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Review Article

Significant Natural Wound Healing Agents: Herbs and Single Bioactive Principles

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Abstract: Wounds are caused by skin injuries that damage the soft tissue. Wound healing is a dynamic process that involves a series of interconnected cellular and molecular processes that result in the restoration of anatomic continuity and function. Herbal therapy has been gaining popularity recently because of plants' usefulness in treating ailments with hardly any negative effects. Over the years, a variety of plant items have been developed and utilized to heal wounds. Throughvarious mechanisms, herbal extracts aid in blood clotting, infection prevention, and wound healing. This review provides a comprehensive look at herbal therapy's potential for hastening wound healing, as well as its antioxidant, anti-inflammatory, and anti-microbial properties that can be manifest in the treatment of injuries, as well as a first attempt at developing new wound-healing formulations with high potency for human use. Furthermore, we have highlighted medicinal plants as natural antioxidant resources in wound repair and healing.

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1. Introduction

In clinical practice, chronic wounds are among the most significant health issues and are considered with a high impact on social health, mainly in elderly people suffering from chronic diseases like diabetes, chronic motor deficit, nutritional abnormalities, cardiovascular diseases, and obesity. These ailments are accompanied by alterations in wound healing mechanisms and skin repair. An injury or wound is a disruption of tissue's cellular and anatomic continuity, or breaks in the skin's epithelial integrity, or a tear in the cellular, anatomic, or functional continuity of living tissue, with or without microbial infection. It can occur with the exploitation of tissues through physical, chemical, thermal, microbial, or immunological means (Lazarus et al., 1994). Chronic wounds affect nearly 60 lakh people worldwide, as per the latest projections. When a wound does not heal properly, it causes inflammation, pain, and swelling in the wound area. Chronic wounds can often cause multiple organ failures in patients (Kumar et al., 2007). Wound recovery begins with a complicated series of interconnected events that are arbitrated by a diverse variety of chemically coordinated biological processes in addition to hormonal influences. These events are mediated through the inflammatory phase, proliferate phase, and finally, the remodeling phase by a wide range of chemically coordinated cellular functions as well as hormonal influences (Chan et al., 2008).

As per WHO reports, traditional remedies are used by more than 80% of the world's population to cure various diseases. Plants and their derivatives are now being used in 25 percent of medical drugs in developed countries (Priya et al. 2002; Steenkamp et al., 2004). Besides, chemical therapeutic agents have inadequate efficacy as well as serious adverse effects. Therefore, natural remedies have been used in medicine for a long period since ancient times for their abilities to encourage wound healing safely without fatal side effects. Natural treatments may be utilized to treat wounds as an alternate technique.
Considering that fatty acids, phytosterols, tocopherols, phenols, and flavonoids derived mainly from plant origin possess important antioxidant, nourishment, protection, soothing potentials, act as stimulators of cell metabolism for fibroblasts, enhance the ability of herbal preparations to promote and hasten the healing process in chronic skin wound (Ragno et al., 2016).

Hence, this systematic review highlights the herbs that can be used for wound healing complications, the phytoconstituents responsible for this activity, and their mechanism of action. Scientific databases like PubMed, Science Direct, and Google Scholar were searched using different keywords.

2. Classification of Wounds

Classification of wounds is characterized into two types such as open wounds or closed wounds based on the primary cause of wound formation and as acute or chronic wounds based on the physiology of wound healing.

2.1. Open wound

In this case, blood exits the body with prominent bleeding. It can also be classified as an incised wound, a laceration wound, or a tear wound. Penetration wounds, abrasions, puncture wounds, and gunshot wounds are all examples of superficial wounds (Mickelson et al., 2016).

2.2. Closed wound

Blood leaves the circulatory system and collects in closed wounds. Contusions or bruises, hematomas or blood tumors, and crush injuries are all examples (Menke et al., 2007).

2.3. Acute wound

These wounds are most caused by small cuts or surgical incisions, and they heal within the expected time frame. Tissue damage in an acute wound is usually caused by a systematic and timely process that leads to the tissue's structural and functional integrity being restored (Shaw and Martin, 2009).

2.4. Chronic wounds

These types of wounds have not finished the normal healing stages and have thus become inflamed for an extended period. Chronic wounds require a long healing time, or they will recur frequently. Trauma, Local infection, hypoxia, foreign bodies, and systemic problems such as diabetes, malnutrition, immunodeficiency, and medication are the most common causes (Roberts et al., 1998).

3. Phases and Mechanisms of Wound Healing

The body's reaction to injury, whether surgically or traumatically induced, is instant, and the harmed tissue goes through three phases: inflammation, proliferation, and remodeling. A description of each phase is given below:

3.1. Inflammatory phase

This begins instantly after the wound and lasts for 24 to 48 hours. In certain cases, it can last up to two weeks. The hemostatic mechanisms immediately stop bleeding from the wound site in this step. Clinically identifiable cardinal signs of inflammation, such as rubor, fire, tumor, and pain, result from this effect. Coagulation in the blood is caused by platelet aggregation and vasoconstriction, which is followed by vasodilation and phagocytosis, which promotes inflammation in the wound area. (Li et al., 2007).

3.2. Proliferative phase

The proliferative phase can last anywhere from 2 to 3 weeks. Granulation, contraction, and epithelialization are the three steps in this phase. During the granulation process, fibroblasts fill the gap with collagen and produce new capillaries. Wound edges are contracted, reducing the defect, and epithelial tissues form throughout the wound site. The proliferative phase, which is common in skeletal muscle injuries, involves the production of repair material (Guo and Dipietro, 2010).

3.3. Remodeling phase

This stage can last anywhere from 3 weeks to 2 years. During this phase, more collagen is produced. The tensile strength of tissues improves because of the intermolecular cross-linking of collagen caused by vitamin-C-dependent hydroxylation (Guo and Dipietro, 2010).

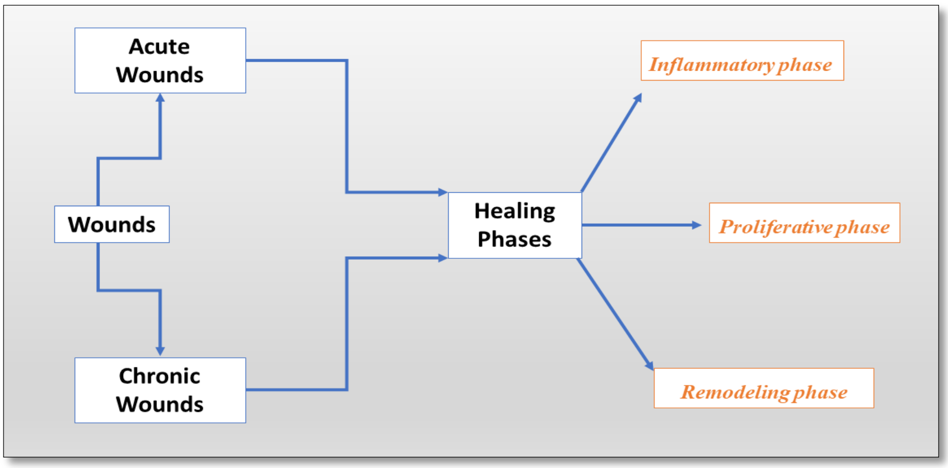


Figure 1. The Phases of wound repair.

4. Role of Natural agents in Wound Healing

Natural extracts were suggested to work with several mechanisms to possess the wound healing activity. Extracts are extensive mixes of many chemical classes that operate together through various methods to produce a safe and synergistic effect on the proposed activity. They have several effects that all help with the wound healing property as being antioxidants, anti-inflammatory, and anti-angiogenic, in addition to cell signaling factors which all lead to enhanced wound healing activity (Sivamani et al., 2012).

Natural compounds are one of the greatest sources of antioxidants, such as polyphenols and flavonoids, which have a radical scavenging effect and control oxygen levels at the injured area, resulting in improved and faster healing.

Natural extracts also control the inflammatory phase that is achieved by decreasing the inflammatory responses of the cells, inhibiting NF-kB, targeting the inflammation pathways, either intracellular transcription or transduction, and downregulating the levels of the proinflammatory cytokine.

4.1. Pharmacotherapy

Plants' wound-healing abilities have been studied in folklore since then. The curing of wounds is aided by a variety of herbal plants. At this point, plants with substantial wound-healing properties are highlighted.

4.1.1. Adhatoda vasica Nees

Adhatoda vasica Nees*,* known as Chue Mue (Family: Acanthaceae), grows in almost all parts of India as a vine. In an experimental wound healing model in Wistar rats, the breaking strength, tensile strength, absorption and extensibility, and the wound repair tissue was improved by *A. vasica* Nees. Moreover, in animal research, treatment with *A. vasica* showed an increase in levels of elastin, collagen, hydroxyproline, hexosamine, and zinc (Bhargava et al., 1988).

4.1.2. Aloe Vera

Aloe vera (L.) Burm. f. *(*Family: Liliaceae) is one of the eldest medicinal plants identified to humans. Topically used for wounds, burns, bruises, insect bites, acne, blemishes and infections, sores, eczema, skin lesions, and sunburns. A wound excision method was utilized to examine the impact of *A. vera* gel on the healing process, and histopathology was employed to study the influence on wound remedy. The consequence of *Aloe vera* gel concerning wound contraction wound closure, the surface area of the wound, tissue regeneration at the wound area, and histopathological characteristics were significantly improved in treated rats. The effect of *A. vera* gel on biochemical tests showed a significant increase in collagen and a decrease in hexosamine and malondialdehyde levels (Panahi et al., 2020). The active agents accountable for this potential include Acemannan, a mucopolysaccharide present in *A. vera*, which has a major role as a potent macrophage stimulator and activator for T-cell and induces proinflammatory mRNAs transcription (IL-1α, IL-1β, IL-6, TNF-α, PGE2, and nitrous oxide) (Shedoeva et al., 2019).

4.1.3. Andrographis paniculata

Andrographis paniculata (Family: Acanthaceae), known as green chiretta, is mainly used in China, India, and Southeast Asian countries. Experimentally, it significantly enhanced wound closure in rats after treatment with 10% of its aqueous leaf extract (Al-Bayaty et al., 2012). In addition, animals showed a reduction in inflammation, and scarring, while angiogenesis and collagen fibers in healed wounds increased (Al-Bayaty et al., 2012). In surgical open wounds, andrographolide, a bicyclic diterpenoid extracted from the leaves of *A.paniculata*, promoted the healing process. (Sridharan et al., 2021).

4.1.4. Anredera diffusa

Anredera diffusa (Family: Basellaceae) is known as “Lloto” (Moura-Letts et al., 2006). The ethanolic extract of the fresh stem and leaves possesses potent wound healing activity. Oleanolic acid is the main active component of *Anredera diffusa* responsible for its wound healing activity (Moura-Letts et al., 2006).

4.1.5. Azadirachta indica

Azadirachta indica (Family: Meliaceae) is commonly recognized as the Neem tree (Subapriya and Nagini, 2005). It contains various chemical compounds, namely alkaloids, triterpenoids, limonoids, flavonoids, fatty acids, and steroids and their glycosides (Maan, Yadav and Yadav, 2017). Several studies showed that *Azadirachta indica* different extracts possess wound curative potential. It was established that applying a paste made from an aqueous extract of the root bark to a wound greatly increased re-epithelialization, hastened wound healing by elevating protein and hydroxyproline levels, and increased cell proliferation (Maan et al., 2017).

4.1.6. Camellia sinensis

Camellia sinensis (Family: Theaceae), as green tea, or aqueous extracts, are distributed all over Asia and are famous for their biological effects (Yang et al., 2014). The dynamic fundamentals responsible for biological activities along with wound healing properties are the presence of polyphenolic compounds known as catechins (Yang et al., 2014). Epigallocatechin-3-gallate (EGCG) is the most prominent compound which possesses *Camellia sinensis* activity as a proliferation stimulant and promotes keratinocytes differentiation (Hsu et al., 2003). EGCG suppresses TGF-β receptors by modifying TGF-β signaling, reducing MMP-1 and MMP-2 expression, and attenuating collagen type 1 in human dermal fibroblasts. These properties propose that EGCG is an active anti-scarring agent (B. R. Klass, 2010). Besides, EGCG was found to induce keloid shrinkage (Syed et al., 2013) and augment the growth and pathological features of keloids by suppressing STAT3 signaling (Park et al., 2008).

4.1.7. Carica papaya

Carica papaya (Family: Caricaceae) is commonly used to treat different hair disorders. It is frequently used throughout developing nations to efficiently heal several wounds, particularly burns, and it is freely available. The hydroxyproline content and epithelialization of laboratory animals have been substantially increased by *Carica papaya* latex in a preclinical test which also showed an increase in the contraction of wounds (Gurung and Skalko-Basnet, 2009). Different extracts of *Carica papaya* showed wound healing potential as the ethanolic extract of the seeds (Ramdeen et al., 2012), the aqueous leaf extract (Mahmood, 2005), different epicarp extracts (Anuar et al., 2008), the aqueous extract of the roots (Tiwari P., 2011), and the latex (Gurung and Škalko-Basnet, 2009).

4.1.8. Catharanthus roseus

Catharanthus roseus (Family: Apocynaceae) plant is a key well-spring of monoterpenoid indole alkaloid, vincristine, and vinblastine which were found valuable in the treatment of malignancy. In an incision wound model, the extract of *Catharanthus roseus* expanded the wound-breaking strength in rats. The extract-treated wounds showed re-epithelialization faster, and the wound constriction rate was additionally increased in contrast with control wounds (Anom-Dddd, 2013; Nayak and Pinto Pereira, 2006). The mechanism of wound repair takes place by increasing wound contraction and tensile strength (Nayak and Pinto Pereira, 2006).

4.1.9. Chamaemelum nobile

Chamaemelum nobile (Family: Asteraceae) is generally known as chamomile. The major active components of chamomile are chamazulene, alpha-bisabolol, bisabolol oxides present in its volatile oil, and flavonoids which are responsible for most of its biological effects. *Chamaemelum nobile* ointment used to treat wounds accelerates the healing progression by increasing the protein and hydroxyproline levels and increasing propagation of the cells. In addition, it acts as a potent antibacterial in infected wounds (Kazemian et al., 2018).

4.1.10. Centella asiatica

Centella asiatica (Family: Apiaceae) is commonly known as Gotu kola, kodavan, Indian pennywort, and Asiatic pennywort. It is used by several cultures as a wound-healing agent where a topical application on wounds led to a decreased in granulation and scar formation of the wound and increases the skin tensile strength, and prevents inflammatory responses (de Fátima et al., 2008). The main active agent found in *Centella asiatica* responsible for wound healing activity is asiaticoside which yields *in vivo* Asiatic acid by deglycosylation, which stimulates collagen synthesis (Lawrence, 1967).

4.1.11. Curcuma longa

Curcuma longa (Family: Zingiberaceae) is commonly stated as turmeric and haldi in Hindi. It has been documented that *Curcuma longa* possesses antibacterial, antifungal, and anti-inflammatory activity. In an investigation, an animal model tested the possible efficacy of fresh turmeric paste for healing wounds. In 18 rabbits, turmeric paste was compared with honey acting as a topical drug against the control of experimentally produced circular full-thickness wounds. Wound healing was measured on treatment days 0, 3, 7, and 14 based on physical, histo-morphological, and histochemical parameters. The tensile strength on day 14 was assessed. It was found that wound healing in both treatment groups was statistically significantly faster than in the control group (Rao SGV, 2003). Curcumin extracted from *Curcuma longa* showed noteworthy wound healing potential as it acts on different stages of the natural wound healing progression to fasten the process (Akbik et al., 2014). Studies confirmed that Curcumin reduces oxidative stress and lipid peroxidation, inhibits AGEs accumulation (Sajithlal et al., 1998), reduces the activation of TNF-α, IL-1β, and MMP-9, increases the levels of IL-10, SOD, catalase, and glutathione peroxidase (Vinay et al., 2014), increases the anti-inflammatory cytokine IL-10, upregulates the expression of VEGF, TGF-β1, HIF-1α, SDF-1α, and HO-1, as a result, increases new vascular formation (Kant et al., 2015).

4.1.12. Gymnema sylvestre

Gymnema sylvestre (Family: Asclepiadaceae). The leaf is commonly used as an antidiabetic, astringent, salty, digestive, acrid, anodyne, thermogenic, anti-inflammatory, and liver tonic in traditional Ayurvedic medication. Tannins and saponins are important chemical constituents of *Gymnema sylvestre* and possess the potential for wound healing. In a model named excision wound model, orally administered *Gymnema sylvestre* leaves ethanolic extract has been found to substantially raise the wound healing rate. The extract demonstrates high healing potential in granuloma models, excision, incision, and dead space model (Malik, 2009). Besides, the increased wound healing activity of the hydroalcoholic extract is related to the presence of phytoconstituents (flavonoids) which act as free radical scavenging candidates that may act individually or possess synergistic effects (Tiwari et al., 2014).

4.1.13. Heliotropium indicum

Heliotropium indicum (Family: Boraginaceae) is commonly known as Indian heliotrope, Indian Turnsole. The wound healing activity of the methanol, chloroform, petroleum ether, and aqueous isolates of *H. indicum* leaves was investigated in rats using incision, excision (infected and normal), and dead space wound models. In the incision wound infection model, the group of animals treated with methanol ex-tract showed significant healing efficacy with an epithelialization period of 16.23 ± 0.98 days, compared to the group of animals treated with regular nitrofurazone medication, which had an epithelialization period of 13.5 ± 1.54 days. In this model, the treated animals with aqueous and methanol extracts showed considerable improvements in wound breaking strength, reaching 378.63 ± 18.02 g and 478.55 ± 12.63 g, respectively, whereas the other extracts failed to provide meaningful effects (Fayed, 2021).

4.1.14. Hibiscus syriacus

Hibiscus syriacus (Family: Malvaceae) is an ornamental shrub distributed through Eastern and Southern Asia. It showed wound healing effect through the acceleration of wound closure possessing a potential decrease in TNF-α, besides an increase in TGF-β and VEGF levels resulting in the enhancement of re-epithelization, angiogenesis, and perfect epithelial remodeling (Bakr et al., 2021). Various phytochemical studies of different organs of *Hibiscus syriacus* revealed positive triterpenoids (Shi et al., 2014), naphthalene, and lignans (Yeon et al., 2019), coumarins (Yun et al., 2001), sterols and flavonoids, anthocyanidin malonyl glucosides which are suggested to contribute to the wound healing activity of the plant (Yun et al., 2001).

4.1.15. Hippophae rhamnoides

Hippophae rhamnoides (Family: Elaeagnaceae) is regularly known as sea buckthorn (SBT). In an experimental study in rodents, it was discovered that the topical utilization of SBT expanded collagen synthesis and healing at the injury site, as confirmed by an expansion in hydroxyproline, and hexosamine levels and a raise in the expression of collagen type-III. The histological assessments and matrix metalloproteinases (MMP-2 and - 9) expression likewise affirmed the property of wound healing of SBT leaf extract (Upadhyay et al., 2011). Omega-7 extracted from the oil of *Hippophae rhamnoides* increased the telomerase activity and keratinocyte growth factors levels which increase wound healing. As a result, the wound healing activity of *Hippophae rhamnoides* was due to the presence of Omega-7 as one of its constituents (Niimi et al., 2021).

4.1.16. Kigelia pinnata

Kigelia pinnata, known as Sausage of the Bignoniaceae family, is a small tree found in southern, central, and western Africa and India. In Wistar rats, the plant had a significant, positive effect on wound healing. It was found that the plant increases the epithelization speed, thus supporting the conventional claim (Sharma UK, 2010). The key components isolated from *Kigelia pinnata* are hentriacontane, *β*-tocopherol, 3-hydro-4,8-phytene, trans-phytol, (9Z,12Z)-methyl octadeca-9, 12-dienoate and 1,3,3,5,6,6-hexamethylcyclohexa-1,4-diene (Olubunmi Atolani, 2012).

4.1.17. Lawsonia inermis

Lawsonia inermis leaves (Family: Lythraceae) is generally known as henna. It is utilized for treating various complications such as wounds, burns, ulcers, and skin inflammations. Lawsone was also tested for wound repairing operations isolated from leaves. It was estimated that in both excision and incision wound models, the ethanolic extract of henna leaves and lawsone had a strong healing response. However, the topical route in the case of ethanolic extract, along with isolated lawsone, showed more active than the oral administration. Thus, the topical route of ethanol extract can be used for wound healing (Sakarkar DM, 2004). Studies showed that the fatty acids of the oil of *Lawsonia inermis* were responsible for full wound re-epithelialization with the reappearance of skin appendages and well-organized collagen fibers without any inflammatory cells (Rekik et al., 2019).

4.1.18. Lycopodium serratum

Lycopodium serratum (Family: Lycopodiaceae) is known as club moss. The wound healing potential of *Lycopodium serratum* reduces the epithelialization duration and raises wound contraction speed, skin brittle strength, granulation tissue brittle strength, granulation tissue dry weight, and elevated hydroxyproline concentration in an experimental study in rats. Histopathology studies of the granulation tissue of the ethanol extract-treated animals showed fewer macrophages with increased production of collagen, suggesting the efficacy of the ethanol extract in facilitating wound healing. The whole plant is ground in hot water, and the thick paste is thus obtained and applied to sores, cuts, wounds, and burns (Manjunatha BK, 2007).

4.1.19. Morinda citrifolia

Morindacitrifolia (Family: Rubiaceae) is a traditional medicinal plant in Polynesia. It is commonly called noni. The key native uses tend to be leaves as a topical treatment for wound healing. In the preclinical test on day 11, the extract-treated animals demonstrated a 71 percent decrease in the wound site relative to the normal control animals, with a 57 percent decrease in the wound site. Non-treated animals had considerably higher granulation tissue weight and hydroxyproline concentration in dead space wounds than controls. Enhanced wound contracting, decreased epithelial time, higher hydroxyproline content, and histological properties propose that leaf extract should have potential wound healing properties (Shivananda et al., 2009).

4.1.20. Moringa oleifera

Moringa oleifera (Family: Moringaceae) has been used in the Indian diet for centuries. The plant leaves have been documented for anti-tumor, antioxidant, radioprotective, hypotensive, anti-inflammatory, and diuretic properties. The aqueous extract investigated for wound healing activity in experimental animals showed a significant reduction in scar area and wound closure time and a rise in the granuloma breaking force, skin breaking strength, hydroxyproline size, and granuloma dry weight (Rathi et al., 2006).

4.1.21. Radix paeoniae

Radix paeoniae (Family: Ranunculaceae), known as Baishao in China, is a widely used medicinal herb in traditional Chinese medication (TCM). The aqueous extract of *Radix paeoniae* roots was estimated for wound healing properties by excision, incision, and dead space wound models on experimental rats. The parameters considered were tissue breaking strength, epithelialization, wound contraction, and granulation tissue dry weight for study. In comparison to nitrofurazone-treated control rats, the extract indicated potential wound healing characteristics (Malviya and Jain, 2009).

4.1.22. Rosemarinus officinalis

Rosemarinus officinalis (Family: Lamiaceae), known as Rosemary, is an evergreen herb that grows wild in most Mediterranean regions (Alizargar et al., 2012). The ethanolic extract of the leaves showed wound healing activity which was suggested to work through the following mechanisms: increase in the division of fibroblasts and the deposition of collagen, neo-vascularization, enhanced granulation tissue formation, reduction in the action of collagenase, and decrease in the bacterial contamination in wounds due to potent anti-bacterial effect (Alizargar et al., 2012). The main active constituents of the ethanolic extract are quercetin, carvacrol, and caffeic acid. Besides, the essential oil of *Rosemarinus officinalis* accelerates wound healing development in infected wounds (Nejati et al., 2015).

4.1.23. Rubia cordifolia

Rubia cordifolia (Family: Rubiaceae), known as Manjistha, Indian madder. This plant's roots comprise high therapeutic value and are officially recognized. *Rubia cordifolia* possesses broad series of uses such as blood purifiers, anti-inflammatory, immunomodulatory, and antioxidants. The alcoholic extract and hydrogel were investigated to evaluate their healing efficiency on the template of excision wounds in mice. A unique alcoholic extract formulation of the roots was applied topically as a single dose on the excision wound surface. To determine the effect on wound healing, wound area measurement and histopathology studies were performed. In treated mice, the effect created by gel was significant in terms of wound contracting capacity, wound closure, declining wound surface area, tissue regeneration at the wound site, and histopathological characteristics. As a result, this research offers a conceptual foundation for the plant's widespread usage in wound care (Thakur et al., 2011).

4.1.24. Sesamum indicum

Sesamum indicum (Family: Pedaliaceae) is a blossoming plant in the genus Sesamum. Various wild relatives of *Sesamum indicum* are present in Africa, and a more modest number in India. To treat the wounds in the experimental rats, a mixture of Sesamum indicum seeds and oil was made using carbopol at 2.5 percent and 5 percent. The formulation handled in this way showed a considerable decrease in the period of epithelization and a 50% reduction in wound contraction in the excision and burn wound models. The breaking strength also increased noticeably in the incision model. Delivered oils and seeds increased the granulation tissue's breaking strength, dry weight, and hydroxyproline content in the dead space wound model. According to the findings, *Sesamum indicum* seeds have wound-healing properties. (Kiran and Asad, 2008).

4.1.25. Solanum xanthocarpum

Solanum xanthocarpum is a very stably permanent herb, found in south-east Asia, Malaya, and tropical Australia. The methanolic fruit extracts showed notable promise for wound healing in a preclinical investigation in rats. At the time of diagnosis, it was also discovered that the healing tissue's tensile strength was much higher than that of the control (37.5%) (More et al., 2013).

4.1.26. Tephrosia purpurea

Tephrosia purpurea (Family: Leguminosae) is also referred to as "Sarwa Wranvishapaka". The wound healing ability of the aerial part of *Tephrosia purpurea* ethanolic extract in the form of simple ointment was tested in experimental animals using three types of wound models in rats such as incision wound, excision wound, and dead space wound. In terms of wound contraction, tensile strength, histopathological and biochemical parameters such as hydroxyproline content and protein rate, the findings are comparable to generic medication (Fluticasone propionate ointment) (Lodhi et al., 2006).

4.1.27. Terminalia bellirica

Terminalia bellirica (Family: Combretaceae) is commonly called belliricmyrobalan. It's been noted that *Terminalia Chebula* treatment showed wound healing at a higher rate than suggested by increased contraction rates and decreased epithelialization duration. Biochemical tests have shown a substantial rise in total protein, collagen, and DNA content in the granulation tissues of the treated wounds. Hexosamine and uronic acid concentrations have also increased in these tissues (Singh et al., 2019).

4.1.28. Trigonella foenum-graecum

Trigonella foenum-graecum (Family: Leguminoseae) is commonly known as Fenugreek. It is an annual herb where its seeds are mostly used as a spice in many kitchens around the world. The seeds of *Trigonella foenum-graecum* are rich in polysaccharides and saponins, which are responsible for wound healing. A study reported the application of polysaccharides of the seeds of *Trigonella foenum-graecum* in the form of a hydrogel, when applied over the wound area, significantly enhanced the wound healing and lead to the acceleration of the wound closure after 14 days of induction of wound (Ktari et al., 2017).

In addition, many other potential herbs that have been assessed for their wound healing property are recapitulated in Tables (1 and 2). The image of medicinal plants with wound healing activity is prearranged in Figure 2.

Figure 2. Some medicinal plants with wound healing activity.

Table 1. Some common wound healing natural agents and their mechanism of action

Natural agent	Active principles	Suggested mechanism of action	Ref.
Azadirachta indica	paste of stem bark	accelerate the healing process through increasing the protein and hydroxyproline levels and increased proliferation of the cells potent antibacterial in infected wounds.	**(Maan et al., 2017)**
Bee pollen	about 250 substances including amino acids, lipids (triglycerides, phospholipids), vitamins, macro- and micronutrients, phenols, and flavonoids.	Burn wound healing	**(Ragno et al., 2016)**
Centella asiatica	topical application	decreased in granulation and scar formation of the wound and increased the skin tensile strength and prevents inflammatory responses	**(De Fátima et al., 2008)**
Chamaemelum nobile	*Chamaemelum nobile* ointment	significant acceleration and increase in wound healing,	**(Kazemian et al., 2018)**
Gymnema sylvestre	hydroalcoholic extract	presence of phytoconstituents (flavonoids) which act as free radical scavenging candidates that may act individually or possess synergistic effects.	**(Tiwari et al., 2014)**
Hibiscus syriacus	mucilage and petroleum ether extract.	In addition to vascular endothelial growth factor, tumor necrosis factor is accelerated, histopathologically examined, and linked inflammatory parameters are modulated.	**(Bakr et al., 2021)**
Honey	hydrogen peroxide, high osmolarity, acidity, non-peroxide factors, nitric oxide, phenols, and flavonoids.	produces enzymes that contain hydrogen peroxide (a known antimicrobial agent). antimicrobial, debriding, deodorizing, and anti-inflammatory properties and it stimulates the growth of new tissue.	**(Ragno et al, 2016; Rajendran, 2018)**
Lawsonia inermis	Oil	full re-epithelialization of wounds with the reappearance of skin appendages and well-organized collagen fibers without any inflammatory cells.	**(Rekik et al., 2019)**
Lycopodium serratum	thick paste	decrease in the epithelialization duration and increase in wound contraction speed, skin brittle strength, granulation tissue brittle strength, dry weight of granulation tissue, and elevated hydroxyproline concentration	**(Manjunatha, 2007)**
Morindacitrifolia	extract of the plant	enhanced wound contracting, decreased epithelial time, raised hydroxyproline content	**(Shivananda et al., 2009)**
Moringa oleifera	aqueous extract of the leaves	The aqueous extract was tested for wound healing potential in experimental animals, and it was found that there was a significant decrease in wound closure time and scar area and an increase in the skin breaking strength, granuloma breaking force, hydroxyproline size, and granuloma dry weight.	**(Rathi et al., 2006)**
Radix paeoniae	aqueous extract of roots	potential wound healing properties of the extract as compared to nitrofurazone-treated control rats.	**(Malviya and Jain, 2009)**
Rosemarinus officinalis	ethanolic extract of the leaves	An increase in the proliferation of fibroblasts • An increase in the deposition of collagen. • Neovascularisation • An enhanced granulation tissue formation • A decrease in the action of collagenase • A decrease in bacterial contamination in wounds.	**(Alizargar et al., 2012)**
Rubia cordifolia	alcoholic extract formulation of the roots	wound contracting capacity, wound closure, declining wound surface area, tissue regeneration at the wound site, and histopathological characteristics.	**(Thakur et al., 2011)**
Sesamum indicum	Seeds and oil	significant decrease in the time of epithelization and 50 % wound contraction.	**(Kiran and Asad, 2008)**
Solanum xanthocarpum	methanolic fruit extract	significant wound healing potential, a high tensile strength of the healing tissue.	**(More et al., 2013)**
Tephrosia purpurea	the aerial parts	wound contraction, tensile strength	**(Lodhi et al., 2006)**
Terminalia bellirica	Extracts	increased contraction rates and decreased epithelialization duration.	**(Singh et al., 2019)**
Trigonellafoenum-graecum	Polysaccharides from the seeds	enhanced the wound healing process and lead to the acceleration of the wound closure after 14 days of induction of wound.	**(Ktari et al., 2017)**

Table 2. Phytochemicals with wound healing activity

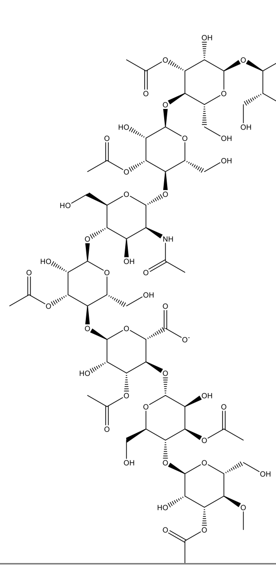
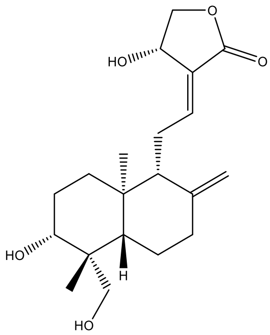
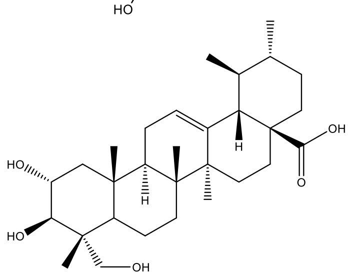
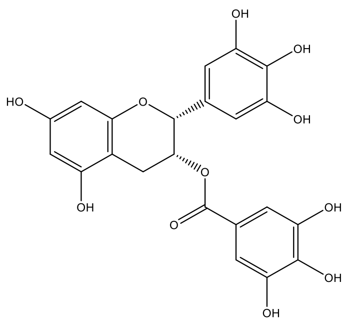
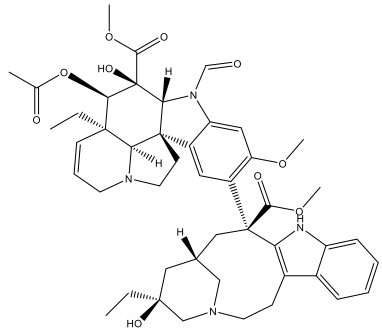
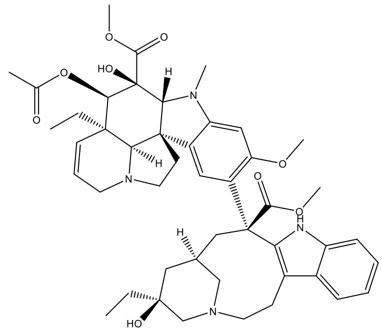
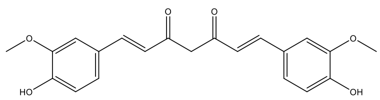
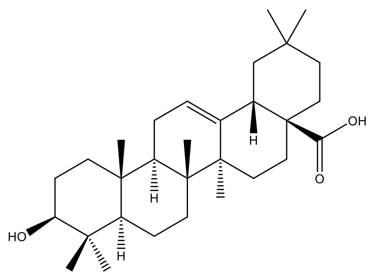
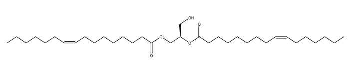
Wound healing agents	Phytochemical class	Structure	Source/ Mechanism of activity	Ref.
Acemannan	mucopolysaccharide		***Aloe vera*** / a potent macrophage stimulator and activator for T-cell and induces proinflammatory mRNAs transcription (IL-1α, IL-1β, IL-6, TNF-α, PGE2, and nitrous oxide).	**(Shedoeva et al., 2019)**
Andrographolide	diterpene lactone		***Andrographis paniculate***/ improved wound healing in surgical open wounds.	**(Al-Bayaty et al., 2012; Sridharan et al., 2021)**
Asiatic acid	Terpenes		***Centella asiaticai/*** stimulates collagen synthesis.	**(Lawrence, 1967)**
Epigallocatechin-3-gallate	Catechins		***Camelia sinensis***/EGCG inhibits TGF receptors in human dermal fibroblasts by changing TGF signaling, lowering MMP-1 and MMP-2 expression, and reducing collagen type 1 synthesis. These characteristics suggest that EGCG could be used as an anti-scarring agent. Furthermore, EGCG has been shown to cause keloid shrinking [124] as well as prevent keloids' growth and degenerative characteristics by decreasing STAT3 signaling.	**(Hsu et al., 2003)**

Table 2. Phytochemicals with wound healing activity (continued)

Wound healing agents	Phytochemical class	Structure	Source/ Mechanism of activity	Ref.
Vincristine	monoterpenoid indole alkaloid		***Catharanthus roseus*** **/** re-epithelialization faster, and the rate of wound constriction was additionally increased.	**(Anom-Dddd, 2013)**
Vinblastine	monoterpenoid indole alkaloid			**(Anom-Dddd, 2013)**
Curcumin	Phenolics		***Curcuma longa*/** acts on different stages of the natural wound healing process to fasten the healing process, in addition reduces the oxidative stress and lipid peroxidation, inhibits AGEs accumulation, reduces the expression of TNF-α, IL-1β, and MMP-9, increases the levels of IL-10, SOD, catalase and glutathione peroxidase, increases the anti-inflammatory cytokine IL-10, upregulates the expression of VEGF, TGF-β1, HIF-1α, SDF-1α, and HO-1, as a result increases new vascular formation.	**(Akbik et al., 2014; V. Kant et al., 2015; Vinay Kant et al., 2014; Sajithlal et al., 1998)**
Oleanolic acid	terpenes		***Anrederadiffusa*** / Oleanolic acid is the main active component of *Anredera diffusa* responsible for its wound healing activity.	**(Moura-Letts et al., 2006)**
Omega-7	fatty acids		***Hippophaerhamnoides*** / increase telomerase activity and keratinocyte growth factors levels which accelerate wound healing.	**(Niimi et al., 2021)**

4.2. Medicinal plants as a resource of natural antioxidants in wound mending

A great number of bioactive natural compounds with substantially lowering as well as free radicals scavenging qualities can be found in medicinal plants and foods. Phenolic compounds, flavonoids, essential oils, carbohydrates, their derivatives, and other natural chemical constituents are just a few of the compounds that can help prevent oxidative assaults. According to investigations, naturally occurring antioxidative molecules added to food products or pet food have been demonstrated to lessen oxidation, enhance as a whole product value, and extend the shelf life. Natural active molecules have also, in recent times, been investigated against harmful microbes such as fungus, viruses, and bacteria that are attacking and resistant to conventional drugs and posing a major threat to human wellness and health (Cardoso, 2019).

Numerous research has suggested that plant compounds, especially flavonoids have several bioactivities such as anti-hypersensitivity, active against the virus, potent anti-inflammatory, vasodilating, and many more biological properties. The antioxidant capacity of flavones or flavonoids and polyphenols, through their responsibility to mitigate free radicals' production, has obtained the most attention in recent days. The majority of consumed flavonoids are broken down into different phenolic acids, some of which show similar properties against free radicals as that of flavonoids (Pietta, 2000).

Reactive Oxygen Species (ROS) are tiny O_2 derived molecules that are made primarily in the cell's powerhouse by the respiratory chain; examples include hydrogen peroxide, superoxide anion, and peroxide (Scialò et al., 2017). They are oxidizing species and mainly contribute to cell membrane damage. Further, they serve a useful purpose, particularly in the case of usual tissue repair. As a result, achieving a balance between higher and lower ROS levels is crucial. Low concentrations of ROS protect body organs or tissues from pathogenic infections and stimulate the impactful healing process of wounds by producing cell survival signaling, however when concentrations exceed, they lead to oxidative assaults, which results in cellular damage and a pro-inflammatory state (Ponugoti et al., 2013). Under usual conditions, the cell's endogenous system, i.e. the body's natural antioxidant defense processes, can minimize the adverse effect of such free radicals or ROS. ROS detoxifying enzymes like catalase, superoxide dismutase, and glutathione peroxidases are among the antioxidant defenses in the body's organs or tissue (Aruoma, 1994). This becomes completely obvious that the only way to fruitfully lower the damaging effect of free radicals is to use an external system. As a result, nutritional supplement with antioxidant properties is required to maintain a continual supply of antioxidants to the physiological system. Antioxidants are thought to aid in reducing wound free radicals and thus speed tissue repair. They play a substantial role in controlling the possible injury that reactive species can cause to cellular molecules like protein, lipids, and nucleic acids.

4.3. Evidence of natural antioxidants in wound healing

Numerous researches conducted on natural herbs have addressed the emergence of new resources with the ability to help in a wide variety of wounds with negligible toxicity, ease of usage, increased efficacy, and economical therapeutic interventions for patients in the latest times. According to the published research works, flavonoids seem to be the greatest important and promising group of plant molecules for wound mending.

Flavonoids were found to have valuable anti-inflammatory characteristics across several research findings, as they lowered the levels of inflammatory facilitators such as prostaglandin, leukotrienes, inflammatory cytokines, and cyclooxygenase while increasing anti-inflammatory mediators, especially IL-10 (Ahmed et al., 2018; Du et al., 2021). NO and ROS are produced by macrophages of the M1 type. Quercetin, a flavonoid, lessens M1 cellular function while increasing M2 macrophage activity; but even so, it does not mean that almost all flavonoids control M1 or M2 macrophages function (Fu et al., 2020), and an inability to control in the regulation of these phenotypes is connected to the progression of the normal wound to chronic state (Anower, 2014; Benoit et al, 2008).

Besides this, flavonoids were demonstrated to function in the down-regulation of NF-κB expression, which is a crucial component in the inflammatory signaling reaction that adds to collapse in the process of wound healing (Dinda et al., 2015). All immune and non-immune cells adversely affected by chronic inflammation show NF-κB induction. NF-κB stimulation promotes the activation of several pro-inflammatory genes, which help to manage and organize the inflammatory activities that trigger tissue injury. However, NF-κB was shown to have a favorable impact on epithelial cells. In epithelial cells, NF-κB signaling is important for maintaining immune homeostasis (Wullaert et al., 2011). Plant extracts have been shown to activate NF-κB, which promotes wound healing. In human immortalized keratinocytes and dermal fibroblast cells, the flavonoid/phenol-rich n-hexane extract of *Calendula officinalis* has been shown to boost the function of NF-κB (Nicolaus et al., 2017).

MMP-2 is involved in angiogenesis matrix remodeling, whereas MMP-9 is a sign of re-epithelization during the initial stages of wound recovery (Baker and Leaper, 2003; Manuel and Gawronska-Kozak, 2006). In the healing process, MMP-8 (collagenase-2) cleaves collagens, and MMP-13 (collagenase-3) indirectly promotes re-epithelialization by influencing wound closure (Caley et al., 2015). It was conceivable to demonstrate the response of flavonoids on MMPs in this review. Flavones (Mohammadi et al., 2019) and flavanols (Jaiswal et al., 2013) caused up-regulation of MMPs 2, 8, 9, and 13, demonstrating their ability to aid tissue repair or wound mending.

Smad is required for TGF cell signaling, according to new research. These markers, particularly Smad 2 and 3, function as latent nuclear transcriptional activators and governs the cellular functions in tissue repair (Ashcroft and Roberts, 2000). TGF also induces Smad 7, but negative feedback prevents Smad 2 and 3 from being phosphorylated and translocating to the nucleus (Shi et al., 2003). Molecules like flavanone, flavonol, and isoflavone have been demonstrated to boost TGF-β expression, resulting in higher Smad 2/3 expression and lowered Smad 7 regulation. Further, TGFβ1 is involved in angiogenesis by up-regulating VEGF, a well-known factor for angiogenesis (Penn et al., 2012). These growth factors bind to their specific receptor in keratinocytes and macrophages, allowing them to perform critical functions throughout the tissue repair. Chronic and nonhealing wounds frequently have woefully inadequate vascularization. Delay wound healing has been observed in hyperglycemia conditions in diabetic animals, with impoverished vascularization being the cause of disrupted wound contraction, epithelialization, and granuloma tissue regeneration (Stallmeyer et al., 2001). *H. rosa-sinensis* extract rich in phenolic or flavonoids compounds has been shown to promote wound healing by raising these growth factors (Shen et al., 2017).

The PI3K pathway promotes cell growth, which is important for wound healing. Akt (serine/threonine-specific protein kinase) is phosphorylated at serine 473 residues when the PI3K pathway is activated, which has been discovered to be critical for the directional immigration of skin and corneal epithelial cells in response to injury or wound (Yu et al., 2014). The PI3K pathway has been linked to the induction of wound healing by medicinal plants. The PI3K pathway is activated by natural herbs like *Calendula officinalis*, which promotes wounded tissue healing (Dinda et al., 2015).

Although ROS generation is required to introduce the healing process of tissue, too much of it is harmful to wound healing, leading to delays in wound closure, keratinocyte migration, and epithelialization (Zhang et al., 2019). Superoxide dismutase, catalase, and glutathione peroxidase are antioxidative enzymes that behave as shielding factors, ensuring that tolerable levels of ROS are maintained for correct body function, with the homeostatic balance among antioxidant enzymes and ROS becoming critical in the tissue healing process (Abdulaziz, 2019). Several flavonoids have been shown to boost endogenous antioxidant capacity, implying a shielding effect and aiding tissue repair.

The several strands of data suggested that wounds are subjected to oxidative assault as a result of increased neutrophil activity due to oxidants and MPO activity. In a chronic wound, enhanced neutrophil activity tends to cause tissue injury due to oxidants and MPO activity (Song et al., 2008). In chronic wounds, the production of ROS causes cytotoxicity and delays wound healing (Mikhal'chik et al., 2006). The availability of multiple phytochemicals in medicinal herbs contributes to their antioxidant activity (Pawar et al., 2007). This has been revealed that using a bioadhesive gel containing an ethanolic extract of Leea macrophylla (5 percent w/v) raised endogenous antioxidant capacity while decreasing MPO action (Joshi et al., 2016).

Flavonoids are, therefore, essential factors in tissue repair, according to the data collected from the articles published. Medicinal herbs and plant-derived antioxidants, on the other hand, are gaining in popularity, and we've highlighted the evidence for their use in wound healing. The use of antioxidants appears to be a great promise for wound healing, but there are few animal investigations, and even fewer clinical researches are available. The use of antioxidants for wound healing as a field of science is still in its early stages, and prospective research will help to better understand this same.

4.4. Herbal combinations in several pharmaceutical dosage forms for wound healing

Antimicrobial dressings, including natural antimicrobial agents, can be used for wound healing (Rajendran, 2018). Honey, Aloe vera, and Neem tree extracts are just a few of the antibacterial agents that are utilized solely in wound dressings (Rajendran, 2018). These are considered potential antibacterial agents for modern wound dressings. Honey dressings help to maintain wound moisture, which facilitates faster healing and decreases the bacterial load by releasing hydrogen peroxide. Honey's osmatic action prevents the development of bacteria and encourages speedy wound healing (Archer et al., 1990). It also promotes autolytic debridement. Aloe vera is extensively utilized for wound healing dressings owing to its active principles of the Aloe vera gel, which has moisturizing, anti-inflammatory, antibacterial, antifungal, antiviral agent, and anti-odor properties.

4.5. Nanomedicine and wound healing activity

Amongst the operative strategies for potent wound healing potential is the formulation of medicinal plant extracts in biocompatible nanoparticles in a green and cost-effective method, producing nanostructures with excellent wound healing effects (Hajialyani, 2018). Loading herbal-based principles in nanoparticles, nano-emulsions, nanoliposomes, and hydrogels, enhance their availability, controls their release like sustained release dosage forms to stay for a longer time on the wound, in addition, the enhancement of the permeability of herbal preparations constituents to the deep skin that is vital for the progression of wound healing to take place properly.

Several topical herbal-based nanostructures mainly contain curcumin which contributed to the increase of healing being most potent in the inflammatory phase through regulating the levels of TNF-α, IL-10, and TGF-β1. Besides, biosynthesized herbal-based silver nanoparticles also have a major potential in wound inflammation control.

5. Need of Innovative Research

The knowledge of phytochemicals and other naturally derived drugs is still in its early stages, with more discoveries to come. Many herbs and plants have still to be researched for their therapeutic efficacy in clinical systems that emphasize phytochemicals, such as traditional Chinese medicine, Ayurveda, and naturopathy. Increased research and use of phytochemicals and other biologically derived compounds suggest that wound care is becoming more complex and difficult, with complex physiology and pathophysiology.

6. Future Developments

Wound healing with phytochemicals and naturally derived substances is a promising development. More prospective, well-controlled studies are needed to assess the importance of these naturally derived products in wound treatment. The impact of the extraction method on the extract's final composition needs to be better defined, and the value of this information is currently undervalued. Naturopathic medicine, Herbal remedies, and homeopathy, unlike allopathic medicine, make substantial use of plant/herbal extracts and naturally derived compounds. Collaboration would be required for future systematic and thoughtful studies into the role of naturally derived products in wound healing.

Conclusion

Plants are excellent wound healers because they innately heal wounds. Throughout different wound models, the rate of wound closure, epithelialization, tensile strength, histopathology, and granuloma weight can all be measured clinically to control the healing process. This study showed that traditional medicines play an important role in wound healing. Herbal medicines are becoming increasingly popular in various countries as they are healthier and more widely accepted than allopathic drugs. As a result, combining traditional and modern expertise can provide better or faster wound healing with minimal toxicity. In addition, the use of nanotechnology and preparation of topical herbal-based nanostructures may contribute to the enhancement of the effect of natural extracts as wound healing agents due to the enhancement of their bioavailability, increasing their absorption at the site of administration in addition to their stability for longer periods. In conclusion, although natural sources showed significant results concerning wound healing activity, still more clinical trials must be carried out to confirm their complete safety and efficacy.

References

Abdulaziz, A. A., Dapar, M.L.G., Manting, M.M.E., Torres, M.A.J., Aranas, A.T., Mindo, R. A.R., Kenny Cabrido, C., and Demayo, C.G. (2019). Qualitative evaluation of the antimicrobial, antioxidant, and medicinally important phytochemical constituents of the ethanolic extracts of the leaves of *gliricidia sepium* (jacq.) Walp. *Pharmacophore, 10*, 72-83.

Ahmed, O. M., Mohamed, T., Moustafa, H., Hamdy, H., Ahmed, R. R., and Aboud, E. (2018). Quercetin and low level laser therapy promote wound healing process in diabetic rats via structural reorganization and modulatory effects on inflammation and oxidative stress. *Biomedical Pharmacotherapy, 101*, 58-73. doi:10.1016/j.biopha.2018.02.040

Akbik, D., Ghadiri, M., Chrzanowski, W., and Rohanizadeh, R. (2014). Curcumin as a wound healing agent. *Life Sciences, 116*(1), 1-7. doi:10.1016/j.lfs.2014.08.016

Al-Bayaty, F. H., Abdulla, M. A., Hassan, M. I. A., and Ali, H. M. (2012). Effect of *Andrographis paniculata* leaf extract on wound healing in rats. *Natural Product Research, 26*(5), 423-429. doi:10.1080/14786419.2010.496114

Alizargar, J., Kuchaki, E., Shaabani, A., and Namazi, M. (2012). Properties of wound healing activities of rosemary extract. *Journal of Biologically Active Products from Nature, 2*(4), 218-224. doi:10.1080/22311866.2012.10719128

Anom-Dddd, K., tBeruto, t K., Putrd-Monudbo, and Damtiosa,I M. (2013). *Catharanthus roseus* leat' extract accelera.tes iiealing of woijnd wistar rat. *Indonesian Journal of Biomedical Sciences, 7*(1), 37-40.

Anower, A. K. M. M., Shim, J.A., Choi, B., Kwon, H.J., and Sohn, S. (2014). The role of classical and alternative macrophages in the immunopathogenesis of *Herpes simplex* virus-induced inflammation in a mouse model. *Journal of Dermatological Sciences, 73*, 198-208.

Anuar, N. S., Zahari, S. S., Taib, I. A., and Rahman, M. T. (2008). Effect of green and ripe *Carica papaya* epicarp extracts on wound healing and during pregnancy. *Food and Chemical Toxicology, 46*(7), 2384-2389. doi:https://doi.org/10.1016/j.fct.2008.03.025

Archer, H. G., Barnett, S., Irving, S., Middleton, K. R., and Seal, D. V. (1990). A controlled model of moist wound healing: comparison between semi-permeable film, antiseptics and sugar paste. *Journal of Experimental Pathology (Oxford), 71*(2), 155-170.

Aruoma, O. I. (1994). Nutrition and health aspects of free radicals and antioxidants. *Food and Chemical Toxicology, 32*(7), 671-683. doi:10.1016/0278-6915(94)90011-6

Ashcroft, G. S., and Roberts, A. B. (2000). Loss of Smad 3 modulates wound healing. *Cytokine Growth Factor Reviews, 11*(1-2), 125-131. doi:10.1016/s1359-6101(99)00036-2

Baker, E. A., and Leaper, D. J. (2003). Profiles of matrix metalloproteinases and their tissue inhibitors in intraperitoneal drainage fluid: relationship to wound healing. *Wound Repair Regeneration, 11*(4), 268-274. doi:10.1046/j.1524-475x.2003.11406.x

Bakr, R. O., Amer, R. I., Attia, D., Abdelhafez, M. M., Al-Mokaddem, A. K., El-Gendy, A. E.-N. G., Gad, Fayed M.A.A., and Sameh S. (2021). In-vivo wound healing activity of a novel composite sponge loaded with mucilage and lipoidal matter of *Hibiscus* species. *Biomedicine & Pharmacotherapy, 135*, 111225. doi:https://doi.org/10.1016/j.biopha.2021.111225

Benoit, M., Desnues, B., and Mege, J. L. (2008). Macrophage polarization in bacterial infections. *Journal of Immunology, 181*(6), 3733-3739. doi:10.4049/jimmunol.181.6.3733

Bhargava M. K., Singh H. and Kumar A. (1988). Evalution of *Adhatoda vasica* as a Wound Healing Agent in Buffaloes—Clinical Mechanical and Biochemical Studies *Indian Veterinary Journal, 65*(1), 33-38.

Caley, M. P., Martins, V. L., and O'Toole, E. A. (2015). Metalloproteinases and Wound Healing. *Advances in wound care, 4*(4), 225-234. doi:10.1089/wound.2014.0581

Cardoso, S. M. (2019). Special Issue: The Antioxidant Capacities of Natural Products. *Molecules (Basel, Switzerland), 24*(3), 492. doi:10.3390/molecules24030492

Chan EWC, L. Y., Wong LF, Lianto FS, Wong SK, Lim KK, Joe CE, and Lim TY. . (2008). Antioxidant and tyrosinase inhibition properties of leaves and rhizomes of ginger species. *Food Chemistry , 109*, 477–483.

de Fátima, A., Modolo, L. V., Sanches, A. C., and Porto, R. R. (2008). Wound healing agents: the role of natural and non-natural products in drug development. *Mini-Reviews in Medicinal Chemistry, 8*(9), 879-888. doi:10.2174/138955708785132738

Dinda, M., Dasgupta, U., Singh, N., Bhattacharyya, D., and Karmakar, P. (2015). PI3K-mediated proliferation of fibroblasts by *Calendula officinalis* tincture: implication in wound healing. *Phytotherapy Research, 29*(4), 607-616. doi:10.1002/ptr.5293

Du, W., Tang, Z., Yang, F., Liu, X., and Dong, J. (2021). Icariin attenuates bleomycin-induced pulmonary fibrosis by targeting Hippo/YAP pathway. *Biomedicine & Pharmacotherapy, 143*, 112152. doi:https://doi.org/10.1016/j.biopha.2021.112152

Fayed, M. A. A. (2021). *Heliotropium*; a genus rich in pyrrolizidine alkaloids: A systematic review following its phytochemistry and pharmacology. *Phytomedicine Plus, 1*(2), 100036. doi:https://doi.org/10.1016/j.phyplu.2021.100036

Fu, J., Huang, J., Lin, M., Xie, T., and You, T. (2020). Quercetin Promotes Diabetic Wound Healing via Switching Macrophages From M1 to M2 Polarization. *Journal of Surgical Research, 246*, 213-223. doi:10.1016/j.jss.2019.09.011

Guo, S., and Dipietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research, 89*(3), 219-229. doi:10.1177/0022034509359125

Gurung, S., and Skalko-Basnet, N. (2009). Wound healing properties of *Carica papaya* latex: in vivo evaluation in mice burn model. *Journal of Ethnopharmacology, 121*(2), 338-341. doi:10.1016/j.jep.2008.10.030

Gurung, S., and Škalko-Basnet, N. (2009). Wound healing properties of *Carica papaya* latex: In vivo evaluation in mice burn model. *Journal of Ethnopharmacology, 121*(2), 338-341. doi:https://doi.org/10.1016/j.jep.2008.10.030

Hajialyani M, T. D., Sobarzo-Sánchez E, Nabavi SM, Farzaei MH, and Abdollahi M. . (2018). Natural product-based nanomedicines for wound healing purposes: therapeutic targets and drug delivery systems. *International Journal of Nanomedicine, 13*, 5023-5043. doi:https://doi.org/10.2147/IJN.S174072

Hsu S., Bollag W.B., Lewis J., Huang Q., Singh B., Sharawy M., Yamamoto T., and Schuster G. (2003). Green tea polyphenols induce differentiation and proliferation in epidermal keratinocytes. *Journal of Pharmacology and Experimental Therapeutics, 306*(1), 29-34.

Jaiswal, M., Gupta, A., Agrawal, A. K., Jassal, M., Dinda, A. K., and Koul, V. (2013). Bi-layer composite dressing of gelatin nanofibrous mat and poly vinyl alcohol hydrogel for drug delivery and wound healing application: in-vitro and in-vivo studies. *Journal of Biomedical Nanotechnology, 9*(9), 1495-1508. doi:10.1166/jbn.2013.1643

Joshi, A., Joshi, V. K., Pandey, D., and Hemalatha, S. (2016). Systematic investigation of ethanolic extract from *Leea macrophylla*: Implications in wound healing, *Journal of Ethnopharmacology, 191*, 95-106. doi:10.1016/j.jep.2016.06.034

Kant, V., Gopal, A., Kumar, D., Pathak, N. N., Ram, M., Jangir, B. L., and Kumar, D. (2015). Curcumin-induced angiogenesis hastens wound healing in diabetic rats. *Journal of Surgical Research, 193*(2), 978-988. doi:10.1016/j.jss.2014.10.019

Kant, V., Gopal, A., Pathak, N. N., Kumar, P., Tandan, S. K., and Kumar, D. (2014). Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. *International Immunopharmacology, 20*(2), 322-330. doi:https://doi.org/10.1016/j.intimp.2014.03.009

Kazemian, H., Ghafourian, S., Sadeghifard, N., Houshmandfar, R., Badakhsh, B., Taji, A., and Heidari, H. (2018). In vivo Antibacterial and Wound Healing Activities of Roman Chamomile (*Chamaemelum nobile*). *Infectious Disorders - Drug Targets, 18*(1), 41-45. doi:http://dx.doi.org/10.2174/1871526516666161230123133

Kiran, K., and Asad, M. (2008). Wound healing activity of *Sesamum indicum* L seed and oil in rats. *Indian Journal of Experimental Biology, 46*(11), 777-782.

Klass B.R., Branford O.A., Grobbelaar A.O., and Rolfe K.J. (2010). The effect of epigallocatechin-3-gallate, a constituent of green tea, on transforming growth factor-*β1*-stimulated wound contraction. *Wound Repair and Regeneration, 18*(1), 80-88.

Ktari, N., Trabelsi, I., Bardaa, S., Triki, M., Bkhairia, I., Ben Slama-Ben Salem, R., and Ben Salah, R. (2017). Antioxidant and hemolytic activities, and effects in rat cutaneous wound healing of a novel polysaccharide from fenugreek (*Trigonella foenum-graecum*) seeds. *International Journal of Biological Macromolecules, 95*, 625-634. doi:10.1016/j.ijbiomac.2016.11.091

Kumar, B., Vijayakumar, M., Govindarajan, R., and Pushpangadan, P. (2007). Ethnopharmacological approaches to wound healing--exploring medicinal plants of India. *Journal of Ethnopharmacology, 114*(2), 103-113. doi:10.1016/j.jep.2007.08.010

Lawrence, J. C. (1967). The morphological and pharmacological effects of asiaticoside upon skin in vitro and in vivo. *European Journal of Pharmacology, 1*(5), 414-424. doi:10.1016/0014-2999(67)90104-5

Lazarus, G. S., Cooper, D. M., Knighton, D. R., Margolis, D. J., Pecoraro, R. E., Rodeheaver, G., and Robson, M. C. (1994). Definitions and guidelines for assessment of wounds and evaluation of healing. *Archives of Dermatology, 130*(4), 489-493.

Li, J., Chen, J., and Kirsner, R. (2007). Pathophysiology of acute wound healing. *Clin Dermatol, 25*(1), 9-18. doi:10.1016/j.clindermatol.2006.09.007

Lodhi, S., Pawar, R. S., Jain, A. P., and Singhai, A. K. (2006). Wound healing potential of Tephrosia purpurea (Linn.) Pers. in rats. *Journal of Ethnopharmacology, 108*(2), 204-210. doi:10.1016/j.jep.2006.05.011

Maan, P., Yadav, K. S., and Yadav, N. P. (2017). Wound Healing Activity of *Azadirachta indica* A. Juss Stem Bark in Mice. *Pharmacognosy Magazine, 13*(Suppl 2), S316-s320. doi:10.4103/0973-1296.210163

Mahmood A. A., S. K., and Salmah I. (2005). Wound healing activity of *Carica papaya* L. aqueous leaf extract in rats *International Journal of Molecular Medicine and Advance Sciences, 1*(4), 398-401.

Malik JK, M. F., Nanjware BR, and Singh S. . (2009). Wound healing properties of alcoholic extract of *Gymnema sylvestre* R.BR. leaves in rats. *J Pharmaceutical Research., 2*(6), 1029–1030.

Malviya, N., and Jain, S. (2009). Wound healing activity of aqueous extract of *Radix paeoniae* root. *Acta Poloniae Pharmaceutica, 66*(5), 543-547.

Manjunatha BK, K. V., Vidya SN, Mankani KL, and Manohara YN. . (2007). Wound healing activity of *Lycopodium serratum*, Indian Journal of Pharmaceutical Sciences *, 69*, 283–287.

Manuel, J. A., and Gawronska-Kozak, B. (2006). Matrix metalloproteinase 9 (MMP-9) is upregulated during scarless wound healing in athymic nude mice. *Matrix Biology, 25*(8), 505-514. doi:10.1016/j.matbio.2006.07.008

Menke, N. B., Ward, K. R., Witten, T. M., Bonchev, D. G., and Diegelmann, R. F. (2007). Impaired wound healing. *Clinical Dermatology, 25*(1), 19-25. doi:10.1016/j.clindermatol.2006.12.005

Mickelson, M. A., Mans, C., and Colopy, S. A. (2016). Principles of Wound Management and Wound Healing in Exotic Pets. *The veterinary clinics of North America, Exotic animal practice, 19*(1), 33-53. doi:10.1016/j.cvex.2015.08.002

Mikhal'chik, E. V., Anurov, M. V., Titkova, S. M., Miroshnikova, E. A., Lukasheva, E. V., Deeva, I. B., and Korkina, L. G. (2006). Activity of antioxidant enzymes in the skin during surgical wounds. *Bulletin of Experimental Biology and Medicine, 142*(6), 667-669. doi:10.1007/s10517-006-0446-z

Mohammadi, Z., Sharif Zak, M., Majdi, H., Mostafavi, E., Barati, M., Lotfimehr, H., and Akbarzadeh, A. (2019). The effect of chrysin-curcumin-loaded nanofibres on the wound-healing process in male rats. *Artificial Cells, Nanomedicine, and Biotechnology, 47*(1), 1642-1652. doi:10.1080/21691401.2019.1594855

More, S. K., Lande, A. A., Jagdale, P. G., Adkar, P. P., and Ambavade, S. D. (2013). Evaluation of anti-inflammatory activity of *Solanum xanthocarpum* Schrad and Wendl (Kaṇṭakāri) extract in laboratory animals. *Ancient science of life, 32*(4), 222-226. doi:10.4103/0257-7941.131976

Moura-Letts, G., Villegas, L. F., Marçalo, A., Vaisberg, A. J., and Hammond, G. B. (2006). In vivo wound-healing activity of oleanolic acid derived from the acid hydrolysis of *Anredera diffusa*. *Journal of Natural Products, 69*(6), 978-979. doi:10.1021/np0601152

Nayak, B. S., and Pinto Pereira, L. M. (2006). *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine, 6*, 41. doi:10.1186/1472-6882-6-41

Nayak, B. S., Ramdeen, R., Adogwa, A., Ramsubhag, A., and Marshall, J. R. (2012). Wound-healing potential of an ethanol extract of *Carica papaya* (Caricaceae) seeds. *International Wound Journal, 9*(6), 650-655. doi:10.1111/j.1742-481X.2011.00933.x

Nayak, B. S., Sandiford, S., and Maxwell, A. (2009). Evaluation of the Wound-healing Activity of Ethanolic Extract of *Morinda citrifolia* L. Leaf. *Evidence-Based Complementary and Alternative Medicine, 6*(3), 351-356. doi:10.1093/ecam/nem127

Nejati, H., Farahpour, M. R., and Nagadehi, M. N. (2015). Topical *Rosemary officinalis* essential oil improves wound healing against disseminated *Candida albicans* infection in rat model. *Comparative Clinical Pathology, 24*(6), 1377-1383. doi:10.1007/s00580-015-2086-z

Nicolaus, C., Junghanns, S., Hartmann, A., Murillo, R., Ganzera, M., and Merfort, I. (2017). In vitro studies to evaluate the wound healing properties of *Calendula officinalis* extracts. *Journal of Ethnopharmacology, 196*, 94-103. doi:10.1016/j.jep.2016.12.006

Niimi, Y., Pérez-Bello, D., Ihara, K., Fukuda, S., Jacob, S., Andersen, C. R., and Enkhbaatar, P. (2021). Omega-7 oil increases telomerase activity and accelerates healing of grafted burn and donor site wounds. *Scientific Reports, 11*(1), 975. doi:10.1038/s41598-020-79597-0

Olubunmi Atolani, S. O., A.P. Oluyori and A. Gabriel Olatunji (2012). New Constituents of *Kigelia pinnata* Leaves. *Singapore Journal of Scientific Research, 2*, 47-53.

Panahi, Y., Rastgar, N., Zamani, A., and Sahebkar, A. (2020). Comparing the Therapeutic Effects of *Aloe vera* and Olive Oil Combination Cream versus Topical Betamethasone for Atopic Dermatitis: A Randomized Double-blind Clinical Trial. *Journal of pharmacopuncture, 23*(3), 173-178. doi:10.3831/KPI.2020.23.3.173

Park G., Yoon B.S, Moon J.H., Kim B., Jun E.K., Oh S., Kim H., Song H.J., Noh J.Y., Oh C., and You S. (2008). Green tea polyphenol epigallocatechin-3-gallate suppresses collagen production and proliferation in keloid fibroblasts via inhibition of the STAT3-signaling pathway. *Journal of Investigative Dermatology, 128*(10), 2429–2441.

Pawar, R. S., Khan, S. I., and Khan, I. A. (2007). Glycosides of 20-deoxy derivatives of jujubogenin and pseudojujubogenin from *Bacopa monniera*. *Planta Medica, 73*(4), 380-383. doi:10.1055/s-2007-967163.

Penn, J. W., Grobbelaar, A. O., and Rolfe, K. J. (2012). The role of the TGF-β family in wound healing, burns and scarring: a review. *International Journal of Burns and Trauma, 2*(1), 18-28.

Pietta, P. G. (2000). Flavonoids as antioxidants. *J Nat Prod, 63*(7), 1035-1042. doi:10.1021/np9904509

Ponugoti, B., Xu, F., Zhang, C., Tian, C., Pacios, S., and Graves, D. T. (2013). FOXO1 promotes wound healing through the up-regulation of TGF-β1 and prevention of oxidative stress. *The Journal of cell biology, 203*(2), 327-343. doi:10.1083/jcb.201305074

Priya, K. S., Gnanamani, A., Radhakrishnan, N., and Babu, M. (2002). Healing potential of *Datura alba* on burn wounds in albino rats. *Journal of Ethnopharmacology, 83*(3), 193-199. doi:10.1016/s0378-8741(02)00195-2

Ragno A., C. E., Marsili D., Apa., D'Erasmo L., and Martin L.S. (2016). Honey, bee pollen and vegetable oil unsaponifiables in wound healing. *Journal of Tissue Viability, 25*(3), 189. doi:https://doi.org/10.1016/j.jtv.2016.03.008

Rajendran S. (2018). Chronic wound care: synthetic and natural antimicrobials *NRC, 20*(8).

Rao SGV, Selvaraj J., Senthil R, Radhakrishnan RN, Murali, and Manokar B. (2003). Efficacy of some indigenous medicines in wound healing in rats. *Indian Journal of Animal Sciences,* (73), 652–653.

Rathi, B. S., Bodhankar, S. L., and Baheti, A. M. (2006). Evaluation of aqueous leaves extract of *Moringa oleifera* Linn for wound healing in albino rats. *Indian Journal of Experimental Biology, 44*(11), 898-901.

Rekik, D. M., Ben Khedir, S., Daoud, A., Ksouda Moalla, K., Rebai, T., and Sahnoun, Z. (2019). Wound Healing Effect of *Lawsonia inermis*. *Skin Pharmacology and Physiology, 32*(6), 295-306. doi:10.1159/000501730

Roberts, P. R., Black, K. W., Santamauro, J. T., and Zaloga, G. P. (1998). Dietary peptides improve wound healing following surgery. *Nutrition, 14*(3), 266-269. doi:10.1016/s0899-9007(97)00468-1

Sajithlal, G. B., Chithra, P., and Chandrakasan, G. (1998). Effect of curcumin on the advanced glycation and cross-linking of collagen in diabetic rats. *Biochemical Pharmacology, 56*(12), 1607-1614. doi:10.1016/s0006-2952(98)00237-8

Sakarkar DM, S. U., Shrikhande VN, Vyas JV, Mandavgade S, Jaiswal SB, and Purohit RN. (2004). Wound healing properties of Henna leaves. . *Natural Products Radiance, 3*(6), 406-412.

Scialò, F., Fernández-Ayala, D. J., and Sanz, A. (2017). Role of Mitochondrial Reverse Electron Transport in ROS Signaling: Potential Roles in Health and Disease. *Frontiers in physiology, 8*, 428-428. doi:10.3389/fphys.2017.00428

Sharma UK, S. A., Sharma U, Kumar M, Rai D, and Agrahari A. . (2010). Wound healing activity of *Kigelia pinnata* bark extract. . *Asian Journal of Pharmaceutical Clinical Research, 3*(4), 73-75.

Shaw, T. J., and Martin, P. (2009). Wound repair at a glance. *Journal of Cell Sciences, 122*(Pt 18), 3209-3213. doi:10.1242/jcs.031187

Shedoeva, A., Leavesley, D., Upton, Z., and Fan, C. (2019). Wound Healing and the Use of Medicinal Plants. *Evidence-Based Complementary and Alternative Medicine, 2019*, 2684108. doi:10.1155/2019/2684108

Shen, H. M., Chen, C., Jiang, J. Y., Zheng, Y. L., Cai, W. F., Wang, B., and Shi, G. G. (2017). The N-butyl alcohol extract from *Hibiscus rosa-sinensis* L. flowers enhances healing potential on rat excisional wounds. *Journal of Ethnopharmacology, 198*, 291-301. doi:10.1016/j.jep.2017.01.016

Shi, L.-S., Wu, C.-H., Yang, T.C., Yao, C.W., Lin, H.C., and Chang, W.L. (2014). Cytotoxic effect of triterpenoids from the root bark of *Hibiscus syriacus*. *Fitoterapia, 97*, 184-191. doi:https://doi.org/10.1016/j.fitote.2014.05.006

Shi, Y., and Massagu´e, J., . (2003). Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell Research, 113*, 685–700.

Singh, M. P., Gupta, A., and Sisodia, S. S. (2019). Wound healing activity of Terminalia bellerica Roxb. and gallic acid in experimentally induced diabetic animals. *Journal of Complementary and Integrative Medicine, 17*(2). doi:10.1515/jcim-2019-0133

Sivamani, R. K., Ma, B. R., Wehrli, L. N., and Maverakis, E. (2012). Phytochemicals and Naturally Derived Substances for Wound Healing. *Advances in wound care, 1*(5), 213-217. doi:10.1089/wound.2011.0330

Song, H. S., Park, T. W., Sohn, U. D., Shin, Y. K., Choi, B. C., Kim, C. J., and Sim, S. S. (2008). The Effect of Caffeic Acid on Wound Healing in Skin-incised Mice. *The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology, 12*(6), 343-347. doi:10.4196/kjpp.2008.12.6.343

Sridharan, B., Lin, Y. L., Liao, J. W., Wang, S., and Lee, M. J. (2021). Effect of andrographolide on the pathological events during the surgical open wound healing process. *IOP Conference Series: Earth and Environmental Science, 858*(1), 012007. doi:10.1088/1755-1315/858/1/012007

Stallmeyer, B., Pfeilschifter, J., and Frank, S. (2001). Systemically and topically supplemented leptin fails to reconstitute a normal angiogenic response during skin repair in diabetic mice. *Diabetologia, 44*(4), 471-479. doi:10.1007/s001250051645

Steenkamp, V., Mathivha, E., Gouws, M. C., and van Rensburg, C. E. (2004). Studies on antibacterial, antioxidant and fibroblast growth stimulation of wound healing remedies from South Africa. *Journal of Ethnopharmacology, 95*(2-3), 353-357. doi:10.1016/j.jep.2004.08.020

Subapriya, R., and Nagini, S. (2005). Medicinal properties of neem leaves: a review. *Current Medicinal Chemistry - Anti-Cancer Agents, 5*(2), 149-146. doi:10.2174/1568011053174828

Syed, F., Bagabir, R. A., Paus, R., and Bayat, A. (2013). Ex vivo evaluation of antifibrotic compounds in skin scarring: EGCG and silencing of PAI-1 independently inhibit growth and induce keloid shrinkage. *Laboratory Investigation, 93*(8), 946-960. doi:10.1038/labinvest.2013.82

Thakur, R., Jain, N., Pathak, R., and Sandhu, S. S. (2011). Practices in wound healing studies of plants. *Evidence Based Complementary Alternative Medicine, 2011*, 438056-438056. doi:10.1155/2011/438056

Tiwari, P., Mishra, B. N., and Sangwan, N. S. (2014). Phytochemical and pharmacological properties of *Gymnema sylvestre*: an important medicinal plant. *BioMedical research international, 2014*, 830285-830285. doi:10.1155/2014/830285

Tiwari P., K. K., Panik R., Pandey A., Pandey A., and Sahu P.K. (2011). Evaluation of aqueous extract of Roots of *Carica papaya* on wound healing activity in albino Rats. *J. Chem. Pharm. Res., 3*(4), 291-295.

Upadhyay, N. K., Kumar, R., Siddiqui, M. S., and Gupta, A. (2011). Mechanism of Wound-Healing Activity of *Hippophae rhamnoides* L. Leaf Extract in Experimental Burns. *Evidence Based Complementary and Alternative Medicine, 2011*, 659705. doi:10.1093/ecam/nep189

Wullaert, A., Bonnet, M. C., and Pasparakis, M. (2011). NF-κB in the regulation of epithelial homeostasis and inflammation. *Cell Res, 21*(1), 146-158. doi:10.1038/cr.2010.175

Yang, C. S., Chen, G., and Wu, Q. (2014). Recent scientific studies of a traditional chinese medicine, tea, on prevention of chronic diseases. *Journal of Traditional and Complementary Medicine, 4*(1), 17-23. doi:10.4103/2225-4110.124326

Yeon, S. W., Kwon, H. Y., Nam, J. I., Ahn, J. H., Jo, Y. H., Turk, A., and Lee, M. K. (2019). Three new naphthalenes from the roots of *Hibiscus syriacus*. *Phytochemistry Letters, 33*, 110-113. doi:https://doi.org/10.1016/j.phytol.2019.08.012

Yu, C., Hu, Z.-Q., and Peng, R.Y. (2014). Effects and mechanisms of a microcurrent dressing on skin wound healing: a review. *Military Medical Research, 1*(1), 24. doi:10.1186/2054-9369-1-24

Yun, B.S., Lee, I.K., Ryoo, I.J., and Yoo, I.D. (2001). Coumarins with Monoamine Oxidase Inhibitory Activity and Antioxidative Coumarino-lignans from *Hibiscus syriacus*. *Journal of Natural Products, 64*(9), 1238-1240. doi:10.1021/np0100946

Zhang, S., Ou, Q., Xin, P., Yuan, Q., Wang, Y., and Wu, J. (2019). Polydopamine/puerarin nanoparticle-incorporated hybrid hydrogels for enhanced wound healing. *Biomaterials Science, 7*(10), 4230-4236. doi:10.1039/C9BM00991D