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Selected Medicinal Plants Used In The Process Of Wound Healing Activity: A Literature Review

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ABSTRACT: The conventional Indian medicine - Ayurveda, Siddha, Unani describes various herbs, fats, oils and minerals with anti-inflammatory as well as wound healing properties. Wounds are injuries that cause a break or disruption in the continuity of the skin, mucous membranes, or underlying soft tissues. They can result from various causes such as trauma, surgery, burns, or pressure. Wound healing can be defined as a complex, dynamic, and well-coordinated process that results in the restoration of the anatomical continuity and physiological function of injured tissues. Various plant products have been used in the treatment of wounds over the years. Wound healing herbal extracts promote blood clotting, fight infection, and accelerate the healing of wounds. Hence in the current review, a list of the plants used in traditional medicine for the treatment of wounds was screened. Conducting detailed research on wound healing, health, and the development of safe, effective, and globally accepted herbal formulations for the treatment of cuts and wounds is of great importance to the scientific community.

Index Terms – wound, wound healing, plant products.

INTRODUCTION: In India, a large proportion of the population—approximately 80%—relies on plants for a variety of purposes, including food, medicine, healthcare, clothing, shelter, and agriculture. Among these, the use of plants as a source of medicine remains particularly significant, as it represents the most affordable and easily accessible form of treatment for many people. It has been reported that around 2,500 plant species are used regularly for medicinal purposes in India. (Pie., 2001). Over the past few decades, there has been a growing global interest in the study of medicinal plants and their traditional uses across different regions of the world. (Lev.,2006; Gazzaneo.,2013; Al 2005; Hanazaki 2000; Rossanto.,1999)

Wounds are a major cause of physical disability (Baddui et al.,2011). A wound is a disturbance of the normal structure and function of tissues caused by physical, chemical, microbial, or immunological insults, and is typically associated with loss of function. According to the Wound Healing Society, wounds are defined as physical injuries that result in an opening or break in the skin, leading to a disruption of the normal skin anatomy and function. (Strodtbeck F.,2001)

Wound healing is a complex and dynamic process involving a cascade of cellular and biochemical events that restore the structural and functional integrity of the injured tissue and help regain its strength. This process involves continuous cell–cell and cell–matrix interactions that occur in overlapping phases, including inflammation, wound contraction, re-epithelialization, tissue remodeling, and the formation of granulation tissue accompanied by angiogenesis. (Martin P., 1991)

Several factors can delay or impair the wound-healing process, including bacterial infections, the presence of necrotic tissue, poor blood circulation, lymphatic obstruction, and metabolic disorders such as diabetes mellitus. Generally, if any therapeutic agent can counteract or modify these factors, an enhanced rate of healing can be achieved. (Chitra p et al.,1998)

Many Ayurvedic plants play a significant role in the wound-healing process. Plant-based remedies are considered potent healers because they promote tissue repair through natural mechanisms (Kumar B., 2007). Such therapies not only accelerate the healing process but also help maintain the aesthetic appearance of the skin. (Galal E el al.,1965)

Approximately 70% of commercially available wound-healing pharmaceutical products are derived from plants, 20% from mineral sources, and the remaining from animal-based materials.

Plant-derived substances are commonly used in first-aid applications as antiseptics, coagulants, and wound cleansers (Biswas TK et al.,2003). In recent years, there has been a growing global interest in medicinal plant research, leading to a substantial body of evidence demonstrating the remarkable potential of these plants in traditional and modern medicine. Over the past five years, more than 13,000 plant species have been scientifically studied for their therapeutic properties (Dahanukar SA et al., 2007). The present review highlights some of the medicinal plants that have shown promising wound-healing activity.

1. Aloe vera

Aloe vera has been known and used for centuries for its numerous health, beauty, medicinal, and skincare benefits. The name Aloe vera is derived from the Arabic word “Alloeh,” meaning “shining bitter substance,” and the Latin word “vera,” meaning “true.” Over 2,000 years ago, Greek scientists regarded Aloe vera as a universal panacea, while the ancient Egyptians referred to it as the “plant of immortality.” In modern times, Aloe vera continues to be widely utilized in dermatology and cosmetic formulations for its therapeutic properties, particularly in wound healing, skin hydration, and anti-in flammatory applications.

1.1 Active components with its properties: Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino Acids. (Atherton P., 1998; Shelton M., 1991; Atherton P., 1997).

a. Vitamins: It contains vitamins A (beta-carotene), C and E, which are antioxidants. It also contains vitamin B12, folic acid, and choline. Antioxidant neutralizes free radicals.

b. Enzymes: It contains 8 enzymes: aliiase, alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, and peroxidase. Bradykinase helps to reduce excessive inflammation when applied to the skin topically, while others help in the breakdown of sugars and fats.

c. Minerals: It provides calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc. They are essential for the proper functioning of various enzyme systems in different metabolic pathways and few are antioxidants.

d. Sugars: It provides monosaccharides (glucose and fructose) and polysaccharides: (glucomannans/polymannose). These are derived from the mucilage layer of the plant and are known as mucopolysaccharides. The most prominent monosaccharide is mannose-6-phosphate, and the most common polysaccharides are called glucomannans [beta-(1,4)-acetylated mannan]. Acemannan, a prominent glucomannan has also been found. Recently, a glycoprotein with antiallergic properties, called alprogen and novel anti-inflammatory compound, C-glucosyl chromone, has been isolated from Aloe vera gel (Ro JY., 2000; Hutten et al., 1996).

e. Anthraquinones: It provides 12 anthraquinones, which are phenolic compounds traditionally known as laxatives. Aloin and emodin act as analgesics, antibacterials and antivirals.

f. Fatty acids: It provides 4 plant steroids; cholesterol, campesterol, β-sisosterol and lupeol. All these have anti-inflammatory action and lupeol also possesses antiseptic and analgesic properties.

g. Hormones*:* Auxins and gibberellins that help in wound healing and have anti-inflammatory action.

h. Others*:* It provides 20 of the 22 human required *amino acids* and 7 of the 8 essential amino acids. It also contains salicylic acid that possesses anti-inflammatory and antibacterial properties. Lignin, an inert substance, when included in topical preparations, enhances penetrative effect of the other ingredients into the skin. Saponins that are the soapy substances form about 3% of the gel and have cleansing and antiseptic properties.

1.2 Pharmacological activities of *Aloe vera*

1.2.1 Healing properties: Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth-promoting hormone, interact with growth factor receptors on fibroblasts, thereby stimulating their activity and proliferation. This enhanced fibroblast function significantly increases collagen synthesis following topical or oral administration of Aloe vera. (Chithra R. et al., 1998) Aloe gel not only elevates the collagen content of the wound but also alters its composition—promoting a higher proportion of type III collagen—and enhances the degree of collagen cross-linking. As a result, it accelerates wound contraction and increases the tensile strength of the resulting scar tissue. (Heggere J. et al 1996) Additionally, treatment with Aloe vera, either orally or topically, has been shown to increase the synthesis of hyaluronic acid and dermatan sulphate in the granulation tissue of healing wounds. (Chithra P. et al.,1998)

1.2.2 Effects on skin exposure to UV and gamma radiation: Aloe vera gel has been reported to have a protective effect against radiation damage to the skin. (Roberts D B. et al., 1995 & Sato Y. et al.,1990) Exact role is not known, but following the administration of aloe vera gel, an antioxidant protein, metallothionein, is generated in the skin, which scavenges hydroxyl radicals and prevents suppression of superoxide dismutase and glutathione peroxidase in the skin. It reduces the production and release of skin keratinocyte-derived immunosuppressive cytokines such as interleukin-10 (IL-10) and hence prevents UV-induced suppression of delayed type hypersensitivity. (Byeon S. et al., 1998)

1.2.3 Anti-inflammatory action*:* Aloe vera inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts. (Hutten et al., 1996)

1.2.4 Effects on the immune system: Alprogen inhibit calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of histamine and leukotriene from mast cells. (Ro JY. Et al., 2000) In a study on mice that had previously been implanted with murine sarcoma cells, acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumour necrosis factor from macrophages in mice, which in turn initiated an immune attack that resulted in necrosis and regression of the cancerous cells.(Byeon S. et al., 1998) Several low-molecular-weight compounds are also capable of inhibiting the release of reactive oxygen free radicals from activated human neutrophils.(Hart LA. Et al., 1990)

1.2.5 Laxative effects: Anthraquinones present in latex are a potent laxative. It increases intestinal water content, stimulates mucus secretion and increases intestinal peristalsis. (Jshii et al., 1994)

1.2.6 Antiviral and antitumor activity*:* These actions may be due to indirect or direct effects. Indirect effect is due to stimulation of the immune system and direct effect is due to anthraquinones. The anthraquinone aloin inactivates various enveloped viruses such as herpes simplex, varicella zoster and influenza. (Sydiskis R J et al., 1991) In recent studies, a polysaccharide fraction has shown to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby preventing the formation of potentially cancer-initiating benzopyrene-DNA adducts. An induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate has also been reported which suggest a possible benefit of using aloe gel in cancer chemoprevention. (Kim H S and Lee BM., 1997)

1.2.7 Moisturizing and anti-aging effect: Mucopolysaccharides help in binding moisture into the skin. Aloe stimulates fibroblast which produces the collagen and elastin fibers making the skin more elastic and less wrinkled. It also has cohesive effects on the superficial flaking epidermal cells by sticking them together, which softens the skin. The amino acids also soften hardened skin cells and zinc acts as an astringent to tighten pores. Its moisturizing effects has also been studied in treatment of dry skin associated with occupational exposure where aloe vera gel gloves improved the skin integrity, decreases appearance of fine wrinkle and decreases erythema. (West D P and Zhu Y F., 2003) It also has anti-acne effect.

1.2.8 Antiseptic effect*:* Aloe vera contains 6 antiseptic agents: Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur. They all have inhibitory action on fungi, bacteria and viruses.

2. Calendula officinalis

Calendula officinalis belongs to the genus calendula of the Asteraceae family, which contains15 species, and it is considered to have originated in the southwest Mediterranean region (Goncalves A.C. et al., 2018). It is either annual or perennial with a woody base and it can reach 70cm height (Tutin T.G. et al.,1964). The species is gyno monoecious and it is capable of both insect and self-pollination (C. Ao, 2007). Calendula has a long history of traditional use as a medicinal herb, dating back to the 12th century. It was cultivated by the Egyptians, Greeks, Hindus and Arabs, and it was named after the Latin word calends, which means the first day of every month, due to its long flowering period (Kemper K.J. 1991).

2.1 Pharmacological activities of Calendula

According to research, Calendula is beneficial for treating various skin diseases since it has anti-inflammatory, antioxidant, and antimicrobial qualities (Shahane K. et al., 2023). High levels of polyphenolic substances, such as flavonoids and phenolic acids, found in *Calendula officinalis* have been linked to anti-inflammatory and antioxidant properties (Givol. O.et al 2019). Additionally, it includes carotenoids, which have been demonstrated to have *anti*-UV radiation and anti-ageing properties [A. Olatunde et al.,2020]. It has been demonstrated to control the activity of wound-healing enzymes, including matrix metalloproteinases, which are crucial for tissue remodelling (P. Saini et al.,2012). In a study on mice model, calendula extract affected the activity and secretion of matrix metalloproteinases (MMP) 2 and 9 induced by UVB radiation (Y.M. Fonseca et al., 2010).

2.2 Mechanism of action of Calendula in wound healing

Calendula promotes wound healing, possibly through mechanisms such as reduced inflammation, improved blood flow, and antimicrobial activity. Flavonoids, like quercetin, in Calendula possess anti-inflammatory properties that help minimise inflammation and swelling, allowing the wound to focus on healing (Shahane K. et al., 2023). Calendula might improve blood flow to the wound area, delivering essential nutrients and oxygen for tissue repair (Deka B. et.al., 2021). It may also have some direct antimicrobial effects by disrupting the cell membrane of microbes (bacteria and fungi), helping prevent wound infections that can delay healing (Faria K.L et.al., 2011). This disruption increases permeability, allowing essential elements to leak out, ultimately leading to cell death. However, the exact blood flow and antimicrobial activity mechanism are not well understood and are still being investigated.

Upon injury, platelets are activated and release various pro-inflammatory cytokines, notably NF-κB, which play a crucial role in the inflammatory response (Basu P.et al.,2022). *Calendula officinalis* exerts its effects by inhibiting the activation of these cytokines, thereby reducing the recruitment of neutrophils and halting

the subsequent release of myeloperoxidase (MPO). This reduction in neutrophil activity diminishes the oxidative stress and tissue damage typically associated with the initial inflammatory phase of wound healing [Abdel-Aziem S.H. et al.,2022]. In addition to this, Calendula may also influence macrophage activity by decreasing the production of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β. This modulation leads to reduced oxidative stress and a lower incidence of apoptosis (programmed cell death) via downregulation of bcl-2-like protein 4 (BAX), a pro-apoptotic protein (Singh R. et al.,2019). which is a key player in apoptosis. Consequently, this creates a more conducive environment for healing by limiting excessive inflammation and cell death. The downregulation of oxidative stress consequently leads to enhanced stimulation of the proliferative and migratory capacity of keratinocytes and fibroblasts, essential for re-epithelialisation and granulation tissue formation (Sanchez M.C. et al.,2018). Enhanced keratinocyte activity and the subsequent epithelialisation of the wound mediated by cues received from IL-6, as well as fibroblast proliferation and migration, are further supported by the increased production of vascular endothelial growth factor (VEGF-c) and Transforming growth factor-β (TGF-β), which are critical for the formation of new granulation tissue and the overall structural integrity of the healing wound.

Another potential mechanism for Calendula officinalis action is the promotes angiogenesis through the upregulation of mothers against decapentaplegic homolog 3 (Smad-3) protein [Flanders K.C. 2004,] and collagen-1 production, both of which are vital for new blood vessel formation and tissue remodelling. The increase in hydroxyproline, a major component of collagen, underscores Calendula's role in enhancing the structural framework of the wound, facilitating more efficient and robust healing. The balance between Smad-3 and mothers against decapentaplegic homolog 7 (Smad-7) pathways is crucial in wound healing, where Smad-3 promotes fibrosis and collagen deposition (Flanders K.c.,2004), and Smad-7 is a negative feedback regulator. Calendula's ability to modulate these pathways ensures a balanced deposition of extracellular matrix components, preventing excessive fibrosis and promoting optimal wound repair. It's important to note that more research is needed to understand the mechanism of action of Calendula in wound healing fully.

3. *Martynia annua*

In India, plants are being used by the large number of population (about 80 %) living in rural as well as urban areas for various purposes such as food, medicine, healthcare, clothing, shelter, agriculture, etc. It is the most affordable and easily accessible source of treatment. It has been reported that about 2500 plant species serve as regular sources of medicine in India (Pei SJ., 2001). During the last few decades there has been an increasing interest to the study of medicinal plants and their traditional use in distinct parts around the world (Rossato S.C. et al.,1999). Among different medicinal plants *M. annua* are used in Indian traditional medicine and in folklore for many diseases. The leaves and fruits are the biologically active part of *M. annua*. (Chopra R.N. et. Al., 1996; Satyavati G.V. 1987)

M. annua belongs to family Martyniaceae (or Pedaliaceae), is a well-known small herbaceous annual plant, distributed throughout India. It is commonly known as the Cat's claw or Devil's claw refers to the inner woody capsule which splits open at one end into two curved horns or claws. They produce strange seed pods that attach to the feet and legs of large animals, and include some of the largest hitchhiker fruits in the world9. In Ayurveda, the plant is known as kakanasika, which is being used in Indian traditional medicines for epilepsy, inflammation, tuberculosis (applied locally to the tuberculosis gland at the neck) (Babu H.B. et al.,2010), sore throat, wound.

3.1 Phytoconstituents of Martynia annua

Sermakkani and Thangapandian reported different phytoconstituents on acetone leaves extracts of M. annua (Sermakkani M. and Thangapandian V.,2010). Phytochemical investigation of acetone extracts of leaves indicates the presence of alkaloids, tannins, saponin, glycosides, flavonoids, anthocyanin, amino acid, steroids and phenols (Katare V. et al 2012). During the phytochemical study, it has been observed that methanol extracts of leaves of M. annua contained higher amount of chemical constituents (Sermakkani M. and Thangapandian V.,2010). Flowers contain cyanidin-3-galactoside whilst p-hydroxy benzoic acid, snapic acid; and gentisic acids are present in leaves and fruits, respectively. The leaves also contain chlorogenic acid; and fatty acids (such as palmitic acid, stearic acid and arachidic acid) are present in seeds (Chatpalliwar VA. Et al., 2002). P-hydroxy benzoic acid, snapic acid and fatty acids such as palmitic acid and stearic acid present in leaves. (Lodhi S, Singhai AK. 2011) GC-MS studied on aqueous and alcoholic extract of M. annua showed the presence of 28 compounds in which oleic acid present in the high amount. Other major biological compounds include pelargonidin-3-5-diglucoside, cyanidin-3- galactoside, p-hydroxy benzoic acid, gentisic acid, arachidic acid, linoleic acid, palmitic acid, stearic acid, apigenin, apigenin-7-oglucuronide (Hosamani KM. et al.,2002; Dhingra AK. et al., 2013; Rastogi RP. Et al 1993)

3.2 Pharmacological activities of *Martynia annua*

3.2.1 Analgesic and antipyretic activity evaluated the analgesic effect of petroleum ether, chloroform, ethanol and aqueous extracts of M. annua fruits in Swiss albino mice by using hot plate and tail flick methods, and for antipyretic effect against brewers-yeast- induced hyperpyrexia in adult Wistar rats. The extracts show significant analgesic and antipyretic activity at 20 mg/kg. It has been also observed that the petroleum ether and chloroform extracts exhibits greater analgesic and antipyretic activities as compared to other extract. (Kar DM et al (2004).

3.2.2 Wound Healing activity evaluated the wound healing potential of ethanol extract of M. annua leaves using excision and incision model on rats. They reported that fraction MAF-C from ethanol extracts of M. annua leave is found most effective in wound healing and histopathological study also showed better angiogenesis, matured collagen fibers and fibroblast cells as compared to the control group. Moreover, phytochemical studies demonstrated that the methanol fraction mainly contains flavonoid luteolin responsible for enhancement of the wound healing process due to the free-radical scavenging mechanism (Lodhi and Singhai (2011).

3.2.3 Antibacterial activity evaluated antibacterial activity of chloroform, ethyl acetate and methanol extract of M. annua leaves against six gram-positive and nine gram-negative bacteria. All the extracts show antibacterial activity against different bacteria. Chloroform extract produces higher antibacterial activity against Proteus vulgaris, Bacillus thuringensis and Bacillus subtilis while ethyl acetate extracts potentially effective against Salmonella paratyphi A, Salmonella paratyphi B, Proteus mirabilis, Proteus vulgaris and Klebsiella pneumonia, whereas the methanol extracts, shows greater antibacterial activity towards Proteus vulgaris, B. subtilis, S. paratyphi B and Pseudomonas aeruginosa. Sermakkani and Thangapandian (2010)

3.2.4 Anthelmintic activity has been demonstrated anthelmintic activity of the petroleum ether extract of M. annua roots against earthworms Pheritima posthuma. The finding of the result exhibited potent anthelmintic activity compared to standard drug Albendazole. Nirmal SA et al (2007)

3.2.5. Antioxidant activity documented antioxidant activity of the methanol and aqueous extracts of M. annua leaves by reducing power assay, DPPH radical-scavenging activity, nitric oxide scavenging activity, H2O2 radical scavenging activity, superoxide radical scavenging assay, hydroxyl radical scavenging activity, and total antioxidant capacity method. The results revealed that the methanol extracts produced higher antioxidant activity than the aqueous extract. Nagda D et al (2009)

3.2.6 Antifertility activity reported antifertility activity of 50% ethanol extract of M. annua root. The finding of authors revealed significant decreases in the weights of testes, epididymides, seminal vesicle and ventral prostate. Moreover, reduction in the testicular sperm count, epididymal sperm count and motility, number of fertile males, the ratio between delivered and inseminated females and number of pups has been observed. Significant reduction in serum concentration of luteinizing hormone and testosterone support the anti-fertility activity of extracts. This plant is more beneficial as compared to other plants

exhibiting anti-fertility activity because no alterations in hematological parameters recorded. Mali PC, et al (2002)

3.2.7 Antidiabetic activity investigated the antidiabetic activity of methanol extracts of M. annua (MEMA) flower in streptozotocin (STZ) and Streptozotocin-Nicotinamide (STZ-NIC) induced diabetes in Wistar rats. MEMA showed excellent reductions in blood glucose, triglyceride and glycosylated haemoglobin levels and increased HDL levels in diabetic rats (after 21 days). A result revealed that the MEMA exhibited good antidiabetic activity in STZ and STZ-NIC induced diabetic rats. Saiyad and Gohil (2013)

CONCLUSION: Aloe vera, Martynia annua, Calendula officinalis is a wild crop plant that grows abundantly throughout most parts of India. According to Ayurvedic literature, its leaves, flower and seeds are anti-aging, anti-inflammatory, and wound healing properties. They are traditionally used in the treatment of pyrecia, inflammation, viral disease, anti-bacterial activity, anti- aging and anti-septic. The major action of these herbal ingredients is found wound healing properties (Givol. O.et al 2019; Lodhi and Singhai 2011).

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