



A REVIEW OF NATURAL PRODUCTS RESPONSIBLE FOR WOUND MANAGEMENT

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Received 26th July 2022; Revised 19th Sept. 2022; Accepted 17th Jan. 2023; Available online 1st Sept. 2023

<https://doi.org/10.31032/IJBPAS/2023/12.9.7427>

ABSTRACT

Wounds have a significant detrimental influence on the economics of a country's health care system, particularly in developing nations with limited resources and finance. It is estimated that around 80% of people in poor nations utilize traditional medicines, which are mostly derived from medicinal plants, to address their basic health care requirements. The wound healing process is a sequence of complicated molecular and physiological activities that restores the integrity of the skin and subcutaneous tissue. It is commonly known that the stages of cutaneous wound healing are haemostasis, inflammation, proliferation, and remodelling. Numerous plant extracts and their phytoconstituents are recognized as a viable option for wound healing agents owing to the existence of numerous active components, their accessibility, and their reduced negative effects. This study thus strives to fill in the gaps in the current literature and provides researchers active in the validation of traditional claims and the creation of safe, efficacious, and universally acknowledged herbal medications for cuts and wounds a vast array of opportunities.

Keywords: Burns, Herbal extracts, Medicinal plants, Phytochemicals, Wound healing

INTRODUCTION

The biggest organ in the body, the skin forms the live organism's outer covering. It is made up of numerous layers of ectodermal tissues that protect the bones, muscles, and internal

organs underneath. It also protects against pathogens, light, heat, and harm [1]. When the natural function and structure of the skin are damaged, a wound is formed [2].

Wounds, according to the Wound Healing Society, are physical injuries that produce an opening or break in the skin, disrupting the normal architecture and function of the skin. They cause the epithelium to lose its continuity, with or without the loss of underlying connective tissue. Wounds are a huge burden for individuals and health care providers all around the globe. They not only have an impact on the physical and emotional health of millions of people, but they also cost them a lot of money. According to current estimates, about 6 million individuals worldwide suffer from chronic wounds [3]. Inflammatory mediators are continually produced by unhealed wounds, causing swelling and pain at the wound site. Injured patients' recuperation is slowed by wounds, which serve as a breeding ground for infection. Chronic wounds may result in the multiple organ failure or patient's mortality [4].

The wound healing process is a complex and necessary controlled sequence of various well-orchestrated cellular and biochemical phenomena that restores the skin's integrity. Wound healing is divided into four stages: haemostatic phase, inflammation, proliferation, and maturation [5]. The materials employed in wound dressings may have a significant impact on wound care and wound healing effectiveness in occlusion of wounded tissue.

In healthy people, normal or acute wound

healing is characterized by the sequential overlap of processes that restore skin integrity and function in a coordinated way. Normal wound healing typically takes seven to ten days. Any changes that disturb the timely regulated healing processes will exacerbate tissue damage and lengthen the repair process, hence leading to chronic wound healing [6]. Chronic wound healing may thus be described as a disturbance of the usual healing route. It may be brought on by underlying disease processes (like cardiovascular disease or diabetes), drugs (steroids), infections, and aging. Complete healing of chronic full-thickness wounds may take months to years [7].

Traditional wound healing remedies have been studied experimentally and therapeutically, and various investigations have uncovered a plethora of information regarding their involvement in easing the underlying reasons of nonhealing wounds [8, 9]. Based on a range of active and beneficial components like essential oils, flavonoids, phenolic compounds, alkaloids, fatty acids, terpenoids, and so on, medicinal plants may be considered as powerful and promising treatments for improving wound healing processes. Because of their reduced side effects, cheap cost, effectiveness, and bioavailability, traditional medicines may be favoured over contemporary treatment [10].

Classification of wounds

Table 1: Depicting Classification of Wounds

S. No.	Type	Explanation
1.	Open wound	Blood seeps from the body via an open wound, causing visible bleeding. The open wound may be further split into types based on the cause of the wound.
2.	Acute wound	Caused due to surgical incisions or cuts.
3.	Closed wound	In closed wounds, blood exits the circulatory system but remains inside the body. It manifests itself in the form of bruises.
4.	Chronic wounds	These are the wounds which have not gone through the normal healing phases and have therefore, reached a level of pathologic inflammation. They need more time to recuperate.
5.	Superficial wound	Abrasion is caused by sliding slide on a rough surface. Abrasion is scraped off the top layer of the skin, the epidermis, at this period, exposing nerve endings and causing a painful injury.
6.	Incised wound	This is a wound with no tissue loss and just little tissue injury. Sharp items, such as a scalpel or knife, are the primary cause.

Stages of wound healing

As maintaining homeostasis is essential for an organism's existence, skin requires and contains a powerful and efficient healing system. The process through which skin heals itself after being injured by trauma, surgery, or burns is known as cutaneous wound healing [11]. The healing process has traditionally been split into four stages:

1. Haemostatic phase

Platelets cling to exposed type 1 collagen after an injury and become activated, secreting glycoproteins that cause platelet aggregation. The complex secretes components that interact with one another to promote the intrinsic clotting cascade by producing thrombin, which then encourages fibrin synthesis from fibrinogen. The fibrin mesh and platelets combine to form a stable hemostatic stopper. Blood arteries contract within minutes after damage, lowering the severity of bleeding via many processes that enable hemostasis to be established [12].

2. Inflammatory phase

The inflammatory phase begins shortly after the injury and lasts between 24 and 48 hours, with rare instances lasting up to two weeks. The haemostatic mechanisms are activated during the inflammatory phase to prevent blood loss from the wound site. As a result of the clinically apparent cardinal sign of inflammation, calor, rubor, dolor, tumour, and function- laesa emerge. This phase is marked by vasoconstriction and platelet aggregation to cause blood clotting, followed by vasodilation and phagocytosis to cause wound inflammation [13].

3. Proliferative phase

This phase is marked by widespread activation of fibroblasts, keratinocytes, endothelial cells, and macrophages in order to coordinate matrix deposition, wound closure, and angiogenesis. Changes in mechanical tension and electrical gradients, as well as exposure to pathogens, hydrogen peroxide, cytokines, and growth factors, activate keratinocytes as early as 12 hours after damage [14]. Keratinocytes near the

wound edge undergo a partial epithelial–mesenchymal transition as a result of this stimulation, becoming more invasive and migratory. Keratinocytes use integrin receptors to navigate through debris and necrotic tissue in the wound bed, interacting with structural proteins in the early matrix [15].

After the inflammatory phase, the fibroblastic stage might last anywhere from 2 to 3 weeks. Granulation, contraction, and epithelialization are the three phases in this phase. Fibroblasts create a collagen bed and new capillaries during the granulation process. Glycosaminoglycans and collagen are produced by fibroblasts, which are important for wound healing. The wound edges come together in the contraction stage to eliminate flaws, and epithelial tissues develop over the wound site in the third step [16]. Driskell *et al.* established that skin fibroblasts come from two different lineages, with the top lineage assisting re-epithelialization and the bottom lineage contributing to ECM deposition in a landmark work [17].

4. Remodelling phase

New collagen is generated during this phase, which is accompanied by improved tissue tensile strength owing to collagen intermolecular cross-linking caused by Vitamin C- dependent hydroxylation. This phase is thought to last anywhere between 3 weeks to 2 years [18].

Traditional medicinal plants

Plants have been used to cure and prevent illnesses for millennia in both traditional and popular medicine. Plants are used in "Ayurveda," which has been practiced in India for over 5000 years as a natural therapy technique to prevent and heal ailments. Traditional Chinese medicine is at least 3000 years old and uses a variety of plant species across eastern Asia [19]. Animal research on a variety of plant species has shown encouraging findings. *Leea macrophylla*, for example, offers therapeutic properties. It boosts antioxidant production, boosts collagen synthesis, boosts cell proliferation, and lowers proinflammatory levels [20]. The cicatricial process was hastened by *Pereskia aculeata*, which increased collagen deposition and blood flow. *Wrightia tinctoria* showed healing activity by increasing the pace at which produced lesions contracted. Antioxidant activity was found in *Cynodon dactylon*, which also enhanced collagen production and repair. *Struthanthus vulgaris* ointment accelerated granulation tissue development, lesion closure, and collagen fiber proliferation and organization [21]. *Caesalpinia mimosoides* caused the epidermal layer to reepithelialize and the lesions to shrink [22]. Plant species that have historically been used to treat ailments have been intensively investigated in contemporary science in order to find

their bioactive ingredients and produce novel medications.

Some examples of medicinal plants and their wound healing effects are listed below-

- ***Aloe vera***



For over 5000 years, *Aloe vera* has been used for ulcers, and surgical wounds by the Romans, Egyptians, and indigenous peoples of Asia, Africa, and the Americas [23]. It includes several naturally occurring bioactive chemicals, such as saponins, pyrocatechol, polysaccharides, anthraquinones, acemannan, oleic acid, glycosides, and phytol [24]. The primary mucopolysaccharide (mesoglycan) of *Aloe vera*, acemannan, stimulates the production of proinflammatory mRNAs (including nitrous oxide, IL-1 α , TNF- α , and PGE2) and is a powerful activator of T-cell and macrophage activity [25].

- ***Azadirachta indica***

Azadirachta indica, often known as Neem, is a multipurpose Indian plant that has been used for over 2000 years and has a broad range of medical properties.

Nimbin, nimbidine, nimbolide, and sodium nimbidate were shown to have antipyretic, antibacterial, and anti-inflammatory activities when extracted from the oil of the seed kernels [31]. In male albino rats, Purohit *et al.* tested the wound healing efficacy of an ethanolic extract of *A. indica* leaves [32].



- ***Calendula officinalis***

Calendula officinalis, sometimes known as pot marigold, is a widespread plant which have been used for a long time to treat a number of skin ailments, like burns, wounds, and dermatitis [36]. *Calendula officinalis* has various pharmacological properties, like anti-inflammatory, antioxidant, antiviral, antibacterial, anticancer, and antifungal properties [37]. However, the precise processes involved in its wound healing effects remain unclear. *Calendula officinalis* flower extracts induce granulation tissue development in excisional wounds of mice through changing the expression of α -smooth muscle actin (α -SMA) and connective tissue growth factor (CTGF) in vivo [38].

A study using cultures of human and mouse fibroblasts showed that extract of *Calendula officinalis* stimulates the migration and proliferation of fibroblast in a PI3K-dependent way [39]. Using a cutaneous wound healing model in rats and the chicken chorioallantoic membrane (CAM) test, it has been established that *Calendula officinalis* stimulates angiogenesis in vivo [40].



Asia, including India, Afghanistan, and Pakistan, Morocco, Indochina, and Senegal, mostly in drier, warmer climates up to 1,050 meters on alkaline, sandy soils [41]. The roots are used to cure asthma, anasarca, bronchitis, ascites, cutaneous disorders, cough, leprosy, and intestinal worms [42].



- ***Calotropis procera***

Calotropis procera (Ait) R. Br. (Asclepiadaceae), also known as Milkweed, Apple of Sodom, or Swallowwort, is a tiny, pubescent, resistant, upright, evergreen, and compact shrub that grows to a maximum height of 4.5 meters and is coated with cottony tomentum. It produces huge amounts of milky sap when cut. It grows naturally in tropical Africa, southeastern

Table 3: Some Recent Studies Evaluating the Wound Healing Efficacy of *Aloe Vera*

No.	Study	Result	Reference
1.	Investigating the wound healing activity of <i>Aloe vera</i> .	The findings indicate that <i>A. vera</i> promotes wound healing by boosting the migration and proliferation of keratinocytes and fibroblasts and by preventing the preservative-induced mortality of keratinocytes.	[26]
2.	Evaluate the potential healing and mutagenic effects of the aqueous extract of <i>A. vera</i> (AEAV) in mice.	At a concentration of 50 mg/kg, the aqueous extract of <i>A. vera</i> demonstrated substantial healing capability in mice.	[27]
3.	A novel alginate dressing containing <i>Aloe vera</i> gel was produced, and Wistar rats with surgical wounds were utilized to examine its cutaneous healing efficacy in vivo.	The assessment of collagen fibers revealed a reduction in type III fibers and an increase in type I fibers in the group treated with aloe-alginate film, indicating wound healing activity.	[28]
4.	To investigate the impact of topical <i>Aloe vera</i> treatment on skin wound healing.	The capacity of 1 percent and 2 percent <i>Aloe vera</i> cream to enhance the ratio of CD4+/CD8+ lymphocytes in the wound region confers wound healing potential.	[29]
5.	This study assessed the feasibility of producing a topical gel formulation of <i>Aloe vera</i> with insulin-loaded nanoemulsions, as well as the gel's ability to promote wound healing in diabetic rats.	<i>Aloe vera</i> with insulin-loaded nanoemulsion shown a synergistic impact on wound healing in diabetic rats and might be a promising and successful therapy for diabetic individuals with wounds.	[30]

Table 4: Some Recent Studies Evaluating the Wound Healing Efficacy Of Neem

No.	Study	Result	Reference
1.	Formulate aqueous topical creams comprising varying doses of aqueous extract of <i>Azadirachta indica</i> leaves (AEAIL) as bioactive components, and assess their stability and wound healing capabilities in male Wistar rats using hydroxyproline (HXP) as a biochemical marker.	The extract of <i>Azadirachta indica</i> leaves produced as an aqueous cream was stable and maintained its wound-healing properties.	[33]
2.	The effects of topical <i>A. indica</i> extract on excisional lesions in hyperglycaemic rats were examined.	The topical administration of <i>A. indica</i> extract to excisional wounds of hyperglycaemic rats hastens wound healing through antioxidant, anti-inflammatory, fibrogenic, and angiogenic actions.	[34]
3.	In the Bundelkhand area of India, the paste made from the stem bark of <i>Azadirachta indica</i> (AI) is historically applied to wounds and scars to promote speedy healing.	The aqueous extract of stem bark of AI has considerable wound-healing properties, supporting its traditional use.	[35]

Table 5: Some Recent Studies Evaluating The Wound Healing Efficacy Of *Calotropis procera*

No.	Study	Result	Reference
1.	Wistar rats were used to assess the wound-healing properties of an aqueous extract of <i>Calotropis procera</i> (AECF) leaves.	Compared to control groups, AECF was associated with a significant ($P < 0.05$) increase in breaking strength and percentage wound contractions with a reduced epithelization duration.	[43]
2.	Assess the antioxidant capacity and wound healing impact of the ethanolic extract of <i>Calotropis procera</i> 's bark.	This research demonstrated the exceptional potential of <i>C. procera</i> . The presumed mechanism of action on cutaneous wound healing involves increased collagen deposition and decreased inflammation.	[44]
3.	In the current research, wound-healing efficacy of <i>Calotropis procera</i> root bark on diabetic rats was examined. The root bark was extracted using the Soxhlet technique from an ethanolic extract.	Extract has a positive impact on diabetic wounds, which heal more quickly than with the regular component. The findings of this investigation indicate that this extract is useful for diabetic wounds.	[45]

- *Centella asiatica*



Centella asiatica, often known as Asiatic pennywort belongs to family Apiaceae and it has been used to enhance wound healing from centuries [46]. According to reports, extracts from the aerial portions of the plant ameliorate the breadth, depth, and duration

of chronic ulcers in Sprague-Dawley rats. Wounds linked with acute radiation dermatitis in rats healed faster when treated with *C. asiatica* extracts compared to the control group that received no therapy [47].

Table 6: Some Recent Studies Evaluating The Wound Healing Efficacy Of *Centella asiatica*

No.	Study	Result	Reference
1.	Determine the effectiveness of an asiaticoside-rich hydrogel formulation in rabbits in vivo.	The asiaticoside-rich hydrogel produced by the freeze-thaw technique proved successful in accelerating wound healing in rabbits.	[48]
2.	Conducting an in vivo examination of wound healing efficacy in diabetic rabbits	Similar to the usual treatment, pegagan extracts-based ointment and its combination were able to reduce erythema, edema, and wound scores in diabetically-induced rabbits.	[49]
3.	Evaluated the effect of asiaticoside on human gingival fibroblasts	As determined by the scratch test, asiaticoside substantially accelerated wound healing ($P < 0.05$).	[50]

- *Curcuma longa*



Curcuma longa (*C. longa*), often known as turmeric, is a ginger family member (Zingiberaceae). It has been used as a condiment and dye since antiquity. It has been taken regularly in Asian nations for generations with no reports of harm [51]. Curcumin (diferuloylmethane), the main curcuminoid present in *C. longa*, is thought to be the most active component. Demethoxycurcumin and

Bisdemethoxycurcumin are two more curcuminoids identified in turmeric [52]. Apoptosis, proinflammatory cytokines, cyclooxygenase-2, NF- κ B, STAT3, 5-LOX, prostaglandin E2, C-reactive protein, cell adhesion molecules, prostate-specific antigen, transforming growth factor- β , phosphorylase kinase, creatinine, ET-1, AST, and ALT, and heme oxygenase-1 are some of the biochemicals targeted [53].

Table 7: Some Recent Studies Evaluating The Wound Healing Efficacy Of *Curcuma longa*

S. No.	Study	Result	Reference
1.	1 percent w/w nano ZnO, <i>Curcuma longa</i> nanoparticles (nano-CUR), and a composite of ZnO and <i>C. longa</i> nanoparticles (nano ZnO/CUR composite) were developed as topical ointments.	The research indicated that nano ZnO/CUR combination ointment would treat third-degree burn lesions more quickly than solus alone application.	[54]
2.	Determined the impact of turmeric extract (<i>Curcuma longa</i>) on white rat wound healing.	The turmeric ethanol extract preparation is comparable to Bioplacenton® in its capacity to heal wounds in mice.	[55]
3.	Electrospinning was used to effectively create a unique multicomponent nanofibrous mat from a solution of honey, polyvinyl alcohol, and <i>Curcumin longa</i> (turmeric) extract for possible use as a wound dressing material.	The created nanomats have the potential to be employed in tissue and as wound dressings.	[56]
4.	Evaluate the efficacy of yellow turmeric infusions of 5 and 10 percent on the healing of grade II perineal wounds.	It has been shown that turmeric reduces oedema, inflammation, and perineal wound healing time.	[57]
5.	Determine the number of new blood vessels that form during the wound healing process when <i>C. longa</i> rhizome extract and zinc oxide are used as a wound dressing.	The combination of <i>C. longa</i> and zinc oxide extract in a wound dressing may improve the number of neovascular in the wound healing process, with 14 days being the optimal period of administration.	[58]

CONCLUSION

Since prehistoric times, medicinal herbs have been used as the first line of defense against trauma, infection, sickness, and damage. Over centuries, people have learnt to detect and convert the local environment's botanical resources into food and medicine, and with the emergence of commerce, as well. It has been proven that plant secondary metabolites are major sources of potential drugs that influence the different phases of wound healing. Modulations of immune cell function, proliferation of skin cells (keratinocytes and fibroblasts), collagen and other ECM proteins, angiogenesis, and cytokines and/or growth factors are among the proven targets of these natural compounds. Since relatively few clinical studies have been conducted to definitively demonstrate the

therapeutic potential of the discovered natural wound healing chemicals, more research should be focused on reaching this objective.

ACKNOWLEDGEMENT: We are very thankful to faculty staff and non-teaching staff of the SGT University, Gurugram for their assistance and help.

CONFLICT OF INTEREST: None

REFERENCES

- [1] Kumar, B.; Vijayakumar, M.; Govindarajan, R.; Pushpangadan, P. Ethnopharmacological approaches to wound healing—Exploring medicinal plants of India. *J. Ethnopharmacol.* 2007, 114, 103–113.
- [2] Tsala, D.E.; Amadou, D.; Habtemariam, S. Natural wound healing and bioactive natural products. *Phytopharmacology* 2013,

- 4, 532–560.
- [3] Kumar B, Vijayakumar M, Govindarajan R, Pushpangadan P. Ethnopharmacological approaches to wound healing—exploring medicinal plants of India. *Journal of ethnopharmacology*. 2007 Nov 1;114(2):103-13.
- [4] Roberts PR, LATG KW, Santamauro JT, Zaloga GP. Dietary peptides improve wound healing following surgery. *Nutrition*. 1998 Mar 1;14(3):266-9.
- [5] Pereira RF, Bártolo PJ. Traditional therapies for skin wound healing. *Adv Wound Care*. 2016;5(5):208–229
- [6] Kurahashi T, Fujii J. Roles of antioxidative enzymes in wound healing. *Journal of Developmental Biology*. 2015 Jun;3(2):57-70.
- [7] Baranoski S, Ayello EA. *Wound care essentials: Practice principles*. Lippincott Williams & Wilkins; 2008.
- [8] Bahmani M, Asadi-Samani M. A short look to the most important medicplants effective on wound healing. *J Inj Inflamm*. 2016;1(1):e07.
- [9] Devi K, Santhi M, Umadevi U. Phytochemical analysis of selected wound healing medicinal plants. *Int J Pharm Sci Res*. 2017;8(2): 852.
- [10] Gamit R, Nariya M, Acharya R, Shukla VJ. Wound healing potential of some medicinal plants with their screening models: a review. *Pharma Sci Monit*. 2017;8(1):208–227.
- [11] Ghahary A, Ghaffari A. Role of keratinocyte–fibroblast cross-talk in development of hypertrophic scar. *Wound Repair and Regeneration*. 2007 Sep;15:S46-53.
- [12] Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, Patel SB, Khalid L, Isseroff RR, Tomic-Canic M. Epithelialization in wound healing: a comprehensive review. *Advances in wound care*. 2014 Jul 1;3(7):445-64.
- [13] Li J, Chen J, Kirsener R. Pathophysiology of acute wound healing, *Clin. Dermatol.*, 25, 2007, 9-18
- [14] Shaw TJ, Martin P. Wound repair: a showcase for cell plasticity and migration. *Current opinion in cell biology*. 2016 Oct 1;42:29-37.
- [15] Santoro MM, Gaudino G. Cellular and molecular facets of keratinocyte reepithelization during wound healing. *Experimental cell research*. 2005 Mar 10;304(1):274-86.
- [16] Stadelmalmann WK, Digenis AG, Tobin GR, Physiology and healing dynamics of chronic cutaneous wounds, *Am. J. Surg.* 176, 1998, 26S-38S.

- [17] Driskell RR, Lichtenberger BM, Hoste E, Kretschmar K, Simons BD, Charalambous M, Ferron SR, Herault Y, Pavlovic G, Ferguson-Smith AC, Watt FM. Distinct fibroblast lineages determine dermal architecture in skin development and repair. *Nature*. 2013 Dec;504(7479):277-81.
- [18] Esimone CO, Nworu CS, Jackson CL. Cutaneous wound healing activity of a herbal ointment containing the leaf extract of *Jatropha curcas* L.(Euphorbiaceae). *Int J Appl Res Nat Prod*. 2008 Dec;1(4):1-4.
- [19] Garodia P, Ichikawa H, Malani N, Sethi G, Aggarwal BB. From ancient medicine to modern medicine: ayurvedic concepts of health and their role in inflammation and cancer. *J Soc Integr Oncol*. 2007 Mar 21;5(1):25-37.
- [20] Joshi A, Joshi VK, Pandey D, Hemalatha S. Systematic investigation of ethanolic extract from *Leea macrophylla*: Implications in wound healing. *Journal of ethnopharmacology*. 2016 Sep 15;191:95-106.
- [21] dos Santos Gramma LS, Marques FM, Vittorazzi C, de Andrade TA, Frade MA, de Andrade TU, Endringer DC, Scherer R, Fronza M. *Struthanthus vulgaris* ointment prevents an over expression of inflammatory response and accelerates the cutaneous wound healing. *Journal of ethnopharmacology*. 2016 Aug 22;190:319-27.
- [22] Bhat PB, Hegde S, Upadhya V, Hegde GR, Habbu PV, Mulgund GS. Evaluation of wound healing property of *Caesalpinia mimosoides* Lam. *Journal of ethnopharmacology*. 2016 Dec 4;193:712-24.
- [23] Garcia-Orue I, Gainza G, Gutierrez FB, Aguirre JJ, Evora C, Pedraz JL, Hernandez RM, Delgado A, Igartua M. Novel nanofibrous dressings containing rhEGF and Aloe vera for wound healing applications. *International journal of pharmaceutics*. 2017 May 25;523(2):556-66.
- [24] Salehi B, Albayrak S, Antolak H, Kręgiel D, Pawlikowska E, Sharifi-Rad M, Uprety Y, Tsouh Fokou PV, Yousef Z, Amiruddin Zakaria Z, Varoni EM. Aloe genus plants: from farm to food applications and phytopharmacotherapy. *International journal of molecular sciences*. 2018 Sep;19(9):2843.
- [25] Ali P, Chen YF, Sargsyan E.

- Bioactive molecules of herbal extracts with anti-infective and wound healing properties. In *Microbiology for surgical infections* 2014 Jan 1 (pp. 205-220). Academic Press.
- [26] Teplicki E, Ma Q, Castillo DE, Zarei M, Hustad AP, Chen J, Li J. The Effects of Aloe vera on Wound Healing in Cell Proliferation, Migration, and Viability. *Wounds: a compendium of clinical research and practice*. 2018 Sep 1;30(9):263-8.
- [27] de Oliveira AC, Tabrez S, Shakil S, Khan MI, Asghar MN, Matias BD, da Silva Batista JM, Rosal MM, de Lima MM, Gomes SR, de Carvalho RM. Mutagenic, antioxidant and wound healing properties of Aloe vera. *Journal of ethnopharmacology*. 2018 Dec 5;227:191-7.
- [28] Koga AY, Pereira AV, Lipinski LC, Oliveira MR. Evaluation of wound healing effect of alginate films containing Aloe vera (*Aloe barbadensis* Miller) gel. *Journal of Biomaterials applications*. 2018 Apr;32(9):1212-21.
- [29] Prakoso YA. The effects of Aloe vera cream on the expression of CD4+ and CD8+ lymphocytes in skin wound healing. *Journal of tropical medicine*. 2018 Feb 15;2018.
- [30] Chakraborty T, Gupta S, Nair A, Chauhan S, Saini V. Wound healing potential of insulin-loaded nanoemulsion with Aloe vera gel in diabetic rats. *Journal of Drug Delivery Science and Technology*. 2021 Aug 1;64:102601.
- [31] Biswas K, Chattopadhyay I, Banerjee RK and Bandyopadhyay U: Biological activities and medicinal properties of neem (*Azadirachta indica*). *Current Science* 2002; 82:1336-1345.
- [32] Purohit SK, Solanki R, Soni R and Mathur V: Evaluation of wound healing activity of ethanolic extract of *Azadirachta indica* leaves in male albino rats. *Asian Journal of Pharmacy and Technology* 2013; 3:73-75.
- [33] Ugoeze KC, Aja PC, Nwachukwu N, Chinko BC, Egwurugwu JN, Oluigbo KE. Evaluation of the Wound healing Potentials of Aqueous Topical creams Containing Aqueous extract of *Azadirachta indica* leaves as Bioactive Ingredient. *Journal of Pharmacy and Pharmacology Research*. 2021;5(1):176-87.
- [34] Silva AC, Eugênio AN, Mariano SS, Poletti S, Gaspi FG, Bittencourt

- JV, Casagrande LR, Silveira PC, Esquisatto MA, Aro AA, Andrade TA. Topical application of *Azadirachta indica* improves epidermal wound healing in hyperglycemic rats. *Comparative Clinical Pathology*. 2021 Jun;30(3):461-72.
- [35] Maan P, Yadav KS, Yadav NP. Wound healing activity of *Azadirachta indica* A. juss stem bark in mice. *Pharmacognosy Magazine*. 2017 Jul;13(Suppl 2):S316.
- [36] Nicolaus C, Junghanns S, Hartmann A, Murillo R, Ganzera M, Merfort I. In vitro studies to evaluate the wound healing properties of *Calendula officinalis* extracts. *Journal of Ethnopharmacology*. 2017 Jan 20;196:94-103.
- [37] Chandran PK, Kuttan R. Effect of *Calendula officinalis* flower extract on acute phase proteins, antioxidant defense mechanism and granuloma formation during thermal burns. *Journal of clinical biochemistry and nutrition*. 2008;43(2):58-64.
- [38] Dinda M, Mazumdar S, Das S, Ganguly D, Dasgupta UB, Dutta A, Jana K, Karmakar P. The water fraction of *Calendula officinalis* hydroethanol extract stimulates in vitro and in vivo proliferation of dermal fibroblasts in wound healing. *Phytotherapy Research*. 2016 Oct;30(10):1696-707.
- [39] Dinda M, Dasgupta U, Singh N, Bhattacharyya D, Karmakar P. PI3K-mediated proliferation of fibroblasts by *Calendula officinalis* tincture: implication in wound healing. *Phytotherapy Research*. 2015 Apr;29(4):607-16.
- [40] Parente LM, Lino Júnior RD, Tresvenzol LM, Vinaud MC, de Paula JR, Paulo NM. Wound healing and anti-inflammatory effect in animal models of *Calendula officinalis* L. growing in Brazil. *Evidence-based complementary and alternative medicine*. 2012 Oct;2012.
- [41] Rais I, Ali M, Rahman S, phytochemical analysis and wound healing activity of *calotropis procera* (ait.) R. Br. Leaves. *International journal of pharmaceutical sciences and research*. 2020 March;12(1):403-413.
- [42] Mhaskar KS, Blatter E and Caius JF: *Kirtikar and Basu's Illustrated Indian Medicinal Plants* (Sri Satguru Publication, Delhi), 2000: 2217-19.
- [43] Patil RA, Makwana AB. Anti-hyperbilirubinemic and wound

- healing activity of aqueous extract of *Calotropis procera* leaves in Wistar rats. *Indian journal of pharmacology*. 2015 Jul;47(4):398.
- [44] Tsala DE, Nga N, Thiery BN, Bienvenue MT, Theophile D. Evaluation of the antioxidant activity and the healing action of the ethanol extract of *Calotropis procera* bark against surgical wounds. *Journal of intercultural ethnopharmacology*. 2015 Jan;4(1):64.
- [45] Mali RP, Rao PS, Vikhe DN. Wound Healing Activity of *Calotropis Procera* Root Bark on Diabetic Rats. *Journal of Drug Delivery and Therapeutics*. 2020 Apr 15;10(2-s):86-9.
- [46] Somboonwong J, Kankaisre M, Tantisira B, Tantisira MH. Wound healing activities of different extracts of *Centella asiatica* in incision and burn wound models: an experimental animal study. *BMC complementary and alternative medicine*. 2012 Dec;12(1):1-7.
- [47] Chen YJ, Dai YS, Chen BF, Chang A, Chen HC, Lin YC, Chang KH, Lai YL, Chung CH, Lai YJ. The effect of tetrandrine and extracts of *Centella asiatica* on acute radiation dermatitis in rats. *Biological and Pharmaceutical Bulletin*. 1999 Jul 15;22(7):703-6.
- [48] Taher M, Mandal UK, Jaffri JM, Susanti D, Mahmood S, Zakaria ZA. Pharmacological properties of *Centella asiatica* hydrogel in accelerating wound healing in rabbits. *BMC complementary and alternative medicine*. 2019 Dec;19(1):1-7.
- [49] Sutrisno E, Sukandar E, Fidrianny I, Adnyana IK. Wound healing in vivo and in vitro study of binahong leaves (*Anredera cordifolia* (ten. Steenis) and pegagan (*Centella asiatica* (L.) Urban) ethanolic extract. *OnLine*. 2018 Apr 30;1:111-6.
- [50] Suriyah WH, Rizal AJ, Nadzirin HS, Ichwan SJ, Isa ML. In Vitro Wound Healing Effect of Asiaticoside Extracted from *Centella asiatica* ('Pegaga') on Human Gingival Fibroblast Cell Line. *InMaterials Science Forum* 2021 (Vol. 1025, pp. 224-229). Trans Tech Publications Ltd.
- [51] Ammon HP, Wahl MA. Pharmacology of *Curcuma longa*. *Planta medica*. 1991 Feb;57(01):1-7.
- [52] Akram M, Shahab-Uddin AA, Usmanghani KH, Hannan AB, Mohiuddin E, Asif M. *Curcuma longa* and curcumin: a review

- article. Rom J Biol Plant Biol. 2010;55(2):65-70.
- [53] Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS journal. 2013 Jan;15(1):195-218.
- [54] Bhutta ZA, Ashar A, Mahfooz A, Khan JA, Saleem MI, Rashid A, Aqib AI, Kulyar MF, Sarwar I, Shoaib M, Nawaz S. Enhanced wound healing activity of nano ZnO and nano Curcuma longa in third-degree burn. Applied Nanoscience. 2021 Apr;11(4):1267-78.
- [55] Ling W, Florenly F, Liena L, Purba DR. Effectiveness of turmeric ethanol extract cream preparation (Curcuma longa) in speeding up wound healing in male wistar rats. Bp Int Res Exact Sci. 2022;4(1):10-21.
- [56] Shahid MA, Ali A, Uddin MN, Miah S, Islam SM, Mohebbullah M, Jamal MS. Antibacterial wound dressing electrospun nanofibrous material from polyvinyl alcohol, honey and Curcumin longa extract. Journal of Industrial Textiles. 2021 Sep;51(3):455-69.
- [57] Mutia WO, Usman AN, Jaqin N, Rahman L, Ahmad M. Potency of complemeter therapy to the healing process of perineal wound; turmeric (Curcuma longa Linn) Infusa. Gaceta Sanitaria. 2021 Jan 1;35:S322-6.
- [58] Faiga NN, Rachmadi P, Meizarini A. Neovascular pattern in wound healing after zinc oxide and Curcuma longa rhizome extract dressing application. Contemporary Clinical Dentistry. 2018 Sep;9(Suppl 2):S337.