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Wound healing and medicinal plants: A systematic review

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ABSTRACT

Wound healing is a complex process in which the skin, and the tissues under it, repairs themselves after injury. The wound healing process proceed in different overlapping phases and processes including haemostasis, inflammation, fibroplasias, formation of granulation tissue with angiogenesis, reepithelialization, and tissue remodeling. The factors that influence repair has been categorized into local and systemic. The potential biomarkers of wound healing are cytokines and proteases.Plant extracts have immense potential for the management and treatment of wounds. The purpose of this review is to describe the various cellular and molecular aspects, factors, and biomarkers involved in the wound healing process. In addition to the above, this study is reference for the role of medicinal plants in wound healing.

INTRODUCTION

Wound is defined as disruption of cellular, anatomical and functional continuity of a living tissue. Wounds can be classified by many ways based their etiology, location, presenting symptoms, type of injury, wound depth and tissue loss or clinical appearance of the wound as Open,Closed, Acute and Chronic wounds. [1-5]A chronic wound should impulse the health care professional to begin a search for unresolved underlying causes. Healing a chronic wound requires care that is patient centered, interdisciplinary, holistic, cost effective and evidence based.[1]Various plant products have been used in treatment and care of wounds over the years. Healing of wound with plant extracts promote blood clotting, fight infection, and accelerate the healing of wounds.[6]

Wound healing

Wound healing is an integrated cellular and biochemical process of restoring normal structure functions of damaged tissue. It involves continuous cell-matrix interaction and cell-cell interactions. The phases of wound healing normally progress in a predictable, timely manner, and if they do not the healing may progress inappropriately to either a chronic wound like venous ulcer or pathological scarring like keloid scar.[7-8]

Mechanism involved in wound healing

Wound healing involves four overlapping phases; haemostasis, inflammation, proliferation and remodeling

a) Phase I: Haemostasis

Haemostasis results from the activation of platelets which initiate the coagulation cascade. Platelet-derived growth factor (PDGF) is one among numerous growth factors that initiate and influence wound healing. Other factors produced by platelets and other cells include, transforming growth factors (TGFs), fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF) [Fig.1].[26]

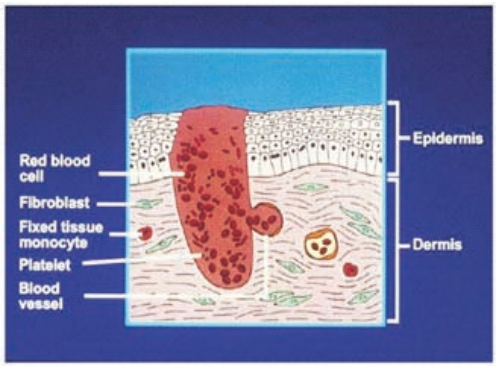

Fig. 1 : Hemostasis

b)Phase II: Inflammation

The inflammation starts within 24 hours and lasts for 2 weeks or more. The inflammatory cells secrete enzymes and various mediators that causes the classical hallmarks of inflammation; pain, redness, warmth and swelling. While several other cells are involved in this process, in terms of healing the key players are the neutrophils, macrophages, and the T-lymphocytes.

Neutrophil cells are the first cells to respond to the platelet products. From the circulation neutrophils reach the affected area in response to the chemotatic characters of some of the mediators. Here neutrophils marginate, adhere to vascular endothelial cells and subsequently migrate to the extravascular space with the help of cell adhesion molecules (CAMs). Fibroblasts too carry CAMs which also function as receptors for cell-cell interaction. Deficiency of the adhesion molecules delays healing. Elastase and collagenase released by neutrophils helps their migration through capillary walls into the extracellular spaces of the wound for phagocytosis. The enzymes also lyses and remove the damaged structural proteins. Some of the growth factors can destroy by the elastase. In addition, neutrophils produce IL-1 and TNF-α that will recruit epithelial cells and fibroblasts.

Macrophages enter to wound area and participate in the phagocytic process. In addition, macrophages release growth factors and cytokines that causes proliferative phase of healing. These factors include PDGF, TGF-β, β-FGF, TNF-α, IL-1 and IL-6.Lymphocytes are the last cells to infiltrate wounds.But they are important in the production of IL-2 which helps recruitment of fibroblasts [Fig.2].[26]

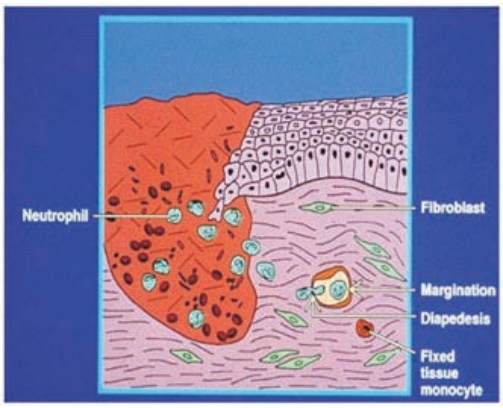

Fig. 2 : Inflammation Phase

c) Phase III: Proliferation

Proliferative phase consists of the following three stages: fibroplasia, granulation, and epithelialization. Proliferation phase begins with fibroblast migration into the wound. Fibroblast migration initiated primarily by the PDGF that has been released by platelets and macrophages. The PDGF stimulates fibroblastic proliferation, chemotaxis and collagenase production.

Fibroblasts lay down structural proteins such as collagen. Fibroblasts produce matrix metalloproteinases (MMPs). The fibroblast movement within the matrix has been facilitated by these proteolyticenzymes(MMPs). Later the fibroblasts decrease their proteolytic activity and start to lay down structural proteins. This step is regulated by two growth factors such as TGF- β and connective tissue growth factor(CTGF).The TGF-β has been secreted by both platelets and macrophages. The connective tissue growth factor (CTGF) secreted by the fibroblasts themselves. The Collagen synthesis involves hydroxylation of proline and is affected by vitamin C deficiency.

Angiogenesis replaces the damaged vasculature with the granulation tissue. Epidermal cells, vascular endothelial cells, fibroblasts and macrophages contribute to angiogenesis by the production of VEGF, βFGF and TGF-β . The proliferative effects of VEGF are regulated by hypoxia which stimulates the VEGF-induced angiogenesis using adenosine as an intermediary. In fact, adenosine, acting via A_{2A} receptors is now considered a potent regulator of the early stages of wound healing [Fig.3].[26]

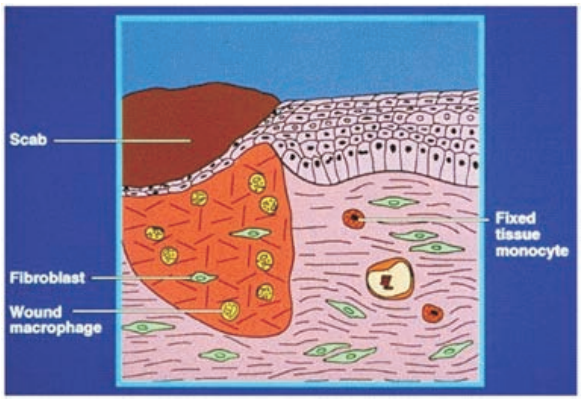

Fig. 3 : Proliferative phase

Epithelialization proceeds with the proliferation and the migration of the epithelial cells and is helped by keratinocyte growth factors (KGFs), EGF and TGF-α. The cells and the extracellular matrix interact closely and continually and stimulating each other.

d)Phase IV: Remodelling

Remodelling is the resolution stage of healing. Inflammatory cells leave and cells that release the growth factors become fewer. Fibroblasts continue to lay down collagen even as they too begin to decrease in number. Further, remodelling takes place by covalent cross-linking of collagen molecules.(Fig.4) In a well-healed wound the final tensile strength may be as high as 80% of that possessed by the normal tissue. [9-15, 26]

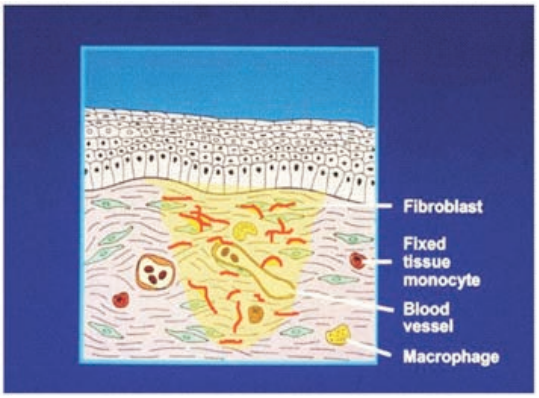

Fig. 4 : Remodeling phase

Factors affecting wound healing

The factors that influence repair has been categorized into local and systemic. Local factors are those that directly influence the characteristics of the wound itself. Systemic factors are the overall health or disease state of the individual that affect his or her ability to heal.

Local Factors Influence Healing:

a) Oxygenation

Oxygen is important for cell metabolism especially in energy production by means of ATP. It prevents wounds from infection, induces angiogenesis, increases keratinocyte differentiation, re-epithelialization and migration.It enhances fibroblast proliferation and collagen synthesis and promotes wound contraction.The level of superoxide production by polymorphonuclear leukocytes is critically dependent on oxygen levels.

b) Infections

Based on state of infection and replication status of the micro-organisms the wound is classified as having contamination, colonization, local infection/critical colonization, and/or spreading invasive infectionwithin a wound with subsequent host injury.Both bacteria and endotoxins can lead to the prolonged elevation of pro-inflammatory cytokines(IL-1 and TNF-α) and elongate the inflammatory phase. If this continues, the wound leads to a chronic state and fail to heal. The bacteria in infected wounds occur in the form of biofilms, which are complex communities of aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix.

*P. aeruginosa*and *Staphylococcus* appear to play an important role in bacterialinfection. Because of the presence of biofilms containing *P. aeruginosa*, many chronic ulcers probably do not heal, thus shielding the bacteria from the phagocytic activity of invading polymorphonuclear neutrophils (PMNs). This mechanism may explain the failure of antibiotics as a remedy for wounds.

Systemic Factors Influence Healing

a) Age

Delayed wound healing in the aged is associated with an altered inflammatory response such as delayed T-cell infiltration into the wound area with alterations in chemokine production and reduced macrophage phagocytic capacity.

b)Sex hormones in aged individuals

Compared with aged females, aged males have been shown delayed healing of acutewounds. The reason is that the female estrogens (estrone and 17β-estradiol), male androgens (testosterone and 5α-dihydrotestosterone, DHT), and their steroid precursordehydroepiandrosterone (DHEA) are appear to have significant effects on the wound-healing process.

c) Stress

Studies in both humans and animals have shown that psychological stress causes a substantial delay in wound healing.

d) Diabetes

Diabetic individuals exhibit a noticeable impairment in the healing of acute wounds. This population is prone to develop chronic non-healing diabetic foot ulcers (DFUs) which are estimated to occur in 15% of all persons with diabetes. The impaired healing of both DFUs and acute cutaneous wounds with diabetes involves multiple complex pathophysiological mechanisms.

e)Medications

Many medications interfere with clot formation or platelet function, or inflammatory responses and cell proliferation have the capacity to affect wound healing.

Glucocorticoid Steroids:

Systemic glucocorticoids are well-known to inhibit wound repair via global anti-inflammatory effects and suppression of cellular wound responses including fibroblast proliferation and collagen synthesis.

Non-steroidal Anti-inflammatory Drugs:

Systemic use of ibuprofen in animal models has shown an anti-proliferative effect on wound healing and resulting in decreased numbers of fibroblasts, reduced wound contraction, delayed epithelialization, weakened breaking strength, and impaired angiogenesis. Effect of low-dose aspirin on healing are not completely clear. Clinical evaluations suggest that to avoid anti-platelet effects, individuals should discontinue NSAIDs for a time period equal to 4 to 5 times the half-life of drugs before surgery. Thus, the majority of surgical patients do not have significant NSAID activity at the time of wound repair. The exception may be those cardiac patients who must be maintained on low-dose aspirin due to severe risk of cardiovascular events .

Chemotherapeutic Drugs:

Most chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, and angiogenesis and thus inhibit many of the pathways that are critical to appropriate wound repair. These medications inhibit DNA, RNA, or protein synthesis, resulting in decreased fibroplasia and neovascularization of wounds.

f) Obesity

Obese individuals frequently face wound complications including skin woundinfection, dehiscence, hematoma and seroma formation, pressure ulcers and venous ulcers.

g) Alcohol Consumption

Animal experiments and clinical evidence have shown that exposure to alcoholimpairs wound healing and increases the chances of infection.

h)Smoking

Patients who smoke show a delay in wound healing and an increase in a variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis and decrease in the tensile strength of wounds. Nicotine probably interferes with oxygen supply by inducing tissue ischemia because nicotine can cause decreased tissue blood flow via vasoconstrictive effects.

i)Nutrition

Most obvious is that malnutrition or specific nutrient deficiencies can have a greatimpact on wound healing after trauma and surgery.

Carbohydrates, Protein, and Amino Acids:

Together with fats the carbohydrates are the primary source of energy in the wound-healing process. Glucose is the major source of fuel helps to create the cellular ATP that provides energy for angiogenesis and deposition of the new tissues.A deficiency of protein can impair capillary formation, fibroblast proliferation, collagen synthesis,proteoglycan synthesis and wound remodeling. A deficiency of protein can also affects the immune system with resultant decreased leukocyte phagocytosis and increased susceptibility to infection .Collagen is the major protein component of the connective tissue and is composed primarily of proline, hydroxyproline and glycine.

Arginine is a semi-essential amino acid that is required for maximal growth, severe stress, and injury.Glutamine is the most abundant amino acid in plasma and is a major source of metabolic energy for rapidly proliferating cells such as fibroblasts, macrophages, lymphocytes and epithelial cells. Glutamine has a crucial role in stimulating the early inflammatory immune response in wound healing.

Fatty Acids:

Lipids are used as nutritional support for surgical or critically ill patients to help meet energy demands. They provide as essential building blocks for wound healing and tissue repair.The effects of omega-3 fatty acids on wound healing are crucial.

Vitamins, Micronutrients, and Trace Elements:

Vitamins C (L-ascorbic acid), A (retinol), and E (tocopherol) show potent anti-inflammatory and anti-oxidant effects. Vitamin C deficiencies have been linked to decreased collagen synthesis and fibroblast proliferation, decreased angiogenesis, and increased capillary fragility. Also, vitamin C deficiency can leads to an impaired immune response and increased susceptibility to wound infection .Similarly, vitamin A deficiency can leads to impaired wound healing.Vitamin E is an anti-oxidant which maintains and stabilizes cellular membrane integrity by providing protection against destruction by oxidation. Vitamin E also has anti-inflammatory properties and has a role in decreasing excess scar formation in chronic wounds.

In case of micronutrients Magnesium functions as a co-factor for many enzymes involved in protein and collagen synthesis. Copper is a required co-factor for cytochrome oxidase, for cytosolic anti-oxidant superoxide dismutase and for the optimal cross-linking of collagen. Zinc is a co-factor for both RNA and DNA polymerases. Zinc deficiency causes a significant impairment in wound healing. Iron is required for the hydroxylation of proline and lysine. As a result the severe iron deficiency can result in impaired collagen production.[16]

Biomarkers of Healing and Non healing Wounds

The necessity of application of biomarkers is important in chronic wounds. Because,the chances of bacterial, fungal and other infections are there and which will affect the healing ofwound. The potential biomarkers are cytokines and proteases.

Cytokines levels

Cytokine levels are higher in nonhealing wounds than in healing wounds, especiallythe levels of IL-1, IL-6, and TNF-α. Trengove*et al*. found that median levels of IL-1 were 9200 U/ml (range 1300-48000) in nonhealing wounds, compared to 2700 (400-14000) U/ml in healing wounds. Similarly, the levels of IL-6 and TNF-α were also significantly higher in nonhealing wounds. Beidler*et al*. reported very high values for IL-8 in chronic wounds.[9]

Protease levels

Protease levels are more reliable biomarkers of poor healing. Utz*et al*. studied 38 wounds in 25 patients and collected samples during successive wound debridement's.[9] They stated that serum MMP-2 and MMP-7 were statistically predictive of wound healing outcome,since, the higher the level, the lower the chance of successful healing. Snyder *et al*. reported the findings of a consensus panel, which concluded that the wound levels of elastase, metalloproteinases, and MMP-9/TIMP ratios could prove good prognosticators of wound behaviour.

Gene expression

Gene expression analysis may be an option in future. Asada and Coworkersreported an experimental study in which they showed changes on gene expression analysis.[9]Using reverse transcription polymerase chain reaction on wound fluid in rats they showed that, virulence factor bacterial genes were more likely to be expressed in the presence ofinvasive infection rather than mere colonization of wounds. Several genes which constitutively expressed to perform the cell's basic functions were more likely to be expressed in healthier wounds, but not in wounds that were infected. They suggested that gene expression analysis would help to establish the status of the wound.

Other substances

The wound fluid myeloperoxidase levels were associated with nonhealing and infected wounds. Chronic wounds contain higher quantities of reactive oxygen species. The healing was invariably successful in wounds with procalcitonin levels lower than 220 pg/ml, suggests that procalcitonin may have potential as a marker of healing.

Tissue bacterial levels

Predictive marker of healing in both chronic and acute wounds is the tissue bacteriallevel. High tissue levels of bacteria inhibit or impair all the processes of wound healing and also prevent satisfactory repair of wound.[9]

Herbalimportance in wound healing.

Plant extracts have immense potential for the management and treatment of wounds. The phyto-medicines for wound healing are cheap,affordable and hyper sensitive reactions are rarely encountered with the use of these agents. These natural agents induce healing and regeneration of the lost tissue by various mechanisms. However, there is a need for scientific validation, standardization and safety evaluation of these medicinal plants before these could be recommended for healing of the wounds.[17]

The aim of herbal treatment is to produce persisting improvements in wellbeing. Practitioners also try to treat the 'underlying cause' of disease and may prescribe herbs aimed at correcting patterns of dysfunction rather than targeting the presenting symptoms. The medicinal value of these plants depends on the bioactive phytochemical constituents that produce definite physiological action on the human body[18]. These constituents include various chemical families like alkaloids, phenolic compounds, flavonoids, tannins,essential oils, terpenoids and saponins.[19]The major problem with pharmacological validation of the wound healing plants was that, the exact mechanism of the healing process of wound was not clearly understood. [20] Hence most of the researchers restricted

the screening of plants into simple healing of wounds and did not go into details. The validation by scientific method of the various plant species could form the basis for their use as alternative treatments or when conventional therapy by Western medicine is unavailable.[21]

The ethnobotanical study of wound healing treatments among the tribal people of Tirunelveli hills in southern India shows, total of 46 plants belonging to 44 genera and 26 families have been documented for their therapeutic use against wounds and related injuries such as cuts, burns, bruises caused by external injury, boils, sores, abscess and wounds created during delivery. Leaves were the most commonly utilized plant part and most herbal remedies are prepared as paste and applied externally. In some cases medicinal preparations were also administered orally. According to Biswas and Mukherjee,70% of the wound healing Ayurvedic drugs are of plant origin, 20% of mineral origin and the remaining 10% consisting of animal products.[22]Astudy reported that some plants have promising wound healing activity. They are *Aloe vera, Azadirachta indica,Lantana camara, Hypericumspp, Tridaxprocumbens, Chromolaenaodorata, Hydnocarpuswightiana, Helianthus annusLinn, Jasminumauriculatum, Ginkgo biloba, Curcuma longa Linn., Centellaasiatica, Cedrusdeodara.* Also reported some prohealers such as *Ocimum sanctum*, *Begiaodorata*, *Euphoribianerrifolia*, *Indigoferaaspalathoides*, and *Mangiferaindica*. This study also reportedthat the poly herbal preparation or various combinations of extracts like *Balsamodendronmukul* (guggul*), Maharasanadikwath, Phyllanthusembica, Tinosporacordifolia, Rubiacordifolia, Glycyrrhizaglabra* and shankabhasma are have wound healing action. Poly-herbal preparations containing these herbs are useful in treating Gram negative and Gram positive infections.[17]

Natural products with wound healing activities:

The bioactive compounds which promotes wound healing events can be therapeutically used to improve the wound-healing activity. Reactive oxygen species (ROS) has a vital role in wound healing. In the inflammation phase neutrophils and macrophages are attracted into the injured tissue. They phagocytize and digest the microorganisms and eliminate wound debris that results in the generation of free radicals such as superoxides. Superoxide is rapidly converted to H_2O_2 by superoxide dismutase. Release of H_2O_2 may promote the formation of other oxidants that are more stable. This suggests that the wound area is rich in oxidants.

Topical applications of compounds with free-radical-scavenging properties in patients shows significant improvement in wound healing and also protect tissues from oxidative damage. Antioxidants thus enhance the healing of bacterial infected and non-infected wounds, by reducing the damage caused by oxygen radicals.Plants provide great variety of phytochemicals that can be used as precursors for the synthesis of new drugs with definite biological effects. [23]Literature survey has revealed that tannins promote wound healing activitythrough several mechanisms including chelation of free radicals, antioxidant, antimicrobial and astringent property. Phenolic acids have been reported to possess anti-inflammatory, anti-oxidant, analgesic and wound healing properties.

Flavonoids may contribute an additive effect to the endogenous antioxidants and to inhibit the eicosanoid biosynthesis. Therefore decreasing the formation of the inflammatory metabolites which responsible for its anti-inflammatory property. Hence, the free radical scavenging, antioxidant and anti-inflammatory properties and flavonoids may help in healing of wounds.[24]Triterpenoids are responsible for wound healing property. Flavonoids reduce lipid peroxidation not only by preventing or slowing onset of cell necrosis and by improving vascularity.Lipid peroxidation is an important process in several types of injuries like burns, skin ulcers and infected wound. Hence any drug that inhibits lipid peroxidation is believed to increase the strength of collagen fibers, by increasing circulation or by preventing cell damage or by promoting DNA synthesis. Flavonoides and triterpenoides are known to promote wound healing process mainly by their astringent and antimicrobial property.[25]

CONCLUSION

Regeneration and tissue repair processes consist of a sequence of molecular and cellular events which occur after the onset of a tissue lesion in order to restore the damaged tissue.

The purpose of this review is to describe the various cellular and molecular aspects involved in the skin healing process. This review gives a brief information about pathology, factors influencing and biomarkers of wound healing,and animportance of herbal plants in wound healing.

REFERENCES

1. Shankar M, Ramesh B, Roopa Kumar D, Niranjan Babu M. Wound healing and it's importance-a review. *Der PharmacologiaSinica.* 2014; 1(1): 24-26.
2. Badri Prakash Nagori, Renu Solanki. Role of medicinal plants in wound healing. *Research Journal of Medicinal Plant.* 2011; (1): 2-3.
3. Kumar B, Vijayakumar M. Govindarajan R, Pushpangadan P. Ethnopharmacological approaches to wound healingexploring medicinal plants of India. *Journal of Ethnopharmacology.* 2007; 114(2): 103-110.
4. KF Chah, CA Eze, CE Emuelosi, CO Simone. Antibacterial and wound healing properties of methanolic extracts of some Nigerian medicinal plants. *Journal of Ethnopharmacology*2006; 104(2): 164-167.
5. Patel DK. Some traditional medicinal plants useful for boil, burn and for wounds healing. *Biodiversity & Endangered Species* 2014; 2(4): 2-4.
6. Hemant Kumar Nagar, Amit Kumar Srivastava, Rajnish Srivastava, Madanlal Kurmi, Harinarayan Singh Chandel, Mahendra Singh Ranawat. Pharmacological investigation of the wound healing activity of Cestrum nocturnum (L.) ointment in Wistar albino rats. *Journal of Pharmaceutics* 2016; (1): 1.
7. PrafullaSabale, Bhargav Bhimani, ChiragPrajapati, Vidya Sabalea. An overview of medicinal plants as wound healers. *Journal of Applied Pharmaceutical Science* 2012; 2(11): 143.
8. Rupesh Thakur, Nitika Jain, Raghvendra Pathak, Sardul Singh Sandhu. Practices in wound healing studies of plants. *Evidence-Based Complementary and Alternative Medicine.* 2011; (1): 1-10.
9. JumaatMohd, Yussof Shah, Effat Omar, Dinker R Pai, SuneetSood. Cellular events and biomarkers of wound healing. *Indian Journal of Plastic Surgery.* 2012; 45(2): 220-228.

10. Richard Sal Salcido. Healing by intention. *Advances in Skin & Wound Care.* 2017; 30(6): 246.

11. Karen Zulkowski. Understanding Moisture-Associated Skin Damage, Medical Adhesive-Related Skin Injuries, and Skin Tears. *Advances in Skin and Wound Care.* 2017; 30(8): 372-380.

12. Janice K Kiecolt-Glaser, Phillip T Marucha, William B Malarkey, Ana M Mercado, Ronald Glaser . Slowing of wound healing by psychological stress .*The Lancet* 1995; 346(): 1-3.

13. Margaret L Novak, Timothy J Koh. Phenotypic transitions of macrophages orchestrate tissue repair. *The American Journal of Pathology.* 2013; 183(5): 1352-1359.

14. Carlos M Minutti, Johanna A Knipper, Judith E Allen, Dietmar MW Zaiss. Tissue-specific contribution of macrophages to wound healing. *Seminars in Cell &Developmental Biology.*2017; 61(): 3-11.

15. Rupesh Thakur, Nitika Jain, Raghvendra Pathak, Sardul Singh Sandhu. Practices in wound healing studies of plants. *Evidence-Based Complementary and Alternative Medicine.* 2011; (1): 1-16.

16. GuoS , DiPietroLA. Factors affecting wound healing. *Journal of DentalResearch.*2010; 89(3): 219-229.

17. Rajinder Raina, Shahid Parwez, VermaP K, PankajN K. Medicinal plants and their role in wound healing. *Vet Scan.* 2008; 3(1): 1-6.

18. Ayyanar M, Ignacimuthu S. Medicinal plants used by the tribal of Tirunelvelihills, Tamilnadu to treat poisonous bites and skin diseases. *Indian Journal of Traditional Knowledge.*2005; 4(3): 229-230.

19. NayakBS, Lexley M Pinto Pereira. Catharanthusroseus flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine.* 2006; 6(41): 2-6.

20. Afolabi C Akinmoladun, Ibukun EO, Emmanuel A for , Akinrinlola BL, OnibonT R, Akinboboye A O et al. Chemical constituents and antioxidant activity of *Alstoniaboonei. African Journal of Biotechnology.* 2007; 6(10): 1197-1199.

21. Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical constituents of some Nigerian medicinal plants. *African Journal of Biotechnology.* 2005; 4(7): 685-688.

22. Ayyanar M, Ignacimuthu S. Herbal medicines for wound healing among tribal people in southern India: ethnobotanical and scientific evidences. *International Journal ofApplied Research in Natural Products.*2009; 2(3): 29-35.

23. Blassan P George, Thangaraj Parimelazhagan, Rahul Chandran. Anti-inflammatory and wound healing properties of Rubusfairholmianus Gard. rootan in vivo study. *Industrial Crops and Products.* 2014; 54: 216-218.

24. Sushilkumar B Varma, Sapna P Giri. Study of wound healing activity of Tectonagrandis Linn. leaf extract on rats. *Ancient Science of Life.* 2013; 32(4): 231-240.

25. Lakshmi DeviS, Madhu C Divakar. Wound healing activity studies of *Wrightiaarborea Phytosome* in rats .*Hygeia: Journal for Drugs and Medicines* 2012; 4(2): 87-94.

26. Gregory S. Schultz, Gloria A. Chin, Lyle Moldawer, Robert F. Diegelmann. Principles of Wound Healing. Mechanisms of Vascular Disease: A Reference Book for Vascular specialists. 23.2011.