ginger extract had a free radical scavenging action on the ABTS cation radical and DPPH, respectively. Ginger extract also reduced lipid peroxidation and enhanced anti-oxidant enzymes, including SOD, CAT, and GSH's intracellular activity. The addition of ginger extract improved the plasma anti-oxidant capacity in diabetic rats, lowering lipid peroxidation. In LPS-stimulated murine macrophages, 6-gingerol inhibited I-κB and NF-κB activation, lowering the production of iNOS and TNF-α. In oxidative stress processes, the mitochondrial membrane potential is disrupted. 6-Gingerol reduced intracellular Ca^{2+} excess, which reduced mitochondrial membrane potential disturbance and ROS generation [77].

2.14.2. Effect on Different Stages of Wound Healing: In rats, when ginger extract was given orally to heal incision wounds, the number of neutrophil cells in the proliferative and maturation stages decreased. In rats, ginger extract administration enhanced fibroblast cell numbers and hastened epithelialization during the proliferation phase. In mouse fibroblast cells, ginger extract altered cell motility and heat tolerance. The Akt/mTOR signalling pathway was activated after ginger extract enhanced phosphorylation of Akt and mTOR. It also increased intracellular phosphatidylinositol 3 phosphate (PI3P) levels, which controlled cell shape and encouraged cell migration. The Akt pathway influences cell proliferation in a range of cell types, including mononuclear macrophages and epithelial cells. After 16 hrs, fibroblasts treated with ginger extract developed laminapodia along the cell's borders, limiting the wound area and boosting cell migration, according to microscopic examinations. In mouse fibroblast cells, ginger extract also stimulated the ERK and p38 MAPK pathways. In this context, the ERK/MAPK signalling pathway is a critical regulator of cell proliferation, differentiation, and migration. Collagen deposition wound contraction, and re-epithelialization are all aided by ginger extract. In wound-infected albino rats, ginger ethanolic extract's wound healing and anti-bacterial activities were investigated and compared to *Fusiderm* ointment as a standard therapy.

Wound healing was quicker in both the positive control and ginger treatment groups, with percentages of 55.7 percent and 51.4 percent on day-4 and 91 percent and 90.6 percent on day-8, respectively. On day-4, the Fusiderm ointment and ginger treatment groups both exhibited a high number of leukocytes, macrophages, collagen fibres, and moderate epithelialization, but the negative control group had no collagen fibres development. On day-8, ginger's anti-microbial action and enhanced epithelialization reduce inflammatory cells, while the negative control group had persistent inflammatory cells. Due to increased fibroblast and epithelial cell migration to the wound site, both the ginger and *Fusiderm* ointment groups had significantly greater collagen levels than the negative control group.

A burn wound animal model was used to test the wound healing efficiency of ginger extract-loaded hydrogel films. On day-16, the ginger extract-loaded hydrogel films substantially increased fibroblast proliferation, granulation tissue development, collagen re-modelling, and re-epithelialization compared to the control group, according to histological analyses. Effects on wound healing circumstances that are delayed or changed Al-Scientists investigated the effects of 6-gingerol-fractions (25 mg/kg of body weight) alone or in conjunction with vitamin D (100 ng/kg per

day) on diabetic wound healing and micro-RNA expression in an animal model. MicroRNAs are single-stranded non-coding RNA molecules that are used for RNA silencing, posttranscriptional gene regulation, and as regulatory biomarkers for type-2 diabetes and associated consequences, such as chronic wounds. Treatment of diabetic wounds with 6-gingerol fraction, vitamin D, and 6-gingerol fraction in conjunction with vitamin-D resulted in downregulation of miR-155 expression and upregulation of miR-146a and miR-15a expression, according to the results of this research. In diabetic wounds treated with 6-gingerol fraction, higher amounts of hydroxyproline, fibronectin and collagen expression were discovered, resulting in a quicker rate of wound closure, complete epithelialization, and scar formation [78].

2.14.3. Methods of application: The researchers created 6-gingerol-loaded cellulose acetate films and fibres using an electrospinning method. According to their controlled release investigation, around 97 percent and 74 percent of 6-gingerol could be released from associated fibres and films into the acetate buffer solution within 4 hours, respectively. Water absorption and 6-gingerol release from the loaded fibres were quicker than the film due to the large number of pores and high surface area. The viability of L929 murine fibroblast cells to 6-gingerol-loaded fibres was determined to be 65 percent using a cytotoxicity test. Using chromatographic and computational approaches, as well as an *in-vivo* examination to measure wound contraction progress, the relationship between wound healing activity and the lipophilicity of 6-shogaol, 6-gingerol, 8-gingerol, and 10-gingerol was investigated. Because 6-shogaol (which has greater lipophilicity than other compounds) exhibited the highest wound healing activity, followed by 10-gingerol, 8-gingerol, and 6-gingerol, the outcomes of this research suggested a significant association between lipophilicity and wound healing capabilities of active compounds [79].

CONCLUSION: Due to their acceptable degree of safety, numerous modes of action, and anti-bacterial activity, medicinal plant extracts and their purified active principles have significant potential to be employed as wound healing therapies, according to many *in-vivo* and clinical trial investigations. Novel wound dressing formulations provide several benefits over traditional dressings. They may be utilized to solve some of the disadvantages of natural materials, such as solubility and wound site activity. Future research is required to understand the mechanisms of action of the most promising natural substances, focusing on their effects on cell-surface receptors (particularly receptor tyrosine kinase). In terms of the chemical structure of most active natural compounds, quinone derivatives seem to be one of the most promising structures that might be investigated further in future research.

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