



HOMOEOPATHIC MEDICINES AS A WOUND HEALER - A CRITICAL REVIEW

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ABSTRACT

A wound is loss of cellular and anatomic continuity of epithelium, with or without loss of underlying connective tissue caused by physical, chemical, thermal, microbial or immunological agents; surgery or as a result of disease, such as leg ulcers or carcinomas.^[1] Wound healing is a natural phenomenon and is divided into four sequential, yet overlapping phases that include haemostasis, inflammation, tissue formation and tissue remodelling.^[2,3] Failure to progress through these stages of healing due to a postponed, incomplete, or uncoordinated healing process leads wounds to enter a state of pathologic inflammation and results in delayed acute wound or chronic wounds. This may be due to factors such as venous or arterial insufficiency, pressure necrosis, physical agents, infection and cancer. Skin ulcers including venous leg ulcers and diabetic foot ulcers are the most common types of chronic wounds.^[3,6] Standard Homoeopathic texts describe several medicines to be therapeutically useful in wound healing. This review was conducted to summarize the available scientific information from standard homoeopathic literature, medical databases, laboratory studies and clinical studies on commonly used homoeopathic medicines- Arnica Montana, Bellis perennis, Calendula officinalis, Echinacea angustifolia and Hamamelis virginica for wound healing. These medicinal plants have important pharmacological properties such as anti-inflammatory, antimicrobial, immunomodulatory, anti-oxidant capacity, scavenging activity over free radical and/or non-radical reactive species, metal-chelating capability and inhibitory activity over radical-generating enzymes that are known to promote wound healing. The homoeopathic preparations of Arnica montana 6CH has shown significant role in wound healing and cicatrization process in rat models^[25,26] and has proven clinical efficacy in post-operative healing.^[27,28,29] However, scientific data on wound healing efficacy of other Homoeopathic medicines is lacking. We need to strengthen research based evidence for Homoeopathic medicines in chronic wounds like diabetic foot ulcers, venous leg ulcers etc. which are a major burden on healthcare resources.

KEYWORDS: Arnica montana, Calendula officinalis, Echinacea angustifolia, Homoeopathy, Wounds.

INTRODUCTION

A wound is loss of cellular and anatomic continuity of epithelium, with or without loss of underlying connective tissue (i.e. muscle, bone, nerves) following injury to the skin or underlying tissues. A wound is caused by physical, chemical, thermal, microbial or immunological agents; surgery or as a result of disease, such as leg ulcers or carcinomas. A wound leads to a breakdown in the protective function of the skin.^[1]

Wound healing is a natural phenomenon which starts immediately after injury and is divided into four sequential, yet overlapping phases that include haemostasis, inflammation, tissue formation and tissue remodelling.^[2,3] These overlapping phases include a series of events including clotting, inflammation, granulation tissue formation, re-epithelialisation, neovascularisation, matrix and collagen remodelling and wound contraction. The process involves a complex

array of cytokines secreted by platelets, macrophages, neutrophils, fibroblasts and epidermal cells.^[4,5] Failure to progress through these stages of healing due to a postponed, incomplete, or uncoordinated healing process leads wounds to enter a state of pathologic inflammation and results in delayed acute wound or chronic wounds. This may be due to factors such as venous or arterial insufficiency, pressure necrosis, physical agents, infection and cancer. Skin ulcers including venous leg ulcers and diabetic foot ulcers are the most common types of chronic wounds.^[3,6]

Local factors that directly influence wound healing are oxygenation and infection. Oxygen especially energy production by means of ATP is critical for nearly all wound-healing processes. Proper oxygenation prevents wounds from infection, induces angiogenesis, increases cell differentiation, migration and re-epithelialisation, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction.^[7] Similarly infection

control is very critical as bacteria and endotoxins released by bacteria in case of ineffective decontamination of wound leads to prolonged elevation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF- α and elongate the inflammatory phase. Two major enzymes that impair the wound healing process are myeloperoxidase (MPO) and collagenase. Reducing the concentration of these protein degrading enzymes together with scavenging and/or inhibition of reduced oxygen species (ROS) in a controlled manner encourage the healing process.^[8]

The systemic factors are the overall health state of the individual that affect the individual's ability to heal. Published literature suggests that every phase of healing undergoes characteristic age-related changes, including enhanced platelet aggregation, increased secretion of inflammatory mediators, delayed infiltration of macrophages and lymphocytes, impaired macrophage function, delayed re-epithelialization, delayed angiogenesis and delayed tissue remodelling and decreased wound strength. Systemic factors in wound healing include- age, stress, diabetes, medications, alcohol consumption, obesity and nutrition.^[9]

Stress may lead to anxiety and depression. Anxiety and depression directly influence endocrine and immune function impairing the cell mediated immunity at the wound site. This causes a significant delay in wound healing process. Also, individuals under stress are more likely to have unhealthy habits such as poor sleep patterns, inadequate nutrition, less exercise and a greater propensity for abuse of alcohol, cigarettes and other drugs.^[10] Diabetic individuals have delayed wound healing due to tissue hypoxia, reduced bactericidal capacity, impaired angiogenesis and neovascularisation, high levels of metalloproteases that support tissue destruction and inhibit normal repair process, damage from oxidative stress due to increase levels of oxygen radicals, decreased host immune resistance and neuropathy.^[7] Medications such as glucocorticoid steroids, non-steroidal anti-inflammatory drugs and chemotherapeutic drugs interfere with clot formation/platelet function and/ or cell proliferation and thereby interfere with the wound healing processes.^[7] In obese patients, the adipokines produced by adipocytes negatively impact the immune and inflammatory response although direct proof for this is lacking.^[11] Animal experiments and clinical studies have reported that exposure to alcohol impairs wound healing and increases the incidence of infection; the exact mechanism of which needs further investigation.^[12] Nutrition is also important for wound healing process as proteins, carbohydrates, arginine, glutamine, polyunsaturated fatty acids, vitamin A, vitamin C, vitamin E, magnesium, copper, zinc and iron play a significant role in wound healing.^[13] Vitamin A deficiency is associated with slowed re-epithelialisation, decreased collagen synthesis and an increased susceptibility to infection. Vitamin C is co-factor during collagen biosynthesis. Vitamin K

deficiency results in a deficiency in the production of vitamin K dependent clotting factors (factors II, VII, IX and X) leading to bleeding diathesis and hematoma formation. Zinc it is a constituent of multiple important metalloenzymes useful in wound healing including collagenase and DNA and RNA polymerases. The deficiency of these vital nutrients affects wound healing⁵.

Standard Homoeopathic texts describe several medicines to be therapeutically useful in wound healing. This review was conducted to summarize the available scientific information from standard homoeopathic literature, medical databases, laboratory studies and clinical studies on commonly used homoeopathic medicines- Arnica Montana, Bellis perennis, Calendula officinalis, Echinacea angustifolia and Hamamelis virginica for wound healing.

WOUND HEALING MEDICINES IN HOMOEOPATHY

ARNICA MONTANA

Geographical distribution- Arnica is a high-altitude perennial plant belonging to Asteraceae (Compositae) family. It is native to the mountain slopes in Europe, northern Asia, Siberia, Canada and America.^[14]

Ethnobotany- It is a popular folk medicine used extensively since centuries as a remedy to heal wounds and reduce inflammation resulting from bruises, sprains and swellings. It is also used as a topical counterirritant for treatment of pain and inflammation resulting from minor injuries, bruises, ecchymoses and haematomas.^[15]

Homoeopathic uses- Homoeopathic Materia Medicae describe that Arnica montana is suitable for traumatic injuries with blunt objects, a muscular tonic for complaints from overuse of any organ, muscular sprains and compound fractures. The patient is nervous, cannot bear pain; whole body over-sensitive. The patient has tendency to haemorrhage, low-grade fever, tissue degeneration, septic conditions and abscesses that do not mature. Arnica controls haemorrhage, prevents suppuration and aids absorption. Sore, lame, bruised feeling all through the body, as if beaten. Uneasiness in the painful parts; has to change position often, every place seems too hard. It is useful in bad effects of remote injuries, stupor from concussion with involuntary faeces and urine, conjunctival or retinal haemorrhage form injuries and ecchymosis from bruises. It prevents post-partum haemorrhage and puerperal complications and suitable for soreness of parts and/ or retention or incontinence of urine after labour. The patient is worse from least touch; motion; rest; wine; damp cold; and better by lying down, or with head low.^[16, 17 & 18]

Phytochemical Properties- The major constituents of Arnica montana include the essential oil (0.5%), fatty acids, thymol, pseudoguaianolide, sesquiterpene lactones (0.2–0.8%; helenalin and 11 α , 13-dihydrohelenalin) and

flavonoid glycosides and/or glucuronides of spinacetin, hispidulin, patuletin and isorhamnetin (0.2–0.6%).^[19]

Experimental Pharmacology– Published In vitro and animal model studies have attributed analgesic and anti-inflammatory properties Arnica montana to Helenalin.^[20] The flavonoids and phenolic acids constituents of Arnica have a good antioxidant activity and cytoprotective effect against oxidative damage in fibroblast-like cells.^[21] Laboratory molecular study has suggested the positive influence of Arnica on neutrophil recruitment and angiogenesis. It also modifies some of the genes that are key regulators of tissue remodelling, inflammation and chemotaxis.^[22] These studies provide scientific support for the traditional use of Arnica Montana in treatment of skin wounds, bruises and contusions.

Clinical Pharmacology - Clinical pharmacological studies have shown effectiveness of Arnica in post-operative healing. A systematic review with meta-analysis retrieved for 11 trials with a total of 627 patients concluded that the occurrence of periorbital edema and ecchymosis that usually occurs after surgical operation of Rhinoplasty was statistically decreased in the Arnica administration groups versus the control group during the first 7 days postoperatively.^[23] Iannitti T et al studied effectiveness and safety of Arnica montana in post-surgical setting, pain and inflammation concluded that it is more effective than placebo and may represent a valid alternative to non-steroidal anti-inflammatory drugs, at least when treating some specific conditions.^[24]

Homoeopathic Experimental Pharmacology- Arnica montana 6CH blocked the action of histamine in increasing vascular permeability in acute and chronic inflammation in rat models.^[25] Another animal model study concluded that Homoeopathic medicine Arnica has a significant role in wound healing and cicatrization process.^[26]

Homoeopathic Clinical Pharmacology- Clinical pharmacological studies have shown effectiveness of homoeopathic Arnica in post-operative healing. A double-blind, randomized comparison of oral and topical Arnica administration versus placebo that assessed the action of Arnica in 37 patients undergoing bilateral endoscopic carpal-tunnel release reported a significant reduction in pain experienced after 2 weeks in the Arnica-treated group (P<.03).^[27]

Twenty-nine patients undergoing face-lift surgery treated with peri-operative homeopathic Arnica Montana or placebo in a double-blind fashion exhibited less ecchymosis in Arnica group and that difference was statistically significant (P<.05) on 2 of the 4 postoperative data points evaluated.^[28] A prospective randomized double-blind study placebo controlled study among patients scheduled for rhinoplasty surgery with nasal bone osteotomy concluded that Arnica Montana

accelerated postoperative healing, with quicker resolution of the extent and the intensity of ecchymosis.^[29]

BELLIS PERENNIS

Geographical distribution- Bellis perennis is a perennial herbaceous plant belonging to Asteraceae (Compositae) family and native in Brazil, Europe, Turkey, Cyprus, Syria and Azerbaijan.^[30]

Ethnobotany- Bellis perennis has been used traditionally in the treatment of bruises, fractures and wounds by European people. 16th century herbal literature has record of the medicinal properties of Bellis perennis. John Gerard, the 16th century herbalist, recommended Bellis perennis to promote healing of bruises and swellings, inflammation of mucous membrane, heavy menstruation and migraine. Chewing the fresh leaves is said to be a cure for mouth ulcers.^[31]

Homoeopathic uses- The Boericke's Materia Medica recommends Bellis perennis as the first remedy for deep tissue injuries and after effects of major surgical work including nerve injuries. It is useful in injuries in nerves with intense soreness and intolerance of cold bathing. It is also one of the top remedies for joint and muscular soreness and sport accidents. It acts upon the muscular fibres of the blood-vessels with exudations, stasis and swelling. It is an excellent remedy for sprains, bruises and venous congestion due to mechanical causes. It is beneficial in trauma of the pelvic organs with sore bruised feeling in the pelvic region. The patient complains of lameness as if sprained; muscular sprains feel contracted as from elastic band around the joint. Varicose veins with bruised sore feeling.

The patient is aggravated by hot bath and warmth of bed; before storms; cold bathing; cold wind.^[18]

Phytochemical Properties- Bellis perennis contains saponins (oleanane-type triterpene saponins, bellissaponins BS5 and BS9, perennisosides- I, II, VII, IX, XI and XVIII, asterbatanoid D, bernardioside B2), flavonoid (apigenin-7-O-glycopyranoside), glycosides (Bayogenin and asterogenic acid glycosides, polygalic acid glycosides) and polyacetylenes.^[32-35]

Experimental Pharmacology- Laboratory studies have reported that Bellis perennis has anti-oxidant, broad-spectrum anti-bacterial and anti-fungal properties. Apigenin-7-O-glycopyranoside- a flavonoid isolated from the flowers of Bellis Perennis showed strong antioxidant potential in vitro, because of its capacity to remove hydroxyl radicals and nitric oxide and also prevented the formation of thiobarbituric acid-reactive substances in addition to inhibiting acetylcholinesterase.^[36] The methanol extract and ethyl acetate fraction of flowers exhibited broad-spectrum antibacterial activity against Streptococcus pyogenes, Staphylococcus aureus, Staphylococcus epidermidis and

Enterobacter cloacae in laboratory studies.^[37] The polyphenols and flavonoids extracted from the plant have antimicrobial effect on *Staphylococcus epidermidis* MU 30 and *Staphylococcus aureus* MU 38.^[38] In vitro and In vivo studies of this plant extract showed antifungal activity; the triterpenoid glycosides obtained from *Bellis perennis* inhibited the growth of human-pathogenic yeasts (*Candida* and *Cryptococcus* species).^[39,40] The above mentioned properties of *Bellis Perennis* support its potential use for inflammation, wounds and rheumatism etc.

The wound healing activity of *Bellis perennis* has been scientifically verified in circular excision wound Wistar albino rats by topically administered ointment prepared from the n-butanol fraction of *Bellis perennis* flowers. The results indicated that it has a wound healing potential without scar formation.^[41] Another study has reported that wound healing property of *Bellis perennis* can be attributed to saponins present in the plant that significantly promoted collagen synthesis at 3-30 μ M without cytotoxicity in animal models.^[42]

Homoeopathic Experimental Pharmacology- *Bellis perennis* in 6C and 30C potency at three different concentrations of 2 μ l/ml, 4 μ l/ml and 8 μ l/ml for 96 h has shown anti-oxidative effect and prevents oxidative damage in rat pheochromocytoma (PC12) cell line as compared with positive control (90% alcohol). The content of LPO was significantly decreased in drug treated groups as compared to positive control while the level of glutathione was significantly increased.^[43]

CALENDULA OFFICINALIS

Geographical distribution- *Calendula officinalis* is a very aromatic flowering annual herb belonging to Asteraceae (Compositae) family. It is indigenous to central, eastern and southern Europe and cultivated commercially in North America, the Balkans, Eastern Europe and Germany.^[44]

Ethnobotany- Traditionally *Calendula* has been used in the treatment of inflammations of the oral and pharyngeal mucosa, wounds and burns.^[45] Crushed leaves of *Calendula* are topically applied on wounds; the topical application of infusion of flowers has been traditionally used as antifungal and antiseptic in wounds, burns, sprain, diaper rash and as eyewash in conjunctivitis.^[46-48]

Phytochemical Properties- The major phytoconstituents present in *Calendula* are triterpene saponins (calendulosides) and flavonoids (quercetin, rutin, narcissin, isorhamnetin, kaempferol). Other constituents include essential oil, sesquiterpenes (caryophyllene), triterpenes (a- and b-amyrins, lupeol and lupenone) and polysaccharides.^[44]

Homoeopathic uses- Homoeopathic Materia Medicae describe that *Calendula* is suitable all type of external

wounds with or without loss of tissue; torn and jagged looking wounds; post-surgical operation; rupture of muscles or tendons; lacerations during labour; wounds penetrating articulations with loss of synovial fluids; neuritis from lacerated wounds where pain is excessive and out of all proportion to injury. *Calendula* is almost specific for clean, surgical cuts or lacerated wounds. It is useful as a haemostatic after tooth extraction, in lacerated scalp wounds; injuries to eyes which tend to suppurate; after operations. It promotes healthy granulation, prevents excessive suppuration and disfiguring scars; and secures rapid healing by first intention. It is useful in injuries to parts rich in sentient nerves where pain is excessive and out of all proportion to injury. Injury with loss of soft parts when union cannot be done by means of adhesive plaster. Open wound that do not heal and lead to ulcer formation. Ulcers those are inflamed raised edges, sloughing, varicose; painful as if beaten with excessive secretion of pus. Old, neglected, offensive wounds threatening gangrene. *Calendula* is effective in superficial burns and scalds. It is most remarkable healing agent applied locally.^[16,18]

Experimental Pharmacology- *Calendula* has antioxidant, anti-inflammatory, antibacterial, and wound healing properties. In vitro studies have suggested that the essential oil of the flowers of *Calendula* inhibited the growth of *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*; a flavonoid fraction isolated from *Calendula* flowers inhibited the growth of *S. aureus*, *Sarcina lutea*, *E. coli*, *Klebsiella pneumoniae*, *Candida monosa* and *Trichomonas vaginalis*.^[49,50] The essential oil of the *Calendula* flowers have shown potential antifungal activity against various fungal strains- *Candida albicans*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei* and yeast isolated from humans using disc diffusion technique at 15 μ l/disc.^[51] The anti-inflammatory activity was shown by topical application of 70% ethanol extract of *Calendula* flower at a dose of 1.2 mg/ear and carbon dioxide extract of the flowers at a dose of 300mg/cm². These interventions suppressed croton oil-induced ear oedema in mice.^[52] Another study reported that the triterpene fraction of an extract of *Calendula* flowers had marked anti-inflammatory activity in mice (1mg/ear) against ear oedema induced by 12-Otetradecanoylphorbol-13-acetate.^[53] The ethanolic extract, the dichloromethane, and hexanic fractions of *Calendula* extract have shown anti-inflammatory and antibacterial activities as well as angiogenic and fibroplastic properties when evaluated through macroscopic, morphometric, histopathologic, and immunohistochemical analysis in cutaneous wounds in rat models. The extracts acted in a positive way on the inflammatory and proliferative phases of the healing process.^[54]

Published laboratory research has attributed that wound-healing activity of *Calendula* to its angiogenic activity

and induction of neovascularisation; increase in the hydroxy proline and hexosamine content in granulation tissue; stimulation of both proliferation and migration of fibroblasts; increase in the concentrations of collagen and non-collagenous proteins, as well as the collagen organization in the initial phase of healing. A 3% aqueous extract of Calendula flowers (freeze-dried) induced vascularisation in the chick chorioallantoic membrane assay. Histological sections of the treated chick chorioallantoic membranes also indicated the presence of yaluronan, a tissue glycosaminoglycan associated with neovascularisation.^[55] The healing and angiogenic activity of Calendula Officinalis ethanolic extract and dichloromethane and hexanic fractions were evaluated using 36 rats and 90 embryonated eggs through the induction of skin wounds and the chorioallantoic membrane, respectively. The angiogenic activity of the extract and the fractions was evidenced in both experimental models.^[56] Calendula Officinalis tincture, hexane and ethanolic extracts and hydroethanol extracts potentiated wound healing by stimulating proliferation and migration of fibroblast in a statistically significant manner in a PI3K-dependent pathway and scratch assay.^[57-59] The topical application of Calendula Officinalis after tendon transection increased the concentrations of collagen and non-collagenous proteins, as well as the collagen organization in the initial phase of healing in Wistar rats.^[60] The effects of oral and topical application of Calendula officinalis flower extract was tested on excision wounds made in rats. The percentage of wound closure was reported to be 90% in the extract-treated group and 51.1% in control group on the eighth day of wounding ($p < .01$). A significant increase was observed in the hydroxy proline and hexosamine content in the extract-treated group compared with the untreated animals. The results of this indicated potent wound healing activity of Calendula officinalis extract.^[61]

Calendula has also shown healing properties in thermal burns. The ethanol extract of the plant's flowers was investigated against experimentally induced thermal burns in rats by making burn injury on shaven back of the rats under anesthesia and treating them orally with different doses of Calendula flower extract (20 mg, 100 mg and 200 mg/kg body weight). Wound healing indicators such as collagen-hydroxyproline and hexosamine contents were significantly increased in the treated group. The antioxidant defense mechanism which was decreased in liver and acute phase proteins-haptoglobin and orosomucoid which were increased due to burn injury were found to be enhanced and decreased significantly respectively. Lipid peroxidation, and tissue damage marker enzymes- alkaline phosphatase, alanine and aspartate transaminases were significantly lowered in the treated groups in a dose dependant manner. The histopathological analyses of skin tissue also give the evidence of the increased healing potential of the extract after burn injury.^[62]

Clinical Pharmacology- Buzzi M et al. studied the effect of Calendula officinalis extract in venous leg ulcers and diabetic foot ulcers. For venous leg ulcer study patients treated with Calendula officinalis extract ($n=38$) and control patients ($n=19$) were evaluated every two weeks for 30 weeks or until their ulcers healed. Assessments included determination of the wound area by planimetry, infection control, and evaluation of the clinical aspects of the wounds. The percentage of healing velocity per week (%HVw), taking the initial area at baseline into account, was also determined. The proportion of the treatment patients achieving complete epithelialisation was 72% in the treatment group and 32% in the control group. The average healing time was approximately 12 weeks in the treatment group and 25 weeks in control patients. Patients with venous leg ulcers treated with Calendula officinalis extract had a significant 4-fold increase in percentage healing velocity per week, 7.4%, compared with 1.7% in the control group.^[63] The clinical benefits of using Calendula officinalis hydroglycolic extract were evaluated in the treatment of Diabetic Foot Ulcers (DFUs) in a prospective, descriptive pilot study. Patients diagnosed with a stable neuropathic ulcer of >3 months' duration; ranging in size from 0.5-40 cm(2); with adequate glycemic control and without osteomyelitis, gangrene, bone exposure, cancer, or deep tissue infection in the age group of 18-90 years and no history of an allergy to Calendula officinalis were enrolled for the study. Patients were evaluated biweekly for 30 weeks or until DFU healing (i.e. full epithelialisation with no wound drainage). Complete wound closure was achieved in 54%, 68% and 78% of the patients after 11, 20, and 30 weeks of treatment respectively with a mean healing time of 15.5 ± 6.7 weeks. The number of colonized wounds decreased from 29 at baseline to 5, and the number of odorous wounds decreased from 19 to 1 after 30 weeks of treatment.^[64] Local application of Calendula ointment has also proved beneficial in venous leg ulcers. Twenty-one patients with 33 venous ulcers were applied an ointment containing Calendula extract twice a day for 3 weeks in the experiment group and 13 patients with 22 venous ulcers in the control group were applied saline solution dressings for the same period. Results of the study showed a statistically significant acceleration of venous ulcer epithelialisation in the experimental group ($p < 0.05$).^[65]

Homoeopathic Experimental Pharmacology- The Homoeopathic preparation of Calendula officinalis has been studied for healing of excision wounds in rat models. The external application of a hydroalcoholic extract of Calendula officinalis accelerated the rate of contraction and epithelialisation of excision wounds in rats.^[66] A combination of an ethanolic preparation composed of equal parts of Arnica montana 4x, Calendula officinalis 4x, Hypericum perforatum 4x and Symphytum officinale 6x (0712-2), its succussed hydroalcoholic solvent (0712-1) and unsuccussed solvent (0712-3) was studied for their effect on wound healing blind trial in vitro in NIH 3T3 fibroblasts. None of the

three preparations affected cell viability or showed a stimulating effect on cell proliferation. Preparation (0712-2) exerted a stimulating effect on fibroblast migration (31.9%) vs 14.7% with succussed solvent (0712-1) at 1:100 dilutions ($p < 0.001$). Unsuccussed solvent (0712-3) had no influence on cell migration (6.3%; $p > 0.05$). Preparation (0712-2) at a dilution of 1:100 promoted in vitro wound closure by 59.5% while succussed solvent (0712-1) caused 22.1% wound closure ($p < 0.001$). Results of this study indicated in vitro wound closure potential of low potency homeopathic remedy (0712-2) in NIH 3T3 fibroblasts. This effect resulted from stimulation of fibroblasts motility rather than of their mitosis.^[67]

ECHINACEA ANGUSTIFOLIA

Geographical distribution- Echinacea angustifolia is an herbaceous perennial plant belonging to Asteraceae (Compositae) family and is native of North America and Canada.^[68]

Ethnobotany- Echinacea angustifolia has a historic reputation of boosting the immune system, in treating and preventing upper respiratory infections. It has also been used to speed wound healing and reduce inflammation. In the late 1800s and early 1900s, the Native Americans and Eclectic physicians used it as an antiseptic, analgesic, for treating toothaches, sore throat, wounds and vaginal candidiasis. It was also used in communicable diseases such as mumps, smallpox and measles; and to treat poisonous insect and snakebites. Echinacea preparations become popular in Germany in the early 1900s where this herb was tested and incorporated for homeopathic purposes.^[69,70]

Phytochemical Properties- The major constituents of this medicinal plant include a volatile oil (pentadeca-(1,8-Z)-diene (44%), 1-pentadecene, ketoalkynes and ketoalkenes), more than twenty alkamides (mostly isobutylamides of C11–C16 straight-chain fatty acids with olefinic or acetylenic bonds), polyalkenes, polyalkynes, caffeic acid derivatives (echinacoside, cynarin, and chicoric acid), and polysaccharides. Trace amounts of pyrrolizidine alkaloids (tussilagene (0.006%) and isotussilagene) are also present.^[68]

Homoeopathic uses- The Boericke's Materia Medica describes Echinacea angustifolia as a "corrector of blood dyscrasia" in cases of septic conditions generally. It is useful in recurring boils, carbuncles, pustules, erysipelas, crushing injuries, chronic tibial ulcers, gangrene and puerperal infections. It is also beneficial in skin irritations from insect bites and poisonous plants; snake bites and bites and stings generally. It is to be given in last stages of cancer to ease pain. The patient complains of foul discharges with emaciation and great debility. Can be taken internally as well as used locally, as a cleansing and antiseptic wash.^[18]

Experimental Pharmacology- Laboratory studies have reported Echinacea angustifolia to have Immunomodulator, anti-oxidant, anti-microbial and anti-inflammatory properties. All these properties of this medicinal plant contribute to wound healing.

The immunostimulant effect of Echinacea root extracts has been reported in over 350 scientific in vitro and in vivo studies. This effect is brought about by: activation of phagocytosis and stimulation of fibroblasts; increasing respiratory activity; and causing increased mobility of the leukocytes.^[71,72,73] Immunomodulating properties of alcohol extracts from three commonly used Echinacea species- Echinacea angustifolia, Echinacea pallida, and Echinacea purpurea were investigated. The results of this study demonstrated that Echinacea is a wide-spectrum immunomodulator and modulates both innate and adaptive immune responses. Echinacea angustifolia and Echinacea pallida may have more anti-inflammatory potential.^[74] The lipophilic amides, alkamides and caffeic acid derivatives present in the alcoholic extracts of Echinacea stimulate phagocytosis of polymorphonuclear neutrophil granulocytes and thereby contribute to the immunostimulant activity of the plant.^[75]

A study that evaluated bactericidal activity of six different commercial Echinacea extracts derived from Echinacea angustifolia roots or mixtures of Echinacea purpurea roots and aerial parts containing different relative amounts of alkylamides and polysaccharides and similar overall concentrations of caffeic acid derivatives concluded that ethanolic extracts of Echinacea has selective bactericidal activities and may be used in upper and lower respiratory infections as well as skin infections, although components of the extracts responsible for these activities could not be identified.^[76] Antifungal activity of root extracts of eight Echinacea taxa including were for antifungal property against Cryptococcus neoformans, two Candida albicans isolates (D10 and CN1A), Trychophyton tonsurans, T. mentagrophytes, Mycosporium gypseum and Pseudallescheria boydii. This study concluded that eight Echinacea taxa, including Echinacea angustifolia showed antifungal activity against most of the pathogenic fungi.^[77] The phagocytotic potential of chemically standardized ethanolic extracts, derived from roots and aerial parts from Echinacea purpurea, E. pallida and E. angustifolia was assessed in the carbon clearance test with mice and in the granulocyte test. All ethanolic root extracts increased phagocytosis in vivo.^[78]

The anti-oxidant potential of three Echinacea species (Echinacea purpurea, Echinacea angustifolia and Echinacea pallida) was analyzed from their alcoholic extracts of the roots and leaves in a free radical scavenging assay and in a lipid peroxidation assay. All three were found to have antioxidant properties.^[79] Another study evaluated the anti-oxidant potential of three Echinacea species (Echinacea purpurea, Echinacea

angustifolia and Echinacea pallida) from their methanolic root extracts in vitro with a spectrophotometric method based on the reduction of an alcoholic 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical solution at 517 nm in the presence of a hydrogen donating antioxidant. This study reported that Echinacea methanolic extracts have radical scavenging activity, are a good source of natural antioxidants and could be used to prevent harmful effects induced by free-radicals.^[80]

The anti-inflammatory action of Echinacea angustifolia has been attributed to its polysaccharide, alkaloids and Echinacoside content. Crude polysaccharide extract of Echinacea angustifolia applied topically reduced inflammation in the rat paw oedema model.^[81] A new alkaloid dodeca-2Z,4E,10Z-trien-8-ynoic acid isobutylamide from Echinacea angustifolia and dodeca-2Z,4E-diene-8,10-diynoic acid isobutylamide from Echinacea purpurea and Echinacea pallida were identified from roots of Echinacea angustifolia by analysis of spectroscopic data. These two along with previously identified alkaloids, exerted inhibition on lipopolysaccharide-mediated activation of a murine macrophage line, RAW264.7 indicating anti-inflammatory effect of Echinacea.^[82] Echinacoside, a naturally occurring phenol has shown unstable free radical scavenging activity; Iron, copper and zinc ions chelation to reduce the lipid peroxidation and stops cell damage from inflammatory cascade.^[83] Another study has reported that the anti-inflammatory activity of Echinacea might be due to multiple active metabolites that work together and switch macrophage activation from classical activation towards alternative activation. This study had evaluated alcohol extracts of three medicinal Echinacea species, Echinacea angustifolia, Echinacea pallida and Echinacea purpurea.^[84]

Clinical Pharmacology- Clinical studies have not shown pharmacological effect and mechanism of Echinacea angustifolia root preparations in adults; the only evidence is immunomodulatory action based on in vitro and in vivo animal experiments. Most of its action including wound healing promoting properties is explained by their antioxidant activity.^[85]

HAMAMELIS VIRGINIANA

Geographical distribution- Hamamelis virginiana is a deciduous, tall shrub that belongs to Hamamelidaceae family. It is indigenous to the Atlantic coast of North America, found in damp woods ranging from Nova Scotia to Florida and as far west as Texas.^[44]

Ethnobotany- Hamamelis preparations have a long history of traditional use in North America and are used primarily for its astringent, anti-inflammatory and local haemostatic effects. In folk medicine it has been used for poor venous conditions, including the treatment of haemorrhoids; as a hemostatic in menorrhagia and dysmenorrhea and there are similar uses in homeopathy. Poultices of hamamelis leaves and barks were used by

Native Americans a remedy for haemorrhoids, wounds, insect bites, painful tumours and ulcers. The bark aqueous infusion was used to treat haemorrhages, inflammations and haemorrhoids.^[86]

Homoeopathic uses- Standard Homoeopathic texts recommend Hamamelis for great value in open, painful wounds, with weakness from loss of blood, after operations. It is useful in wounds that are incised, lacerated, contused; resulting from falls; trauma to the eye with intense soreness; chronic effects of mechanical injuries. Hamamelis checks haemorrhage, removes pain and soreness like Arnica. It is suitable for traumatic inflammations, burns, ecchymosis, varicose veins and ulcers; very sore. Hamamelis acts upon the coats of the veins causing relaxation with consequent engorgement and passive venous haemorrhage from any part of the body; of skin and mucous membranes; phlebitis, varicose veins; ulcers, varicose, with stinging, pricking pain; haemorrhoids; bowel ulcers; epistaxis; menorrhagia. Bleeding is profuse, long-lasting, dark, blood non-coagulable and drains the system with severe prostration. There is bruised soreness of affected parts like Arnica. The patient is worse in warm, moist air. Like Arnica and Calendula, Hamamelis can be used as a local application for external injuries.^[16,17,18]

Phytochemical Properties- Tannins, both hydrolysable and condensed tannins are the major constituents of the dried leaf and bark (up to 10%). The leaf tannins are a mixture of gallic acid (10%), hydrolysable hamamelitannin (1.5%) and condensed proanthocyanidins (88.5%). Cortex tannins have a much higher hamamelitannin level (up to 65% of a hydroalcoholic extract).^[87]

Experimental Pharmacology- In vitro studies have reported that Hamamelis has anti-inflammatory, antibacterial, anti-oxidant activity; it prevents suppuration and promotes wound healing. In vivo studies have shown that Hamamelis has anti-inflammatory and astringent activity. Hamamelis virginiana bark crude hydroalcoholic extract was subjected to ultrafiltration (UF); the UF-concentrate displayed radical scavenging properties in vitro. Intraperitoneal administration of a 70% ethanol extract of the leaves (200 mg/kg body weight) exhibited strong anti-inflammatory effects in the croton oil ear edema test in the mouse. The isolated chemical constituents from the leaves exhibited anti-inflammatory activity both in vitro and in vivo.^[88] Another study reported that topical application of a hydroalcoholic extract of the bark (250mg/ml) inhibited croton oil-induced ear oedema in mice and thus had anti-inflammatory activity. This study also demonstrated that the proanthocyanidin fraction of the hydroalcoholic extract was active against herpes simplex virus type 1 (ED₅₀ 11mg/ml).^[89]

In vitro studies have reported that Hamamelis leaves aqueous extract inhibited the growth of Escherichia coli

(MIC 0.4 mg/ml), *Staphylococcus aureus* (MIC 0.4 mg/ml), *Bacillus subtilis* (MIC 1.1mg/ml) and *Enterococcus faecalis* (MIC 3.0mg/ml). Hamamelis bark aqueous extract inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC for all 10.0 mg/ml).^[90] The tannins (Hamamelitannin and gallic acid) extracted from Hamamelis have shown free radical scavenging / antioxidant activity. Hamamelitannin inhibited the production of superoxide anion radicals and hydroxyl radicals as measured by electron spin resonance spectrometry. Hamamelitannin also suppressed the depolymerization of hyaluronic acid and protected human dermal fibroblasts against oxidative damage induced by superoxide anion radicals.^[91] Studies have shown that the phenolic constituents particularly the tannins (hamamelitannin), aldehydes and oligomeric proanthocyanidins are responsible for astringent activity of Hamamelis. The application of Hamamelis preparations on skin and mucosa in low concentrations sealed cell membranes and reduced capillary permeability. Higher concentrations precipitated proteins and formed a thin membrane in wound area. Alcohol extracts of Hamamelidis had strong astringent action, the bark extract being slightly more superior to the leaf extract.^[87]

Polymeric proanthocyanidins from Hamamelis virginiana L. bark increased proliferation of human keratinocytes and aided regeneration of irritated skin in vivo. This study proved the efficacy of procyanidins in an irritation-skin model which may be utilized for skin healing^[92]. The chronic wound healing promoter potential of polyphenol extract from Hamamelis Virginiana was evaluated in vitro. The polyphenolic extracts showed a multifunctional antioxidant capacity and were able to scavenge radical and non-radical species such as hypochlorous acid (HOCl). The extract also showed ability to act as peroxidase substrate for matrix metalloproteinases (MPO) thereby inhibiting chlorination activity of the enzyme, responsible for the HOCl production. It also caused inhibition of the proteolytic activity of collagenase. As chronic ulcer fluids contain elevated levels of reactive oxygen species (ROS) and enzymes such as MPO and collagenase that impair wound healing, the strong antioxidant and proteolytic enzymes inhibitory activity shown by Hamamelis polyphenolic extract can be potentially beneficial for wound healing process.^[93]

Clinical Pharmacology- Clinical studies have shown anti-inflammatory efficacy, vasoconstrictive effects and keratinocyte proliferative effects of Hamamelis extracts. A randomized, double-blind study assessed the anti-inflammatory efficacy of topical application of a Hamamelis distillate in a phospholipid-containing vehicle, hydrocortisone, camomile and four drug-free vehicle-based preparations in 48 patients. Erythema induced by ultraviolet light or repeated stripping of the skin with adhesive tape was suppressed only by the

Hamamelis preparation (0.64 mg per 100 g vehicle) and hydrocortisone cream (1%).^[94] The vasoconstrictive effects of a Hamamelis ointment containing 25g aqueous distillate/100g ointment base (about 4 g drug) were analysed in five patients with dermatoses and 22 healthy volunteers. Fluvography measurements indicated that the ointment reduced the thermal conductivity of the skin due to vasoconstriction in both groups, suggesting a mild anti-inflammatory activity.^[87]

CONCLUSION

In recent years, medicinal plants have received much attention due to their curative properties and their medicinal virtues have been evaluated on modern scientific lines such as phytochemical analysis, pharmacological screening and clinical trials. *Arnica montana*, *Bellis perennis*, *Calendula officinalis*, *Echinacea angustifolia* and *Hamamelis virginiana* are important medicinal plants used in Homoeopathy for wound healing. These medicinal plants have important pharmacological properties such as anti-inflammatory, antimicrobial, immunomodulatory, anti-oxidant capacity, scavenging activity over free radical and/or non-radical reactive species, metal-chelating capability and inhibitory activity over radical-generating enzymes that are known to promote wound healing. In vitro studies have proved wound healing efficacy of *Arnica Montana*^[22], *Calendula officinalis*^[67] and *Hamamelis virginica*^[93] extracts while In vivo studies have shown wound healing efficacy of *Bellis perennis*^[41, 42], *Calendula officinalis*^[66] and *Hamamelis virginica*^[87, 92] extracts. The homoeopathic preparations of *Arnica montana* 6cH has shown significant role in wound healing and cicatrization process in rat models^{25, 26} and has proven clinical efficacy in post-operative healing^{27, 28 & 29}. However, scientific data on wound healing efficacy of other Homoeopathic medicines prepared from these medicinal plants is lacking. In conclusion, we need to strengthen research based evidence for Homoeopathic medicines in chronic wounds like diabetic foot ulcers, venous leg ulcers etc. which are a major burden on healthcare resources.

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