IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Natural Compounds Used In Wound Healing: A Comprehensive Review

Abhishek Singh[1], Dr. Ratan Deep Chauhan[2], Dr. Pushpendra Kannojia[3] [1]M.pharm (Pharmacology) Research Scholar, [2] Associate Professor, [3] Principal

BIU COP Bareilly International University, Pilibhit Bypass Road, Bareilly, Uttar Pradesh (U.P.) – 243006, India.

ABSTRACT

The process of repairing damaged tissues through the replacement of malfunctioning, damaged cellular structures is known as wound healing. For millennia, natural substances have been utilized extensively to cure wounds. Studies of natural compounds for wound healing uses were presented in a number of published publications, which divided the methods according to many categories such traits, bioactivities, and modes of action. Nonetheless, recent research offers summaries of natural substances derived solely from plants or animals. Strong antioxidant, anti-inflammatory, antibacterial, and immunomodulatory qualities have been demonstrated for a variety of natural substances obtained from plant or animal sources. By creating multipurpose bioactive wound dressings, these substances may help control wound healing. However, due to their sensitivity, bioavailability, and contact allergies, many of these substances-especially essential oils and phytochemicals-cannot be used in their free form, which could hinder their application in wound healing.

KEYWORDS: Wound healing, Natural compounds, Bioactivity, Anti-inflammation, Anti- oxidant, Anti-bacterial, Collagen promotion, Targeting phase

INTRODUCTION

A wound is a disruption in the integrity of the skin's epithelial lining, which can result from physical or thermal injury. The four primary stages of wound healing are the coagulation phase, which occurs right after injury; the inflammatory phase, which may cause swelling; the proliferation phase, which involves the development of newly formed blood vessels and tissue; and the maturation phase, which involves the remodelling of new tissues. These stages take place in a clear sequence and are integrative. The type of wound has a significant impact on how well the healing phases are completed [1]. There are two types of wounds: acute and chronic. Replacing damaged and malfunctioning cellular structures and tissue layers is a complicated process involved in wound healing [2]. Within four weeks, acute wounds begin to show clear evidence of healing. Four weeks is not enough time for chronic wounds to show signs of healing because they do not go through the healing phases normally. One could argue that the type of injury, systemic mediators, the wound site, and any underlying illness all affect how quickly a wound heals [3]. Sutures, dressings, and physical healing of the wound margin are the basic methods used to treat wounds. When the wound is inaccessible, keep it open so that the injured region can mend itself and filled with connective tissue. The healing process happens in stages. For thousands of years, people have employed natural substances to heal wounds. Numerous plants and animals contain natural chemicals, which are a readily available source for treating wounds. Using ancient Chinese and Indian remedies, they have shown promise in healing [4]. Damage or injury to the skin is referred to as cutaneous wounds. But wounds are not the same. Knowing the kind of wound is essential before choosing the best course of treatment because each form of wound differs greatly from the others due to its unique biology and pathophysiology [5]. There are a number of internal and external variables that can cause cutaneous wounds. There are a number of internal and external variables that can cause cutaneous wounds. While internal variables may result from dysregulation in certain metabolic pathways, such as diabetes, external factors are primarily environmental factors that can cause skin damage, such as injuries from accidents [5].

THE PROCESS OF WOUND HEALING

Haemostasis, inflammation, proliferation, and remodelling are the four stages of the wound healing process. An example of how a wound heals is shown in the given figure:

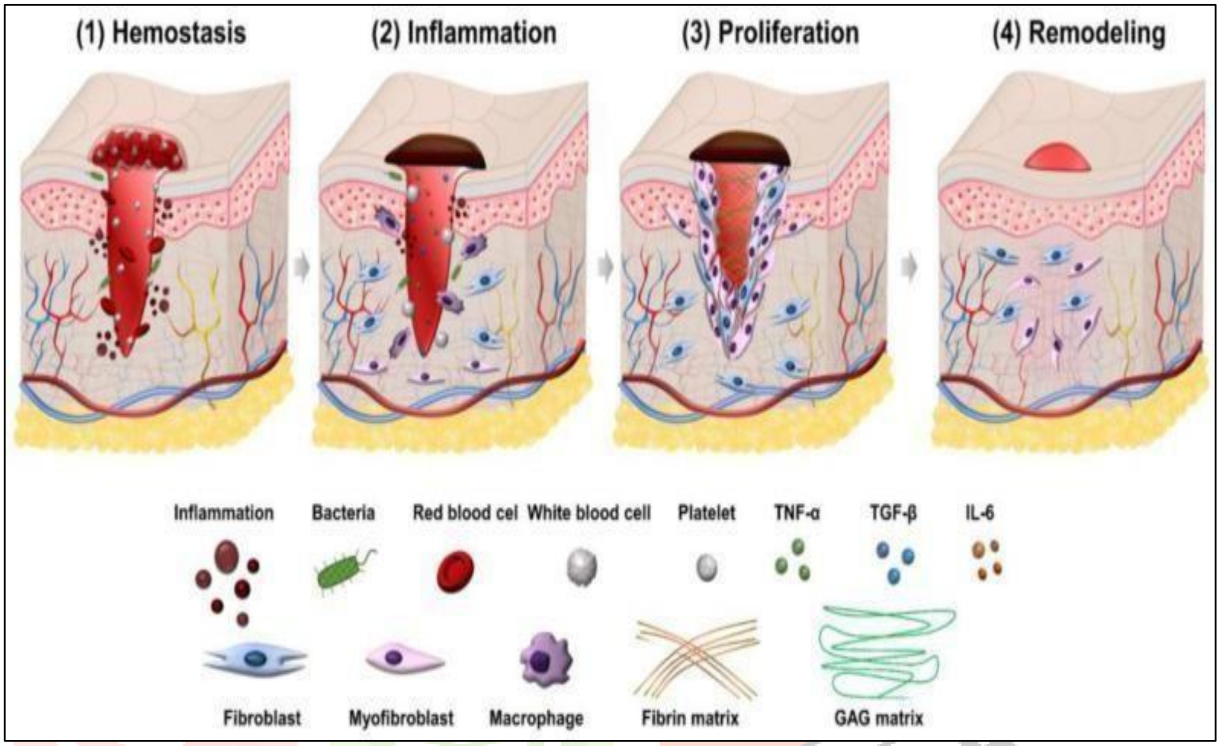

Fig 1: The process of wound healing [4]

i. Haemostasis Phase

Haemostasis is the initial step in wound healing. In order to eliminate microbes and antigens, blood rushes out of the damaged lymphatic capillaries during this phase [6]. When exposed collagen is present, the body will trigger several clotting cascades and thrombocytes to clump together. In order to minimize blood loss and replace tissue gaps in damaged arteries with blood clots that carry growth factors and cytokines, platelets simultaneously cause vasoconstriction [7]. The molecules fibrin, fibronectin, vitronectin, and thrombospondin are found in the clot. These molecules create a temporary matrix that serves as a scaffolding structure for the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells. Additionally, the clot is a reservoir of growth factors that prevent bleeding and stabilize blood clots [4].

ii. Inflammation Phase

Inflammation, the second stage of wound healing, aims to clean the wound and get it ready for the development of new tissue. This phase, which appears as neutrophils, lasts for two to five days after the wound gets infected. Proteases (elastase, cathepsin G, and proteinase 3) that aid in the destruction of germs in the wound and the removal of debris can be phagocytized and secreted by neutrophils. Additionally, neutrophils stimulate VEGF and IL-8 to respond to repair during wound healing by releasing mediators (TNF-α, IL-1, and IL-6) to intensify the inflammatory response [8]. The macrophage process then contributes to the continuing process by secreting growth factors, chemokines, and cytokines and phagocytosing the debris [9]. Macrophages enhance cell proliferation and tissue healing following injury, reduce apoptosis, and promote and manage inflammation [10].

iii. Proliferation Phase

The most crucial stage for the wound healing process, known as the proliferation phase, lasts between six to twenty-one days. Fresh collagen and extracellular matrix tissue are added to the wound in the proliferation phase of wound healing. After then, when new tissues grow, the wound gets smaller. Granulation tissues need a new blood artery network to stay healthy and get enough oxygen and nutrients. Granulation tissue development is facilitated by fibroblast regulation toward myofibroblasts. Myofibroblasts are distinguished by their ability to generate force and produce extracellular matrix components which facilitate granulation tissue contraction [11]. Myofibroblasts employ a method similar to smooth muscle cells to seal the wound by grasping its edges and drawing them together. Granulation tissue has an irregular texture and appears pink or crimson during the early phases of wound healing. Moreover, granulation tissue in good health is resistant to clots [12]. Infection, ischemia, or inadequate perfusion can all result in dark granulation tissue. The wound is resurfaced by epithelial cells close to the end of the proliferation phase. Epithelialization is accelerated when wounds are kept wet. When occlusive or semi-occlusive dressings are administered within 48 hours after the injury, epithelialization takes place. This is due to the maintenance of appropriate tissue humidity. One achievement of the proliferation phase is the restoration of tissue structure and function by substituting a new matrix made up of collagen fibres, proteoglycans, and fibronectin for the transient fibrin matrix [4].

iv. Remodelling Phase

In most clinical settings, the closure of both acute and chronic wounds is considered the wound healing endpoint; nevertheless, wounds can undergo tissue maturation or remodelling for a few years or months [13]. This last phase of wound healing determines whether scarring will develop and whether the wound will recur. The remodelling phase includes granulation tissue restoration to scar tissue, periodic deposition to the extracellular matrix, and regression of the neovascular system [14]. Granulation tissue is mostly composed of collagen III, which gets replaced over time as the wound heals with the stronger collagen I. This happens as a result of concurrent creation of collagen I and lysis of collagen III, followed by remodelling of the extracellular matrix [15]. Scar tissues are formed during the remodelling phase, which may take a few months or years to finish, depending on the location and severity of the wound and the treatment techniques used. The regenerated tissue progressively gains strength and flexibility during this period. Collagen synthesis is increasing the skin's tensile strength and elasticity. Macrophages restore their phagocytic nature during re- epithelialization. M2c-like macrophages phagocytose extra cells and matrix that are no longer needed for wound healing [16].

NATURAL COMPOUNDS FOR WOUND HEALING

Thousands of years ago, natural substances were widely utilized to cure wounds. These substances can be separated into natural compounds originating from plants and those derived from animals based on where they come from. Both sources are plentiful and simple to produce or extract [17]. Based on their bioactivities, natural chemicals for wound healing can also be categorized as pro- angiogenesis, anti-inflammatory, antioxidant, antibacterial, and collagen-promoting [17].

I. Essential oils

More than 17,000 plant species produce essential oils (EOs). With the exception of sassafras, vetiver, and cinnamon oils, these essential oils are insoluble volatile liquids with distinctive odours and comparatively low densities. Several plant sections are used to store essential oils obtained from plants. Orange and lavender flowers, roots (vetiver, sassafras), leaves (mint, thyme, and eucalyptus), bark (cinnamon, sandalwood, and rosewood), seeds (carvi and coriander), fruits (fennel and anise), and plant resins (frankincense) are other examples. These are secondary metabolites that have a distinct scent, are mostly composed of volatile hydrocarbons and terpenes, and have antibacterial, antifungal, and deterring properties that help plants protect themselves or appropriately adapt to their surroundings [18]. When essential oils for wound treatment are used topically, they come into direct contact with the skin and can be absorbed until they reach deeper layers [19].

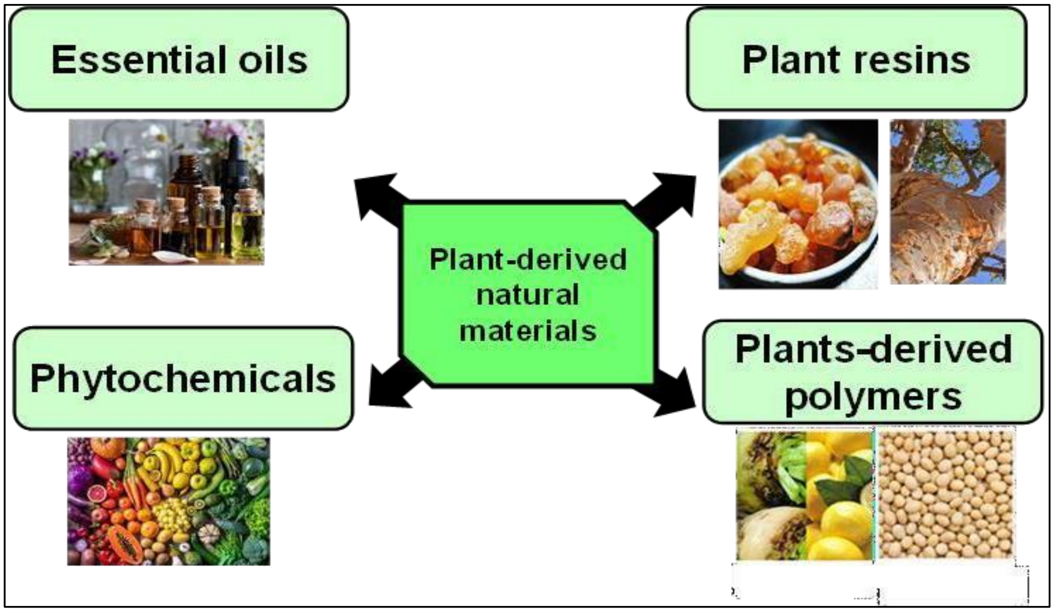

Fig 2: An illustration showing different plant-derived natural materials [18]

Table 1. Some essential oils with their storage parts in plants [18]

Essential oil	Storage part in plants	Density
Orange	Flowers	Less than one
Lavender	Flowers	Less than one
Vetiver	Roots	More than one
Sassafras	Roots	More than one
Mint	Leaves	Less than one
Thyme	Leaves	Less than one
Eucalyptus	Leaves	Less than one
Cinnamon	Bark	More than one
Sandalwood	Bark	Less than one
Rosewood	Bark	Less than one
Carvi	Seeds	Less than one
Coriander	Seeds	Less than one
Fennel	Fruits	Less than one
Anise	Fruits	Less than one
Frankincense	Plant resin	Less than one

II. Phytochemicals

For ages, traditional medicine has used plant phytochemicals-non-nutritive plant components-to treat wounds [20]. Based on their role in plants, they can be divided into primary and secondary metabolites. Plant viability depends on primary metabolites such lipids, proteins, carbohydrates, pyrimidines, and purines. Conversely, a class of plant compounds known as secondary metabolites is created by a variety of metabolic processes and may originate from fundamental metabolic cascades [21]. These secondary phytochemicals are thought to shield plants from infections because of their antiviral, antifungal, and antibacterial properties, according to numerous research. These substances can also shield plant leaves from severe light damage because they are potent UV absorbers [22]. Based on their chemical composition, secondary plant phytochemicals are divided into three main groups: (1) phenolic compounds like flavonoids and phenylpropanoids; (2) nitrogen- containing compounds like glucosinolates and alkaloids; and (3) terpenes [23]. Pentose phosphate and phenylpropanoid pathways in plants are the sources of phenolic chemicals. They include a few hydroxyl groups in an aromatic ring [24]. Plants create alkaloids, a type of nitrogen-containing chemicals, in response to the biotic or abiotic environmental stimuli. They are distinguished by the variety of their structures and functions [25]. In addition to being stable under typical circumstances, glucosinolates are distinguished by the inclusion of both nitrogen and sulphur atoms inside their structure [26]. One of the most prevalent classes of phytochemicals found in plants, terpenoids have a variety of biological functions. Roots, blooms, and vegetative tissues are among the plant parts that produce them [27]. These chemicals' strong anti-inflammatory and antioxidant properties [28], along with their capacity to speed up tissue epithelization and encourage angiogenesis [29], may account for most of their positive effects on wound healing. These phytochemicals have a wide range of pharmacological uses, but their low bioavailability, hydrophobicity, light sensitivity, and restricted skin penetration make them difficult to use in wound healing [30].

III. Resins

Resins are metabolic products that some plants release as natural exudates from wounds or injuries to their bark. *Commiphora myrrha* and *Boswellia serrata* are examples of oleo-resins. Typically, they have traces of the plant's essential oil. Resins are frequently utilized as thickeners, emulsifiers, stabilizers, and binding agents in the pharmaceutical industry. Resins were applied topically in the majority of studies as an ointment or cream with a specific concentration to control wound healing. The findings showed that formulations based on resin could improve tissue strengthening, wound contraction, and early collagen tissue development in the injured area [31]. Frankincense resin, which is made from the bark of Boswellia trees, is one of the most well-known plant resins [32]. It is mostly made up of alcohol-soluble substances including di- and triterpenes (30–60%), essential oils (5-10%), and gum, which is made up of water-soluble saccharides like pentose and hexose [33]. Numerous cosmetic formulations, such as soaps, creams, and lotions promoting skin softening and the treatment of certain skin conditions, contained frankincense resin [34]. Because boswellic acids (BA) can inhibit 5-lipoxygenase, which is responsible for the manufacture of leukotrienes, this resin has been demonstrated to possess an anti-inflammatory action [34]. Furthermore, frankincense resin can cause consistent skin pigmentation and lessen skin irritation, indicating that it may be a sophisticated substance for wound healing [35]. This resin was used in a recent study to create a biocompatible film for wound healing.

IV. Biopolymers

Since most plant-based biopolymers are multifunctional, adjustable, and may be made in a variety of forms with prolonged drug release depending to the assigned application, they have been studied for biomedical applications for many years [36]. Plant-derived biopolymers are broadly classified into proteins like soy, gluten, and zein [37] and polysaccharides like pectin, starch, alginate, and cellulose [38]. Researchers are drawn to these biopolymers because they have some advantageous characteristics in common. They are plentiful, non-carcinogenic, non-immunogenic, and biocompatible [37].

According to a number of research, these biopolymers can be employed in wound healing by being formulated into various structures, including hydrogels, membranes, nanofibers, and composites, to provide intelligent and multipurpose wound dressing materials [39].

V. Chitosan

Animal-derived polymers are abundant in nature and have a wide range of medicinal uses. These polymers are all nontoxic, non-immunogenic, biodegradable, and biocompatible [40]. Chitosan represents one of the greatest often used polymers generated from animals. N-acetylglucosamine and glucosamine are joined by a 1-4 glycosidic link to form this co-polymer. In addition to being found in yeasts, fungi, and insects, chitosan is a derivative of chitin, which is widely distributed in the exoskeleton of marine crustaceans like crabs and shrimp [41]. Since it is the only positively charged polysaccharide because of the presence of amino groups in its structure, which boosts its potential to interact with negatively charged molecules found in the bacterial cell membrane, it can be used in wound healing because of its strong antibacterial activity [42]. However, because chitosan is only soluble at pH values lower than 6.5, it cannot be utilized in its free form for wound healing [43].

VI. Hyaluronic acid

Our bodies contain large amounts of hyaluronic acid (HA), a naturally occurring polymer. N-acetyl- D-glucosamine and D-glucuronic acid are repeating units in this extremely anionic and hydrophilic polymer. Depending on the intended use, this intriguing biopolymer can be readily altered to produce a variety of derivatives. Furthermore, hyaluronic acid serves as a targeting molecule that can bind to CD44 receptors that are overexpressed in certain conditions [44]. It was discovered that HA's role in wound healing varies depending on its size. Large chains can operate as a space filler during the creation of granulation tissue, but they are necessary during the inflammatory phase to function as a porous network. On the other hand, short and light HA fragments can promote appropriate collagen deposition and fibroblast migration [45]. To control wound healing, numerous formulations based on HA or its analogues combined with other polymers were created in the form of films, hydrogels, or nanocomposites [46].

VII. Bee products (Apitherapeutic)

Apitherapy is the use of certain bee products to treat certain human conditions [47]. All varieties of honey can be summed up as an acidic (pH 3.6) concentrated aqueous solution that contains enzymes, minerals, and vitamins along with sugars in various ratios (40% glucose, 40% fructose, and 20% water) [48]. Because the natural enzyme glucose oxidase produces hydrogen peroxide, bee honey essentially acts as an antibacterial agent during wound healing. Reactive free radicals are produced when hydrogen peroxide breaks down, and these radicals have the ability to directly contact with bacteria and kill them [49]. However, depending on their high sugar content and low pH, some honey varieties function as antibacterial agents and do not create hydrogen peroxide [50]. Propolis, another component of honeybees, is made up of at least 300 different substances, mostly amino acids, steroids, and phenolic compounds [51]. Because they include phenolic chemicals and cinnamic acids, they have strong antibacterial activity [52]. Additionally, some plant sources like birch, beech, and willow contain propolis [53].

VIII. Hydrogels

Due to their water absorption qualities, hydrophilicity, non-adhesiveness, and capacity to replicate the skin microenvironment, hydrogels made from natural polymers are an excellent option for encapsulating natural compounds with increased potency in wound management [54]. They can be combined directly with active compounds or put into nanoparticles containing active chemicals. Gelatin is a naturally occurring protein that is generated from collagen. Because of its well-known action in cellular migration, proliferation, and adhesion, it can be used to make wound dressings [55]. Its poor mechanical qualities, however, prevent it from being used exclusively in the creation of wound dressings; instead, it should be crosslinked or combined with other biomaterials, like plasticizers or nanoparticles, to enhance its mechanical qualities [56].

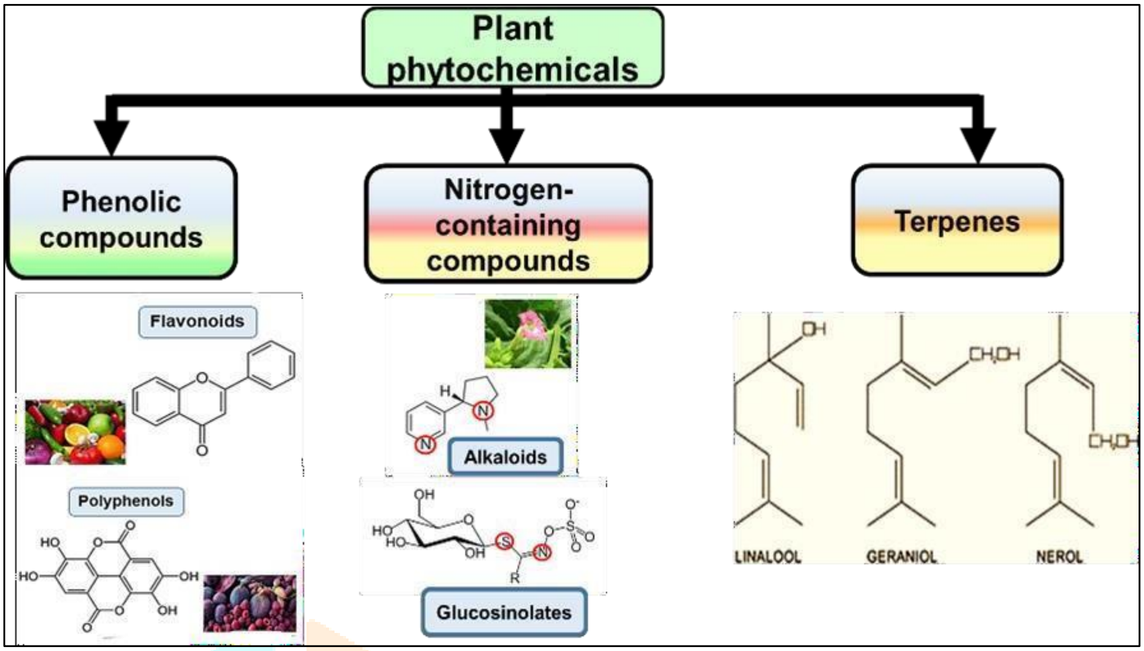

Fig 3: Different plant phytochemicals with wound healing potential [18]

CONCLUSION

In reaction to a cut or injury to the skin, wound healing is a typical physiological overlapping process that takes place concurrently. Conventional wound dressings are often composed of inert materials that have no effect on the healing process and only operate as a barrier to reduce bacterial infections. Natural materials are becoming more and more popular as wound-healing materials because of their affordability, safety, and—most importantly—their special multifunctionality and bioactive qualities. These organic substances may have antibacterial, anti-inflammatory, antioxidant, or collagen synthesis-promoting properties. Researchers may encounter certain obstacles while attempting to apply these substances to wound healing, though. The creation of formulations based on natural ingredients that effectively control the healing of various wound types has advanced significantly. These formulations include hydrogels based on natural polymers, films based on plant resins, and composites of nanoparticles in nanofibers. Before these polymer-based formulations are used in clinical settings in the future, their clinical potential should be assessed. Scaling up these formulations is a significant issue, though, since they must be made in big quantities in a repeatable manner and successfully finish all formulation stages and clinical review before being released into the market.

REFERENCES

1. Pena OA, Martin P. Cellular and molecular mechanisms of skin wound healing. Nat Rev Mol Cell Biol. 2024; 25:599-616.
2. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin Wound Healing: An Update on the Current Knowledge and Concepts. Eur Surg Res. 2017; 58:81-94.
3. Schreml S, Szeimies RM, Prantl L, Landthaler M, Babilas P. Wound Healing in the 21st Century. J Am Acad Dermatol. 2010; 63:866-81.
4. Trinh XT, Long NV, Van Anh LT, Nga PT, Giang NN, Chien PN, Nam SY, Heo CY. A Comprehensive Review of Natural Compounds for Wound Healing: Targeting Bioactivity Perspective. Int J Mol Sci. 2022 Aug 24; 23(17):9573.
5. Irfan-Maqsood M. Classification of wounds: know before research and clinical practice. J Genes Cells. 2018;4(1):1-4.
6. Strodtbeck F. Physiology of Wound Healing. Newborn Infant Nurs Rev. 2001; 1:43-52.

7. Martin P. Wound HealingAiming for Perfect Skin Regeneration. Science. 1997; 276:75-81.

8. Eming SA, Krieg T, Davidson JM. Inflammation in Wound Repair: Molecular and Cellular Mechanisms. J Investig Dermatol. 2007; 127:514-25.

9. Tziotzios C, Profyris C, Sterling J. Cutaneous Scarring: Pathophysiology, Molecular Mechanisms, and Scar Reduction Therapeutics. J Am Acad Dermatol. 2012; 66:13-24.

10. Koh TJ, DiPietro LA. Inflammation and Wound Healing: The Role of the Macrophage. Expert Rev Mol Med. 2011;13: e23.

11. Desmouliere A, Darby IA, Laverdet B, Bonte F. Fibroblasts and Myofibroblasts in Wound Healing. Clin Cosmet Investig Dermatol. 2014; 7:301.

12. Grey JE, Enoch S, Harding KG. Wound Assessment. BMJ. 2006; 332:285-8.

13. Eriksson E, Liu PY, Schultz GS, Martins-Green MM, Tanaka R, Weir D, *et al.* Chronic Wounds: Treatment Consensus. Wound Repair Regen. 2022; 30:156-71.

14. Xue M, Jackson CJ. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. Adv Wound Care. 2015;4: 119-36.

15. Czubryt MP. Common Threads in Cardiac Fibrosis, Infarct Scar Formation, and Wound Healing. Fibrogenesis Tissue Repair. 2012; 5:19.

16. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol Rev. 2019; 99:665-706.

17. Trinh XT, Long NV, Van Anh LT, Nga PT, Giang NN, Chien PN, *et al.* A comprehensive review of natural compounds for wound healing: targeting bioactivity perspective. Int J Mol Sci. 2022;23(17):9573.

18. Baptista-Silva S, Borges S, Ramos OL, Pintado M, Sarmento B. The progress of essential oils as potential therapeutic agents: a review. J Essent Oil Res. 2020;32(4):279-95.

19. Nascimento ASD, Tamiasso RSS, Morais SFM, Rizzo Gnatta J, Turrini RNT, Calache ALSC, *et al*. Essential oils for healing and/or preventing infection of surgical wounds: a systematic review. Rev Esc Enferm USP. 2022;56 (spe): e20210442.

20. Shah A, Amini-Nik S. The role of phytochemicals in the inflammatory phase of wound healing. Int J Mol Sci. 2017;18(5):1068.

21. Hussein RA, El-Anssary AA. Plants secondary metabolites: the key drivers of the pharmacological actions of medicinal plants. Herbal Med. 2019;1(3).

22. Bourgaud F, Gravot A, Milesi S, Gontier E. Production of plant secondary metabolites: a historical perspective. Plant Sci. 2001;161(5):839-51.

23. Jan R, Asaf S, Numn M, Lubna, Kim K. Plant secondary metabolite biosynthesis and transcriptional regulation in response to biotic and abiotic stress conditions. Agronomy. 2021;11(5):968.

24. Rathod NB, Elabed N, Punia S, Ozogul F, Kim S, Rocha JM. Recent developments in polyphenol applications on human health: A Review with current knowledge. Plants (Basel). 2023;12(6):1217.

25. Takooree H, Aumeeruddy MZ, Rengasamy KRR, Venugopala KN, Jeewon R, Zengin G, *et al.* A systematic review on black pepper (Piper nigrum L.): from folk uses to pharmacological applications. Crit Rev Food Sci Nutr. 2019;59(sup1): S210-43.

26. Del Carmen Martínez-Ballesta M, Moreno DA, Carvajal M. The physiological importance of glucosinolates on plant response to abiotic stress in brassica. Int J Mol Sci. 2013; 14:11607-25.

27. Baccouri B, Rajhi I. Potential antioxidant activity of terpenes. Terpenes and Terpenoids-Recent Advances. Intech Open; 2021. p. 53-62.

28. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. Food Chem. 2019; 299:125124.

29. Carvalho MTB, Araújo-Filho HG, Barreto AS, Quintans-Júnior LJ, Quintans JSS, Barreto RSS. Wound healing properties of flavonoids: A systematic review highlighting the mechanisms of action. Phytomedicine. 2021; 90:153636.

30. Micale N, Citarella A, Molonia MS, Speciale A, Cimino F, Saija A, *et al.* Hydrogels for the Delivery of Plant- Derived (Poly) Phenols. Molecules. 2020;25.

31. Zaheri-Abdevand Z, Badr P. A Review of the wound-healing properties of selected plant exudates. J

Herbal Med. 2023; 41:100715.
32. Bekana D, Kebede T, Assefa M, Kassa H. Comparative phytochemical analyses of resins of Boswellia species (B. papyrifera (Del.) Hochst., B. neglecta S. Moore, and B. rivae Engl.) from Northwestern, Southern, and Southeastern Ethiopia. Int Sch Res Notices. 2014; 2014:374678.
33. Cao B, Wei X, Xu X, Zhang H, Luo C, Feng B, *et al*. Seeing the unseen of the combination of two natural resins, frankincense and myrrh: Changes in chemical constituents and pharmacological activities. Molecules. 2019;24(17):3076.
34. Elhaddad HM, Hammoda HM, Ghareeb DA, Mahmoud, Hussein A, Yousef MI, *et al*. Investigating the effect of extraction procedure on the anti-inflammatory metabolites of olibanum resin from different Boswellia species through LC–MS/MS-based metabolomics. Food Biosci. 2024; 53:102668.
35. Solanki N, Gupta G, Chellappan DK, Singh SK, Gulati M, Paudel KR, *et al*. Boswellic acids: a critical appraisal of their therapeutic and nutritional benefits in chronic inflammatory diseases. Endocr Metab Immune Disord Drug Targets. 2024;24(1):116-29.
36. Smith AM, Moxon S, Morris GA. 13-Biopolymers as wound healing materials. Wound Healing Biomaterials. Woodhead Publishing; 2016. p. 261-87.
37. Gheorghita R, Anchidin-Norocel L, Filip R, Dimian, Covasa M. Applications of biopolymers for drugs and probiotics delivery. Polymers. 2021;13(16):2729.
38. Qasim U, Osman AI, Al-Muhtaseb AH, Farrell C, Al-Abri M, Ali A, *et al*. Renewable cellulosic nanocomposites for food packaging to avoid fossil fuel plastic pollution: a review. Environ Chem Lett. 2021;19(1):613-41.
39. Moholkar DN, Sadalage PS, Peixoto D, Paiva-Santos AC, Pawar KD. Recent advances in biopolymer-based formulations.
40. Marin MM, Albu Kaya M, Kaya DA, Constantinescu R, Trica B, Gifu IC, *et al.* Novel nanocomposite hydrogels based on crosslinked microbial polysaccharide as potential bioactive wound dressings. Materials. 2023;16(3):982.
41. Rinaudo M. Chitin and chitosan: Properties and applications. Prog Polym Sci. 2006;31(7):603-32.
42. Bhattarai N, Gunn J, Zhang M. Chitosan-based hydrogels for controlled, localized drug delivery. Adv Drug Deliv Rev. 2010;62(1):83-99.
43. Mohamed RR, Abu Elella MH, Sabaa MW. Cytotoxicity and metal ions removal using antibacterial biodegradable hydrogels based on N-quaternized chitosan/poly (acrylic acid). Int J Biol Macromol. 2017; 98:302-13.
44. Sabra S, Abdelmoneem M, Abdelwakil M, Mabrouk MT, Anwar D, Mohamed R, *et al.* Self-assembled nanocarriers based on amphiphilic natural polymers for anti-cancer drug delivery applications. Curr Pharm Des. 2017;23(35):5213-29.
45. Frenkel JS. The role of hyaluronan in wound healing. Int Wound J. 2014;11(2):159-63.
46. Sudhakar K, Ji S, Kummara M, Han SS. Recent progress on hyaluronan-based products for wound healing applications. Pharmaceutics. 2022;14(10).
47. Sabra S, Ragab DM, Agwa MM, Rohani S. Recent advances in electrospun nanofibers for some biomedical applications. Eur J Pharm Sci. 2020; 144:105224.
48. Patel B, Kothari V, Acharya N. Mainstreaming traditional practices for wound management. In: Kumar P, Kothari V, editors. Wound Healing Research. Singapore: Springer Singapore; 2021. p. 219-45.
49. Manyi-Loh CE, Clarke AM, Ndip RN. An overview of honey: therapeutic properties and contribution in nutrition and human health. Afr J Microbiol Res. 2011;5(8):844-52.
50. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed. 2011;1(2):154-60.
51. Huang S, Zhang CP, Wang K, Li GQ, Hu FL. Recent advances in the chemical composition of propolis. Molecules. 2014;19(2):19610-32.
52. Czyzewska U, Konończuk J, Teul J, Drągowski P, Pawlak-Morka R, Surazynski A, *et al*. Verification of chemical composition of commercially available propolis extracts by gas chromatography-mass

spectrometry analysis. J Med Food. 2018;18(5):584-91.
53. Bosio K, Avanzini C, D'Avolio A, Ozino O, Savoia D. In vitro activity of propolis against streptococcus pyogenes. Lett Appl Microbiol. 2000;31(2):174-81.
54. Alsakhawy MA, Abdelmonsif DA, Haroun M, Sabra SA. Naringin-loaded arabic gum/pectin hydrogel as a potential wound healing material. Int J Biol Macromol. 2022;222(Pt A):701-14.
55. Abdollahi S, Raoufi Z. Gelatin/persian gum/bacterial nanocellulose composite films containing frankincense essential oil and teucrium polium extract as a novel and bactericidal wound dressing. J Drug Deliv Sci Technol. 2022; 72:103423.
56. Gaspar-Pintiliescu A, Stanciuc AM, Craciunescu O. Natural composite dressings based on collagen, gelatin and plant bioactive compounds for wound healing: A review. Int J Biol Macromol. 2019; 138:854-65.