


REVIEW

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Exploring the use of herbal drugs and advanced supporting techniques for wound healing

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Abstract

Background: A wound may define as an interruption within the continuity of the epithelial lining of the skin or mucosa that occurs as a result of physical or thermal damage. Wound healing is an intricate process that is highly synchronized censorious in the management of the protective means of the skin. There are a variety of systemic and local factors that influence wound healing, including oxygenation, inflammation, age, stress, diabetes, nutrition, and nicotine. Hemostasis, inflammation, proliferation or granulation, remodeling or maturation are the principle phases of wound healing.

Main body of the abstract: The authors of the current review attempt to convey that the usage of herbal drugs has extreme importance in the current era. The authors reviewed a total of 38 herbal plants with their mechanism of wound healing and the chemical constituents responsible for it. Hyperbaric oxygen therapy, negative pressure therapy, platelet-rich plasma therapy, stem cell therapy, and biosurgery are some of the most often used supporting procedures for wound healing with these herbal drugs.

Short conclusion: There are a variety of herbal plants that have wound healing properties. This evaluation covers a wide range of plants. However, a review of the literature on diverse plants reveals that diverse chemical contents are found in different plant species, but did not mention of which chemical compounds are important for wound healing.

Keywords: Wound healing, Herbal drugs, Phases, Supporting techniques

Background

A wound may be defined as an interruption within the continuity of the epithelial lining of the skin or mucosa that occurs as a result of physical or thermal damage (Chhabra et al. 2017). Since skin is the largest organ of the human body, any obstruction in its continuity, such as a wound or a cut, compromises health and immunity. As a result, the wound must be treated as soon as possible with suitable treatment. Wound healing may be a complicated and unique process, with the changing wound

environment in response to the overall health status of an individual (Dhivya et al. 2015).

Many conditions must come together for a superficial wound to heal, and wound dressings and coverings have changed significantly to address potential barriers to wound healing, ranging from infection to hypoxia. Even in the best of circumstances, wound tissue never recovers its pre-injury strength, and chronic non-healing wounds can be developed from several aberrant healing phases. After the certain circumstances such as trauma, either by accident or by surgery wound healing play an important role in preserves the integrity of skin (Mukty 2018; Wang et al. 2018).

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Factors affecting wound healing

Wound healing can be hampered by a variety of circumstances. The elements that affect repair are frequently divided into two categories: local and systemic. Local factors have a direct impact on the wound's features, whereas systemic factors have an impact on the individual's overall health or disease state, which influences their ability to heal. Because many of these elements are interconnected, systemic variables influence wound healing via local consequences (Guo and DiPietro 2010).

Oxygenation

For wound healing, oxygen is a very essential component. It is a complicated procedure that involves several biological processes like cell proliferation, angiogenesis, and protein synthesis, all of which are required for tissue function and integrity to be restored. Appropriate wound tissue oxygenation can affect healing responses and, in turn, the outcomes of various treatment options, depending on what the patient or physician is aiming for (Castilla et al. 2012). The effect of oxygen is dependent on the state of oxygen, such as when it is hypoxic, normal, or hyperoxic. The mitochondrial cytochrome oxidase enzyme requires oxygen during energy consumption. This produces high-energy phosphates, which are then required for a variety of cellular functions. In collagen synthesis, oxygen is implied within the hydroxylation of proline and lysine into procollagen which results in collagen development. Angiogenesis requires hypoxia to begin, but it has been demonstrated that if oxygen is used, vessel growth can be accelerated and sustained (Kimmel et al. 2016).

Role of the macrophage in wound healing: (inflammation)

In wounds, macrophages perform slightly different functions, such as host defense, promoting and determining inflammation, removing apoptotic cells, and so supporting cell proliferation and tissue regeneration after injury. According to recent literature, macrophages exist in various sets of observable characteristics within the wound healing, and their impact on each step of repair differs depending on the phenotype (Gonzalez et al. 2016). As wounds heal, the local macrophage populace transitions primarily on pro-inflammatory (M1-like phenotypes) followed by anti-inflammatory (M2-like phenotypes). The chronic wound which unable to cure including pressure, arterial, venous, or diabetic ulcers indefinitely stay within inflammation. Thus, macrophages keep pro-inflammatory characteristics during wound healing (Krzyszczczyk et al. 2018).

The macrophage, on the other hand, is essential for the repair of regularly healing wounds, but, in some circumstances, this pleiotropic cell type may cause excessive

inflammation or fibrosis. According to new findings, macrophage dysfunction could play a role in the pathophysiology of non-healing and ineffectual healing wounds. Whereas advancements within the communication of multifunctional cells, the macrophage remains a promising therapeutic target for reducing fibrosis and scarring as well as improving chronic wound healing (Koh and DiPietro 2011; Atri et al. 2018; Leibovich and Ross 1975).

Age

In healthy people, ageing causes epithelialization to be delayed. Collagen synthesis is unaffected by ageing; however, wound non-collagenous protein deposition is reduced. In older people, this decline may compromise the mechanical qualities of scarring (Holt et al. 1992).

Stress

Stress is defined as a process in which there is an increase in external requirements of individuals perceiving capabilities to cope up with the responsibilities resulting in behavioral and physiological changes (Cohen et al. 1997). Insufficient healing enhances the complications of wound infections, extends hospital stays, intensifies patient discomfort, and slows recurrence to routine activities. Physiological stress responses can directly influence wound healing processes (Gouin and Kiecolt-Glaser 2011). The sources of stress include pain, odor, and social isolation. Uncontrollable stress has been shown in clinical studies to boost the risk of a non-healing, lower standard of life, and lead to the adoption of unhealthy habits, highlighting the significance of a multidisciplinary approach to wound healing (Wynn and Holloway 2019).

Pitiable recovery of wound is linked with unmitigated risk for wound infection and additional complications; affected person may get stress due to discomfort, prolonged sanatorium stays, and delays between one's return to regular activities. It is stated on the basis of observational, investigational, and interventional experiments that stress and other factors which affect on regular routine activities delayed the wound healing. This same phenomenon also affects on immunity (Seiler et al. 2020).

Diabetes

Diabetic foot ulceration has been a big concern in several Asian countries for decades, producing economic and social concerns. As a result, identifying and reducing diabetic foot risk factors is highly important (Xia et al. 2019). Diabetes mellitus is a complicated metabolic condition with several direct and indirect consequences on wound healing (Morain and Colen 1990). Hyperglycemia or uncontrolled glycemic levels in diabetes mellitus affect

white blood cell function and increase the risk of infection. Diabetes also affects multiple other body systems that each one plays a task in wound healing. One example is neuropathy that develops in response to the impact of diabetes on the systema nervosum. The lack of protective feeling caused by neuropathy will limit the individual's capacity to detect changes in the extremity and, as a result, the wound, resulting in further trauma (Goodson and Hung 1977). Controlling diabetes, maintaining nutrition, and treating a systemic illness are important factors in promoting of wound healing (Yue et al. 1987).

Nutrition

Protein deficit may have a deleterious impact on the immune system as a whole, while adequate carbohydrate consumption is necessary for fibroblast migration during the proliferative phase. Vitamins A, B, C, and D, zinc, and iron, in addition to micronutrients, arginine, and glutamine, are required for the inflammatory process and collagen formation (Barchitta et al. 2019). Clinical application is achieved by ingesting a formulation containing the aforementioned nutritious components. This improves healing time, results in healthier outcomes, and reduces comorbidities (Heintschel and Heuberger 2017).

Nicotine

According to epidemiological research, smoking is a significant risk factor for the progression of a variety of chronic diseases. Nicotine, the addictive substance found in cigarettes, has potent pathophysiological effects on the human body. Although a study on the effects of cigarette smoking on corneal re-epithelialization is underway, little is known about the effects of nicotine on corneal wound healing-related neovascularization and fibrosis. Finally, we can say that chronic nicotine administration accelerated the angiogenic and fibrogenic healing processes in corneal tissue that had been alkali-burned (Kim et al. 2017).

Phases of wound healing

Following the onset of a tissue lesion, rejuvenation and tissue refurbishing processes take place, which includes a series of molecular and cellular circumstances aimed at reviving the damaged tissue. The proliferative, excreted, and extracellular matrix remodeling phases are all linked together by unique processes involving soluble mediators, blood cells, and parenchyma cells. Tissue edema is the emissive circumstance observed after the wound. The proliferative phase explores scale back of tissue damage by shrinking myofibroblasts and fibroplasia. At this phase, angiogenesis and re-epithelialization processes can quite be perceived (Gonzalez et al. 2016).

In vivo experimental studies demonstrate that wound healing occurs in four phases including acute and chronic wounds.

The phases of wound healing are as follows:

1. Hemostasis
2. Inflammation
3. Proliferation or granulation
4. Remodeling or maturation

Hemostasis

In tissue repair, the platelet is that the cell which acts because our body repairing of the off the damaged blood vessels the blood vessels get constricted in response to the damage, and the spasm get relaxed. To aid in this process, platelets emit vasoconstrictive chemicals, but their primary function is to form a stable clot that seals the injured vessel. Platelets cluster are attached to exposed collagen with the impact of adenosine diphosphate (ADP) discharged from ruptured tissues. They also release substances that interact with and promote the intrinsic coagulation cascade by assembling thrombin, which starts the synthesis of fibrin from fibrinogen. The fibrin mesh helps to form a stable hemostatic plug out of the platelet aggregation. Finally, platelets release cytokines like platelet-derived protein (PDGF), which is known as functional key mediators that originates subsequent processes. If there are no underlying clotting abnormalities, hemostasis occurs within minutes of the original injury (Rodrigues et al. 2019; Pool 1977; Rumbaut and Thiagarajan 2010).

The early response to a wound on the skin is vasoconstriction of the artery walls to avoid bleeding. Following that, primary and secondary hemostasis is achieved by two parallel and mechanistically connected routes. Platelet plug development is stimulated by collagen manifestation inside the subendothelial matrix in primary hemostasis. The activation of the coagulation cascade, in which soluble fibrinogen is transformed to insoluble strands that form the fibrin mesh, is referred to as secondary hemostasis. The platelet plug and fibrin mesh unite to construct a thrombus that prevents bleeding, releases complement and growth factors, and acts as a temporary scaffold for infiltrating wound healing tissue (Tennent et al. 2007; Kaplan et al. 1979; Fujiwara et al. 2013).

Inflammation phase

Inflammation is another phase of wound repair, characterized by erythema, swelling, followed by heat and all of which are accompanied by pain. This period might last up to four days after an injury. In the wound healing

comparison, the first task after the utilities have been turned off is to clear the debris. This is a non-skilled laborer's job. The neutrophils, also known as polymorphonucleocytes (PMNs), are non-skilled workers who help heal wounds. Blood vessels become leaky as a result of the inflammatory reaction, spilling plasma, and PMNs into the surrounding tissue. Neutrophils are the first line of defense against infection, phagocytizing debris, and bacteria. They are helped by mast cells in the area. The degradation products attract the following cells engaged because fibrin is weakened as part of this cleanup. Rebuilding a home is a difficult process that necessitates the use of a project manager or a contractor. The macrophage is a cell that aids with wound healing by acting as a contractor (Millington and Norris 2000).

Proliferation or granulation

Throughout the process of proliferation, the injury is reassembling with advanced granulation tissue. This granulation tissue is consisting of collagen and extracellular matrix and a modern set of blood vessels develop this activity is said to be angiogenesis. Healthy granulation is observed when the fibroblast receiving enough level of oxygen and the required nutrition from the blood vessels. These tissues have an uneven texture. The color and state of the granulation are usually a marker of how the wound is healing. Dark granulation is often indicative of ineffective perfusion, ischemia, and infection. In the end, epithelial cells disappear from the wound which is considered as "epithelization" (Rosen 2002; Carmeliet 2003).

Remodeling or maturation

Remodeling is the ultimate stage of healing, which begins two to three weeks after the commencement of the lesion and can last a year or longer. The changing stage's main goal is to achieve maximum durability by reorganizing, degrading, and re-synthesizing the extracellular matrix. At this point in the healing process, an attempt is made to restore the typical tissue structure, and the granulation is gradually reformed, resulting in connective tissue which is least cellular and vascular, with a continuous exceeding in collagen fiber concentration (Martin 1997).

The weather has matured, resulting in deep alterations within the extracellular matrix and, as a result, the early inflammation has subsided. When a monolayer of keratinocytes covers the lesion's surface, epidermal migration stops, and a replacement stratified epidermis with a subjacent basal lamina is construct the wound linings to its interior. The matrix is being deposited and its composition is changing at this point. Type III collagen degrades as the wound heals, but type I collagen synthesis increases. During transformation, hyaluronic and

fibronectin acid, which is destroyed by cells and plas-matic metalloproteinase, are depleted, increasing type I collagen expression (Li et al. 2007).

Main text

Herbal plants and their chemical used for wound healing

Traditionally, herbal plants are widely employed for the cure different types of wounds (Sharma et al. 2021). Medicinal plants and its chemical constituents are necessary to test for its therapeutic action on wound healing. Nowadays, the era is interested toward the use of plant derivative due to less side effects. Some of the experiments showing the better progress for treatment of various wound such as diabetic, infected, and opened wounds (Farahpour 2019). For the treatment of wound, herbal crude drugs and their chemical constituents are found to be more effective in the current modern era (Shedoeva et al. 2019). Phytoconstituent present in herbal plant has the promising effect to provide improved tissue remodeling and shows its function as proangiogenic agents when employed on wounds (Thangapazham et al. 2016).

This study describes role of *Aloe vera* (Teplicki et al. 2018), *Centella asiatica* (Sh Ahmed et al. 2019), *Pinus pinaster* (Dogan et al. 2017), *Lavandula angustifolia* (Mori et al. 2016), *Argania spinosa* (Avsar et al. 2016), *Bursera morelensis* (Salas-Oropeza et al. 2020), *Hypericum patulum* and *H. perforatum* (Wölflle et al. 2014), *Copaifera paupera* (Amorim et al. 2017), *Avicennia schaueriana* (Lopes et al. 2019), *Cucurbita pepo* (Bardaa et al. 2016), *Ximenia americana* (Souza Neto Júnior et al. 2019), *Fumaria vaillantii* (Davoodi-Roodbordeii et al. 2019), *Panax ginseng* (Park et al. 2019), *Astragali radix* (Lee et al. 2018), *Sauromatum guttatum* (Said et al. 2019), *Sapindus mukorossi* (Chen et al. 2019), *Euphorbia hirta* (Tuhin et al. 2017), *Vaccaria segetalis* (Hou et al. 2020), *Berula angustifolia* (Sanaei et al. 2018), *Pupalia lappacea* (Udegbunam et al. 2014), *Cydonia oblonga* (Tamri et al. 2014), *Ampelopsis japonica* (Lee et al. 2015), *Chrozophora tinctoria* (Maurya et al. 2016), *Nigella sativa* (Sallehuddin et al. 2020), *Elaeis guineensis* (Sasidharan et al. 2010), *Ficus racemose* (Bopage et al. 2018), *Sida corymbosa* (John-Africa et al. 2013), *Blechnum orientale* (Lai et al. 2011), *Annona muricata* (Moghadamtousi et al. 2015), *Artocarpus communis* (Yeh et al. 2017), *Aegle marmelos* (Gautam et al. 2014), *Moringa oleifera* (Muhammad et al. 2013), *Bacopa monniera* (Murthy et al. 2013), *Cinnamomum verum* (Daemi et al. 2019), *Anacardium occidentale* (da Silveira Vasconcelos et al. 2015), *Ephedra alata* (Kitana et al. 2017), *Ficus racemose* (Murthi and Kumar 2012), *Calotropis procera* (Aderounmu et al. 2013), in wound healing. Chemical constituents present in above-mentioned plants contains glycosides, alkaloids, tannins, steroids, carbohydrates, terpenoids, carotenoids, flavonoids,

cardenolides, vitamins, tocopherols, essential oils, resins, fatty acids; various phenolic compounds are responsible for wound healing.

Maximum plants and their chemical constituents show its effects by the mechanism by angiogenesis are NF- κ B, TGF- β , VEGF, tumor necrosis factor (TNF), and inducible nitric oxide synthase (iNOS) effect on cytokines (Thangapazham et al. 2016); apart from this different mechanism especially IL-4, IL-5, IL-13, and TGF- β 1, reduction in wound size by reepithelialization is also involved in wound healing.

In Table 1, the all mentioned plants are searched from the literature and their chemical constituents and mechanism by which it shows its action is explained. The chemical structure for the isolated chemical constituents present in plant is mentioned in Fig. 1.

Recently developed different wound healing technique

The most frequent wound healing treatments include hyperbaric oxygen therapy (HBOT), negative pressure therapy (NPT), platelet-rich plasma therapy (PRP), stem cell therapy (SCT), and biosurgery.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) is an efficient supporting treatment in conditions where normal healing is damaged. In HBO 100 percent oxygen at two- to three-fold, the air pressure stumped level is run and this end in arterial oxygen tension in more than 2000 mmHg and oxygen tension in the cells of just about 400 mmHg. Such type of oxygen doses in HBR therapy has many advantages in biochemical cellular and biochemical effect (Raveenthiraraja and Manoharan 2013).

The majority of hyperbaric conditions and HBO therapy applications are drawn directly from physics concepts and rules evolved over millennia.

- (a) Boyle's law, or the theory of compressibility, holds that the volume of a gas is inversely proportional to pressure at a constant temperature.
- (b) The law of partial pressure, often termed as Dalton's law, asserts that the pressure of a gaseous mixture is equivalent to the sum of the partial pressures of its constituent gases.
- (c) Henry's law describes the pathophysiology of decompression disorder and its treatment with hyperbaric oxygen.

Though HBO treatment has several drawbacks and hazards, the benefits outweigh the risks. Few disorders, such as aeroembolism and clostridial myonecrosis, have more conclusive evidence. As a result, much study must be done to determine the symptoms, medication, and

duration of the treatment. Doctors must be trained to deliver this form of care, and more centers must adopt it as a routine therapy option because it has synergistic effects with other treatments (Buboltz et al. 2021).

Negative pressure therapy

Negative pressure therapy commonly referred to as topical negative pressure therapy or vacuum therapy aids wound healing. It can be used as first-line therapy for intense and composite wounds, as well as an adjuvant for time being wound closing and wound bed composition before surgical operations such as skin grafts and flap surgery. The device has a long history of widespread and successful use, even though the physiological basis of its action is still unknown, and proof-based data are slowly becoming available. Systematic analytical literature provides information on the efficacy of inducing wound healing mechanisms, particularly in the early stages. Following a review of the literature, it was discovered that it had positive efficacy in the treatment of infection. Even though this therapy appears to be beneficial and that it outperforms normal procedures, there are still some doubts about its efficacy. More prospective, randomized, blinded trials are needed since the mechanisms of action are still unknown, and since there is still a gap between evidence-based data and the great clinical outcome. When performed as directed by an expert surgeon, negative pressure therapy is a great technique for wound healing (Schintler 2012).

Platelet-rich plasma therapy

Platelet-rich plasma (PRP), also called autologous platelet gel (APG), plasma rich in growth factors (PRGF), and platelet concentrate (PC), is plasma that has been centrifuged to increase the concentration of plasma-rich platelets suspended in a small amount of plasma. Patient blood is collected during the process and centrifuged at variable speed till it is separated into three layers, viz. platelet-poor plasma (PPP), platelet-rich plasma (PRP), and red blood cells. Normally in this process, two spins are used. The primary spin is known as hard spin which separates the PPP from the red fraction and PRP. The second spin is known as soft spin which separates the red fraction from the PRP. During this process, the material having larger specific gravity will be settled down at the bottom of the tube. Directly before application, a platelet activator/agonist a mixture of topical bovine thrombin and 10% calcium chloride is included to activate the clotting cascade, producing a platelet gel. The entire operations will take near about twelve minutes to complete and produce a platelet concentration of 3–5 \times that of parent plasma (Marx et al. 1998; Petruogaro 2001).

Table 1 Depiction of plants used for wound healing

| Sr. no | Plant name | Part used | Chemical constituent | Mechanism of wound healing |
|--------|--|-----------------------|---|--|
| 1. | <i>Aloe Vera</i> (Asphodelaceae (Liliaceae)) (Teplicki et al. 2018) | Leaf | Anthraquinone C-glycosides, Anthrones, anthraquinones, and lectins | Wound healing results from <i>Aloe Vera</i> by elevating the proliferation and relocation of fibroblasts and keratinocytes and by defending keratinocytes from preservative-induced death |
| 2. | <i>Centella asiatica</i> (Apiaceae) (Sh Ahmed et al. 2019) | Aerial part | Asiaticoside, asiatic acid, and madecassic acid | Asiaticoside is an important chemical constituent present in <i>Centella asiatica</i> which act by different step like in initial step it acts by stimulation of antioxidant, then during skin wound repair promote angiogenesis and finally by promoting fibroblast proliferation and extracellular matrix synthesis which results in wound healing |
| 3. | <i>Pinus pinaster</i> (Pinaceae) (Dogan et al. 2017) | Bark | Pycnogenol | Pycnogenol the chemical constituent present in pine bark causes a at the site of the wound |
| 4. | <i>Lavandula angustifolia</i> (Lamiaceae) (Mori et al. 2016) | Leaves and Flowers | Monoterpene alcohols, esters, monoterpene hydrocarbons, sesquiterpene hydrocarbons, ketones | Lavender oil promotes wound elevation by increasing the number of receptors on the surface of target cells, making the cells more sensitive to healing agents by development of granulation tissues, tissue remodeling by collagen replacement, and wound contraction through TGF- β receptor activation |
| 5. | <i>Argania spinosa</i> (Sapotaceae) (Avsar et al. 2016) | Kernels | Tocopherol (Argan oil) | Anti-oxidant present in argan oil known as alpha-tocopherol shows its effect on cytokines, especially IL-4, IL-5, IL-13, and TGF- β 1, lipid peroxidation, and expression of various inflammatory genes which results in considerable changes in the treatment of burn wound healing |
| 6. | <i>Bursera morelensis</i> (Burseraceae) (Salas-Oropeza et al. 2020) | Stems | p-menthane, β -phellandrene, α -pinene, caryophyllene, caryophyllene oxide, β -myrcene, sabinene, and p-cymene | <i>B. morelensis</i> contains essential oil which promotes wound healing by collagen synthesis and also stimulates the migration of fibroblast at the site of the wound |
| 7. | <i>Hypericum patulum</i> , <i>H. perforatum</i> (Hypericaceae) (Wölfe et al. 2014) | Leaf | Hypericin, pseudohypericin | It promotes wound healing by collagen synthesis and migration of fibroblast |
| 8. | <i>Copaifera paupera</i> (Fabaceae) (Amorim et al. 2017) | Trunk | Oleoresin | Oleoresin shows wound healing activity by decreasing the synthesis of MCP-1 and TNF- α and by increasing IL-10 synthesis |
| 9. | <i>Avicennia schaueriana</i> (Acanthaceae) (Lopes et al. 2019) | Leaves | Alkaloids, tannins, flavonoids, saponins, and triterpenes | The chemical constituents present in <i>Avicennia schaueriana</i> having the characteristic of astringent and antimicrobial activity which is helpful for wound healing by wound contraction and increasing epithelialization rate |
| 10. | <i>Cucurbita pepo</i> (Cucurbitaceae) (Bardaa et al. 2016) | Seeds | Tocopherols, fatty acids (linoleic acid), and phytosterols | Wound healing was observed due to full re-epithelialization with the recurrence of skin appendages and systematic collagen fibers without inflammatory cells |
| 11. | <i>Ximenia americana</i> (Olacaceae) (Souza Neto Júnior et al. 2019) | Stern, Roots and Bark | Tannins, flavonoids, and terpenoids | <i>Ximenia americana</i> is responsible for angiogenic effects and improves the replacement of collagen results in a wound healing effect |
| 12. | <i>Fumaria vaillantii</i> (Papaveraceae) (Lee et al. 2018) | Aerial parts | Flavonoids, alkaloids, tannins, and saponins | Wound healing is due to chemical constituents present in <i>F. vaillantii</i> which causes wound contraction and an enhanced rate of epithelialization |

Table 1 (continued)

| Sr. no | Plant name | Part used | Chemical constituent | Mechanism of wound healing |
|--------|---|---------------------|--|---|
| 13. | <i>Panax ginseng</i> (Araliaceae) (Park et al. 2019) | Root | Ginsenosides, gypenoside LXXV | Gypenoside LXXV (G75) accelerates the proliferation and migration of keratinocytes and fibroblasts which promotes wound closure |
| 14. | <i>Astragal Radix</i> (Fabaceae) (Lee et al. 2018) | Dried roots | Astragalosides | <i>Astragal radix</i> accelerates EGFR activity which is present in HaCat cells and also increases the extracellular signal-regulated kinase (ERK) activity in a dose-dependent manner |
| 15. | <i>Sauromatum guttatum</i> (Araceae) (Said et al. 2019) | tubers | Flavonoids and alkaloids | <i>Sauromatum guttatum</i> enhanced wound healing activity by a different mechanism like upregulating various growth factors, cell division, maturation, and migration of various cells involved in healing |
| 16. | <i>Sapindus mukorossi</i> (Sapindaceae) (Chen et al. 2019) | Seed | Unsaturated fatty acids, monounsaturated fatty acids, β -sitosterol, and δ -tocopherol | Wound healing is effective by improvement in CCD-966SK cell proliferation |
| 17. | <i>Euphorbia hirta</i> (Euphorbiaceae) (Tuhin et al. 2017) | Leaves | Flavonoids, triterpenoids, and alkaloids | Flavonoids, triterpenoids, and alkaloids present in a plant enhanced the viability of collagen fibrils, increasing the strength of collagen fibers by a different mechanism such as augmenting the circulation or preventing the cell damage, or by promoting DNA synthesis |
| 18. | <i>Vaccaria segetalis</i> (Caryophyllaceae) (Hou et al. 2020) | Seeds | Vaccarin | Vaccarin the chemical constituent present in the seeds of the given plant is responsible for wound healing activity by enhancing the expressions of protein kinase B, ERK, and p-bFGFR |
| 19. | <i>Berula angustifolia</i> (Apiaceae) (Sanaei et al. 2018) | Leaves | – | The leaves of <i>Berula angustifolia</i> are used in diabetes-impaired wound healing and this plant is acted by a different mechanism such as intensified wound contraction, decreased epithelialization time, enhanced hydroxyproline content, improved mechanical indices, and histological characteristics |
| 20. | <i>Pupalia lappacea</i> (Amaranthaceae) (Udegbunam et al. 2014) | Leaves | Stigmaesterol, 20-hydroxyl ecdysyne, docosanol | 20-hydroxyl ecdysyne is responsible for wound healing by enhancement of protein synthesis |
| 21. | <i>Gydonia oblonga</i> (Rosaceae) (Tamri et al. 2014) | Fruits (Seeds) | Phenolic compounds (Caffeoylquinic, 4-ocaffeoylquinic, 5-O-caffeoylquinic, 3,5-dicaffeoylquinic acids, lucenin-2, vicenin-2), Organic acids (Citric, ascorbic, malic, quinic, shikimic and fumaric acids) Amino acids (Glutamic and aspartic acids and asparagine) | <i>Gydonia oblonga</i> enhanced the collagen synthesis and tensile strength of the affected wound tissue. It also increases the wound fluid levels of EGF, TGF- β 1, VEGF, and PDGF which play a very important role in wound healing activity |
| 22. | <i>Ampelopsis japonica</i> (Vitaceae) (Lee et al. 2015) | Dried tuberous root | Catechin, resveratrol, epicatechin, epicatechin gallate, and galocatechin | <i>Ampelopsis japonica</i> extract shows wound healing activity during two phases one is inflammatory and another one is a proliferative phase and acts by increasing the scald wound repair |
| 23. | <i>Chrozophora tinctoria</i> (Euphorbiaceae) (Maurya et al. 2016) | Leaves | Chrozophorin, apigenin, rutin, and acacetin | This plant acts by enhancing the level of collagen in the granulation tissues which results in wound healing activity |

Table 1 (continued)

| Sr. no | Plant name | Part used | Chemical constituent | Mechanism of wound healing |
|--------|---|----------------------|--|--|
| 24. | <i>Nigella sativa</i> (Ranunculaceae) (Sallehuddin et al. 2020) | Seeds | Thymoquinone | The seeds of <i>Nigella sativa</i> contain Thymoquinone as an active constituent which shows wound healing activity due to its anti-inflammatory, antioxidant, and antibacterial properties |
| 25. | <i>Elaeis guineensis</i> (Arecaceae) (Sasidharan et al. 2010) | leaves | Tannins, alkaloids, steroids, saponins, terpenoids, and flavonoids | Among all the different chemical constituents Terpenoids present in <i>Elaeis guineensis</i> terpenoids are having a crucial role in wound healing activity. Methanolic extract enhances wound repair by different processes like collagen synthesis and maturation, wound contraction, and epithelialization |
| 26. | <i>Ficus racemose</i> (Moraceae) (Bopage et al. 2018) | Bark | Lupeol and β -sitosterol | <i>Ficus racemose</i> contains Lupeol and β -sitosterol shows wound healing activity by accelerating the cell migration which is equal to cell proliferation |
| 27. | <i>Sida corymbosa</i> (Malvaceae) (John-Africa et al. 2013) | Leaves | Tannins, saponins, alkaloids, flavonoids, carbohydrates, terpenes, and sterols | <i>Sida corymbosa</i> hastens wound area contraction and decreases the epithelialization period. It also involves various processes like vasoconstriction and platelet accumulation which results in fibrin synthesis and inflammation which causes vasodilatation and phagocytosis. It also promotes collagen deposition from new collagen, wound contraction, epithelialization, and an increase in tensile strength |
| 28. | <i>Blechnum orientale</i> (Blechnaceae) (Lai et al. 2011) | Leaves | Tannins | It accelerates its activity as wound healing by acting on the proliferative stage including angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and shrinking of wound |
| 29. | <i>Annona muricata</i> (Annonaceae) (Moghadamtousi et al. 2015) | Leaves and stem bark | Alkaloids and essential oils | Ethanolic extract of <i>Annona muricata</i> enhances wound healing by contraction, epithelialization, collagen synthesis, decreasing oxidative and inflammatory stress in the affected area |
| 30. | <i>Artocarpus communis</i> (Moraceae) (Yeh et al. 2017) | Heartwood | Artocarpin | Artocarpin enhances wound healing in different ways such as improving myofibroblast differentiation, proliferation and migration of fibroblasts and keratinocytes, collagen synthesis and maturation, re-epithelialization, and angiogenesis |
| 31. | <i>Aegle marmelos</i> (Rutaceae) (Gautam et al. 2014) | Fruit pulp | Carotenoids, phenolics, alkaloids, pectins, tannins, coumarins, flavonoids, and terpenoids | Histopathology studies suggest that the fruit pulp of <i>Aegle marmelos</i> decreases the inflammation. Fruit pulp decreased free radicals and increases collagen deposition results in an increase in wound healing |
| 32. | <i>Moringa oleifera</i> (Moringaceae) (Muhammad et al. 2013) | Leaves | Methanolic extract: Kaempferol, quercetin Aq. Extract Vicenin-2 | Wound healing results from increased proliferation and migration of HDF (human dermal fibroblast) cells |
| 33. | <i>Bacopa monniera</i> (Plantaginaceae) (Murthy et al. 2013) | Whole plant | Saponins, glycosides, and alkaloids | Due to a decrease in free radicals' generation, antioxidant, increase collagen deposition whole plant of <i>Bacopa monniera</i> shows wound healing property |

Table 1 (continued)

| Sr. no | Plant name | Part used | Chemical constituent | Mechanism of wound healing |
|--------|---|-------------|---|--|
| 34. | <i>Cinnamomum verum</i> (Lauraceae) (Daemi et al. 2019) | Bark | Cinnamaldehyde, 2-hydroxyl cinnamaldehyde | Hydroethanolic extract of the plant increased cyclin D1 expression in different cells such as fibroblasts, fibrocytes, and keratinocytes result in increased proliferation. The study shows that the preparation of ointment formulation enhances wound healing properties |
| 35. | <i>Anacardium occidentale</i> (Anacardiaceae) (da Silveira Vasconcelos et al. 2015) | Fruits | Vitamin C, carotenoids, phenolics, anthocyanins, yellow flavonoids, tannin | Unripe cashew apple juice (UNCA) gives better fibroblast activation due to the presence of mononucleocytes (MNC) and polymorphonucleocytes (PMN) results in promotes the wound healing effect |
| 36. | <i>Ephedra alata</i> (Ephedraceae) (Kittana et al. 2017) | Whole plant | Flavonoids, alkaloids, phytoosteroids, phenolic compounds, volatile oils, and tannins | <i>Ephedra alata</i> increases the deposition of collagen and fibrosis process which results in wound healing |
| 37. | <i>Ficus racemose</i> (Moraceae) (Murti and Kumar 2012) | Roots | Saponins, tannins, alkaloids, and flavonoids | An increase in collagen synthesis increases epithelialization which shows that <i>Ficus racemose</i> have wound healing activity |
| 38. | <i>Calotropis Procera</i> (Apocynaceae) (Aderounmu et al. 2013) | Fresh latex | Cardenolides, tannins, and alkaloids | Calotropis latex induces fluid granulation tissues and the ability to inhibit the exaggerated response of fibroblasts which improve wound healing |

Structure of Chemical Constituents:

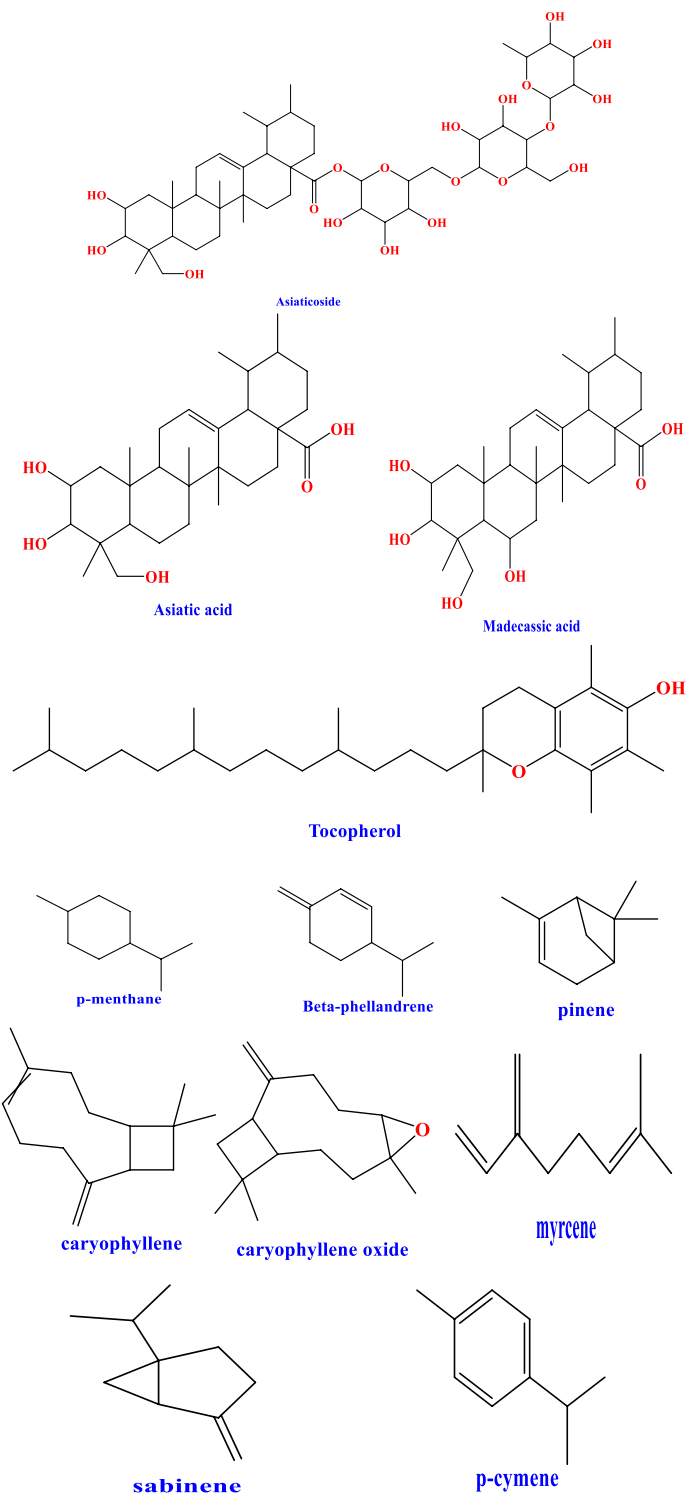


Fig. 1 Chemical structures of important chemical constituents present in the plant

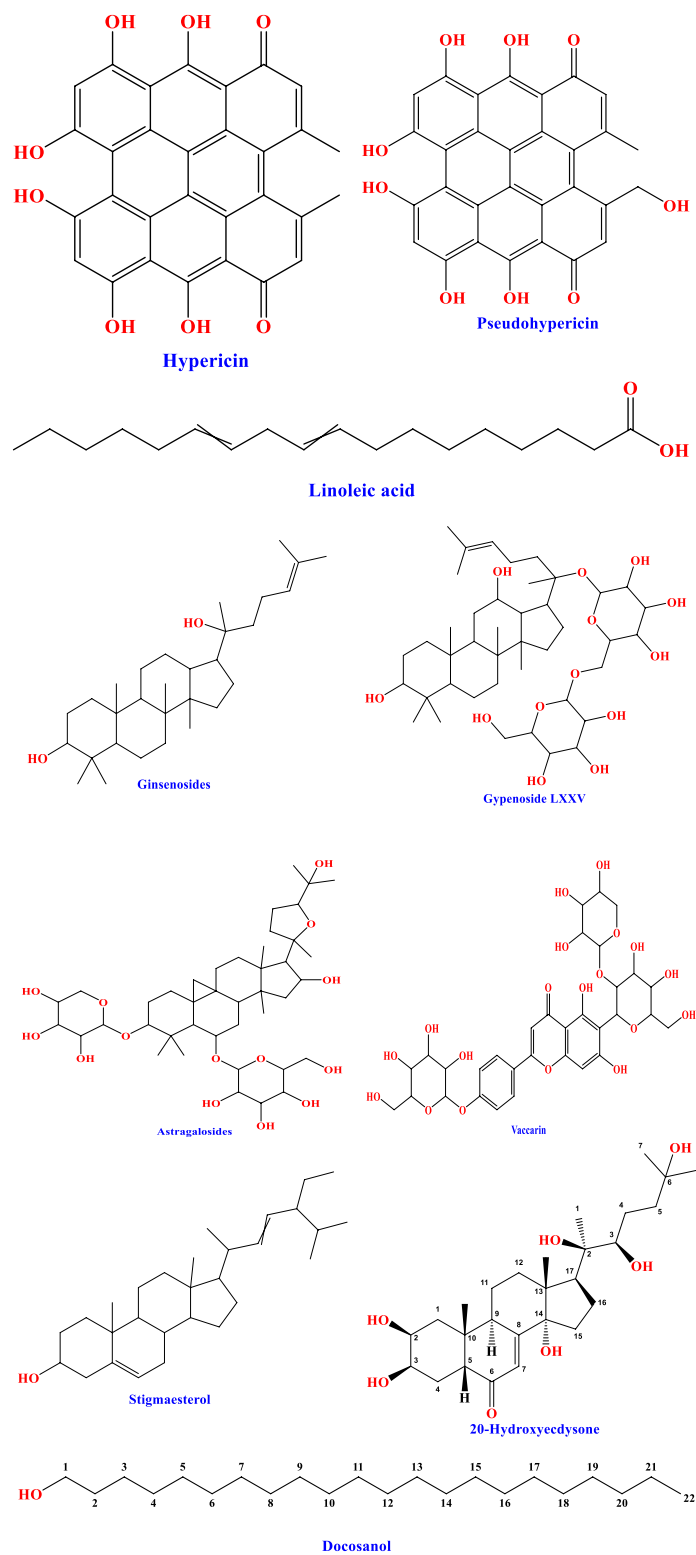


Fig. 1 continued

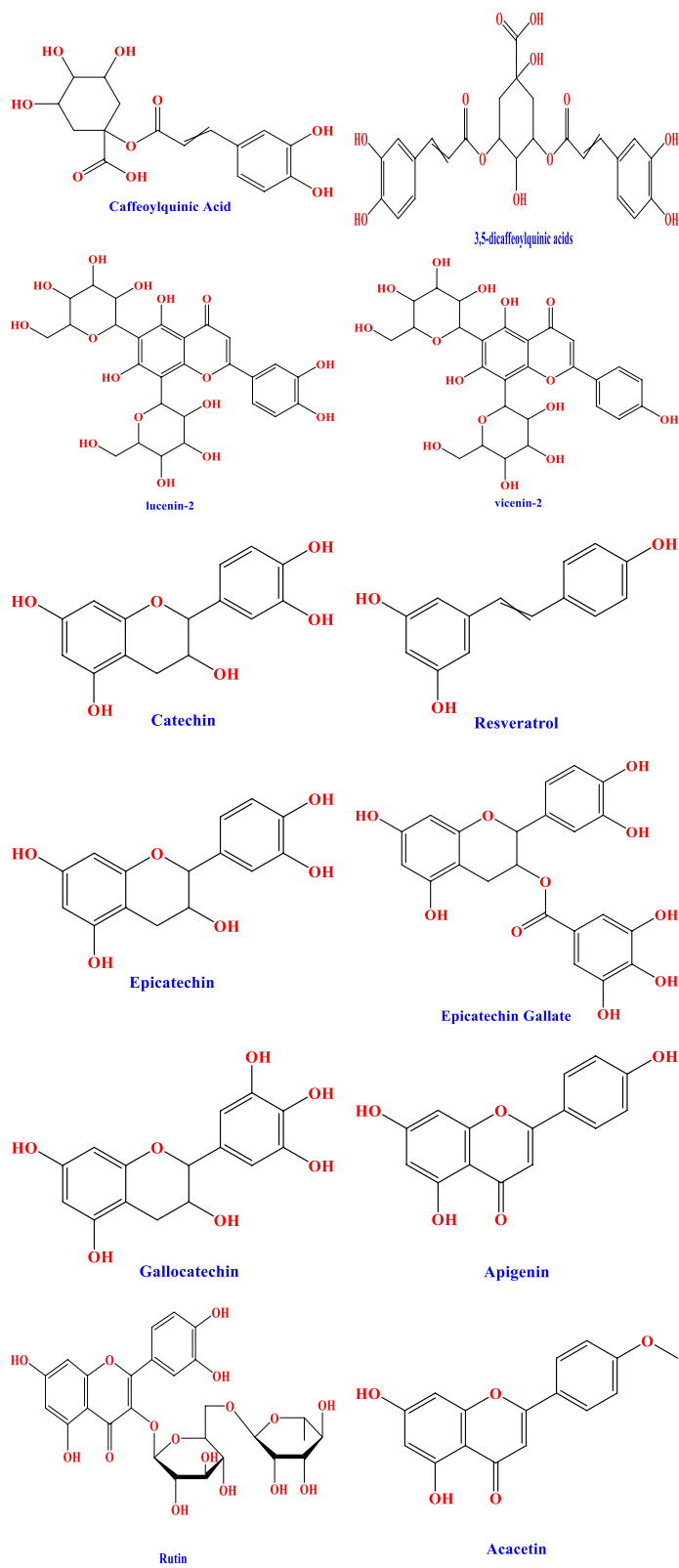
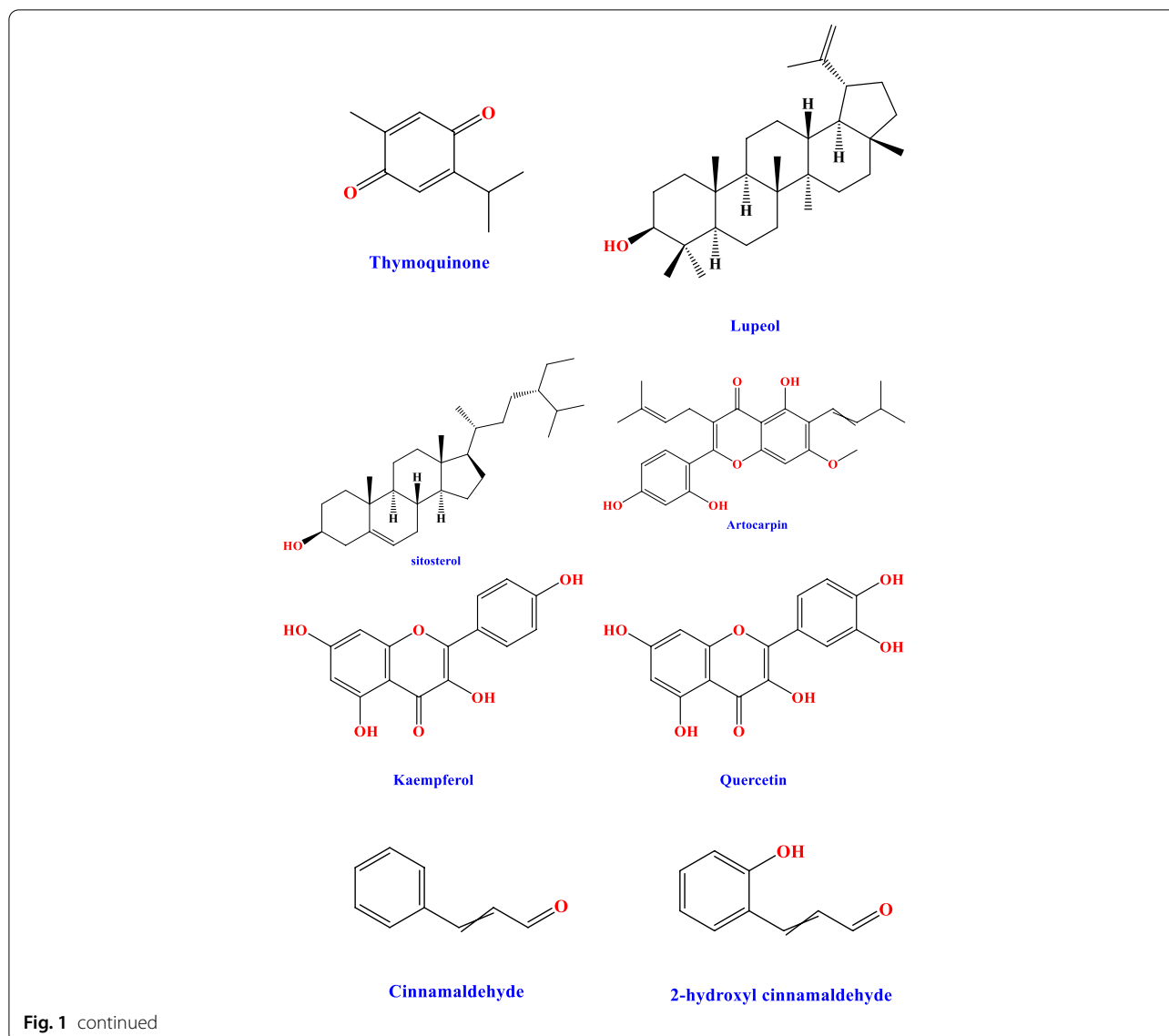


Fig. 1 continued



Since PRP is rich in different growth factors like PDGF, VEGF, EGF, and others that are efficient to activate angiogenesis and enhance fibroblast cell differentiation, using PRP the soft tissue healing process has been introduced. It has been also proposed that PRP also speeds up the wound maturity and epithelialization which results in prevent dermis from damaged and lessen scar formation. PDGF and EGF are the important growth factors involved in fibroblast migration, proliferation, and collagen synthesis. Greater concentrations of those growth factors are likely the rationale for the fast soft tissue wound healing, which is usually recommended to be a minimum of two- to threefold rapid than that of normal (Whitman et al. 1997; Carlson and Roach 2002; Anitua et al. 2004).

Stem cell therapy

In advanced, stem cell-based therapies are mostly used for skin-regenerative and anti-fibrotic properties and effective trail on human disease. The human amniotic membrane (HAM) is considered the interior layer of the fetal membrane and is obtained from the epiblast as early as 8 days after fertilization and before gastrulation. HAM is also considered as a particular tissue which has additionally anti-inflammatory and anti-fibrotic properties. The amniotic membrane can be stored during pregnancy and has a lot of therapeutic promise due to its importance as a source of progenitor cells from the fetus's cells. Amniotic epithelial cells (AECs) and amniotic mesenchymal cells (AMCs) are the two types of stem cells that can be extracted from the AMCs. Both types of stem cells

can self-renew and specialize into a variety of cell types. When compared to adult tissue-derived stem cells, primary human AECs have the following benefits once they are deemed majority engaging for cellular therapies: AECs are ample and can be collected without injury and expensive procedures from term placenta;

1. When contrast to embryonic stem cells, AECs have no tumor induction and no ethical limitations.
2. AECs retain the ability to develop into adipogenic, osteogenic, chondrogenic, skeletal myogenic, neurogenic, hepatic, and pancreatic lineages.

All of these studies suggest the use of AECs as a replacement anti-fibrotic therapeutic method, like reducing wound inflammation and reprogramming local cells to promote tissue regeneration and fibrosis prevention. The most essential mechanism behind the pharmacological actions of stem cells is thought to be paracrine signaling (Lai et al. 2015; Wu et al. 2017; Litwiniuk and Grzela 2014; Ding et al. 2017).

Biosurgery

Biosurgery is referred to as the use of sterile maggots, a selective technique of slough and necrotic tissue digestion from wounds without damaging the encompassing healthy tissue. Biosurgery is most feasible for wounds with slough and infection, in addition to its antibacterial impact. It is cost-effective, and it has great tolerance. There appear to be no contraindications other than the presence of fistulas and hence the wound's proximity to major blood vessels or essential organs. The deficiencies of aesthetic appeal, the less shelf-life of maggots, and more pain that occur at the wound site in certain individuals are also drawbacks (Kumar et al. 2004; Wollina et al. 2002).

Conclusions

Wounds may become a key stumbling block in our day-to-day task order in the modern human life scenario. Wound healing is influenced by a variety of factors, both local and systemic. It may result in a more stressful lifestyle. Diabetes and other significant chronic comorbidities have gotten exceedingly dangerous. A variety of allopathic medicines are available to quickly heal this condition. But, as we all know, there are some major side effects, thus individuals from all over the world are turning to herbal therapy for wound healing. There are a variety of herbal plants that have wound healing properties. This evaluation covers a wide range of plants. However, a review of the literature on diverse plants reveals that diverse chemical contents are found

in different plant species, but did not mention of which chemical compounds are important for wound healing. The majority of the literature only mentions studies on extracts in various solvents that have wound healing activity, but they do not specify the chemical elements that are responsible for wound healing. So, finding chemical constituents (phytochemical screening) using various chromatographic and spectroscopic techniques and determining which chemical constituents contained in plants exhibit wound healing has a lot of potential in the future. In addition to herbal medications, wound healing procedures such as HBOT, NPT, PRP, SCT, and biosurgery are some of the most widely used. Aside from these difficulties, the development of recurrences is a key issue associated with wound healing.

Abbreviations

ADP: Adenosine diphosphate; AEC: Amniotic epithelial cells; AMC: Amniotic mesenchymal cells; APG: Autologous platelet gel; bFGFR: Basic fibroblast growth factor receptors; DNA: Deoxyribonucleic acid; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; HAM: Human amniotic membrane; HBOT: Hyperbaric oxygen therapy; HDF: Human dermal fibroblast; IL: Interleukin; MCP: Monocyte chemoattractant protein; MNC: Mononucleocytes; NPT: Negative pressure therapy; PC: Platelet concentrate; PDGF: Platelet-derived growth factor; PMN: Polymorphonucleocytes; PPP: Platelet-poor plasma; PRP: Platelet-rich plasma; PRGF: Plasma rich in growth factors; SCT: Stem cell therapy; TGF: Transforming growth factor; TNF: Tumor necrosis factor; UNCAJ: Unripe cashew apple juice; VEGF: Vascular endothelial growth factor.

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Authors' contributions

The Concept was discussed by NK while CJ prepared the writing original draft of the article followed by RB with validation and data analysis, PB contributed to data curation, MJ and IL checked the grammar and removed all the plagiarism, then RJ reviewed and edited the article, and finally, JM did the formal analysis of the article. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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