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Medicinal Plants for Wound Healing: A Review

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ABSTRACT

Cutaneous healing of wounds involves four cumulative phases namely haemostasis, inflammation, proliferation and remodeling. The Keratinocyte initiates re-epithelialization for closing the wound surface by generating new healthy binding tissues and further undergoes alterations until getting rejuvenated to its original state. The Substantial use of naturally occurring products and their derivatives obtained from traditional and native medicinal plants is increasing day by day. This review article discusses the active role of traditionally used herbal medicines for healing cutaneous wounds due to the presence of different phytoconstituents like alkaloids, tannins, flavonoids, phenolic acids etc.. Generally the use of traditional phytoconstituents with modern formulation skills leads to production of better wound healing dosage form, with their effective strength and minimal side effects.

Keywords: Medicinal plants, Phytoconstituent, Wounds, Wound healing

INTRODUCTION

Any disruption in basic constitutional and biological activity of tissues due to any physical, chemical, microbial, thermal or immunological imbalance leads to wound[1]. Wounds directly or indirectly interfere with basic skin anatomy and functioning [2]. Based on the cause of wound or injury, these are either open or closed wounds [3, 4]. Open wound leads to imperfect skin surface and basal tissues will be directly exposed with the external environment and unprotected from any kind of infection and bleeding; whereas in closed wounds the skin surface remains unbroken or flawless. The basal tissue will not be directly exposed with the outside environment [4]. Wounds can either be acute or chronic depending on the time of healing [5]. Acute wounds caused by some

injury that could be blunt or penetrating [6] and tends to restore themselves with time and through systematic healing pathway [5]. Various efforts are now being explored for new mediums or vehicles that are proven to be used in enhancing the healing activity and promoting the fast recovery of injuries[7,8]. Studies conclude for medicinal plants proving their importance in cuts and burns etc. Wound repair constitutes a multiplex process which involves a systemized process of tissue self repairing that further go through different overlapping phases, involving cellular inflammation and proliferation and remodeling [8].

Wound healing

Healing of wounds comprises replacement of weakened and misplaced cells or tissues. This process involves a series of biochemical events in a systemized manner that allows repairing of damaged tissues [9]. Frequently the wound healing process is divided in three different phases, initially the inflammatory phase, then the proliferative phase and in the end remodeling phase. The initial inflammatory phase starts immediately after the injury which initiates haemostatic mechanisms to stop bleeding straight away [10]. This leads to vasoconstriction and aggregation of platelets which allows inducing vasodilatation and phagocytosis that results in cellular inflammation at the site of wound. The proliferative phase involves the granulating process and wound contraction which covers the denuded epithelial surface i.e. Epithelialization. In the granulation process, fibroblastic cells will form a collagen base that helps in producing new capillaries [10]. During the process of contraction of the wound, myofibroblasts decrease the wound proportion by squeezing the linings of the wound and contraction it through the mechanism as likely of smooth muscle cells. After the completion of the process the unwanted cells undergo apoptosis i.e. cell death[11]. Epithelialization consists of expansion of epithelial cells allows to crawl towards the wound bed at the top to cover the new tissues. At last, the remodeling phase that takes place over a period of time in which the dermis layer responds to injury along with collagen fibers production and matrix protein revives its pre-injury phenotype. The outcome or resultant of wound healing treatment is considered to either shorten required healing time or reduce the risk of undesirable risk factor [12].

Mechanism of wound healing

Different factors can affect or interfere with the wound healing process that can cause impaired tissue repairing. In general, wounds or injuries that show impaired healing includes retardation in acute wound healing and also cause failure of chronic wound healing process. Such types of wounds undergo a pathological inflammation due to delayed, incomplete or uncoordinated

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process of healing and also changes in temperature ranges are the basic cause of tissue injuries [13,14,15].

Cytokines present in cells helps to promote the healing process that undergoes from different pathways initially it stimulates the building up of essential constituents that form basement membranes, altering the insufficiency or dehydration, reducing the inflammatory action and formation of discrete tissue. The hemostasis phase allows the process of activating and producing upcoming new tissue components such as transforming growth factors (TGFs), vascular endothelial growth factors (VEGFs), platelet derived growth factor (PDGF) and fibroblast growth factors (FGFs) [16]. The inflammation phase allows the genesis of clot forming fibrin tissues and initiates the release of already existed mediators to connective tissues that generates the cellular structures like platelets that initiates chemotactic factors required for forming leukocyte cells especially neutrophils and also stem cells derived from bone marrow at wound site. Further fibroblastic and epithelial cells are formed by using tumor necrosis factor (TNF)-α and interleukin-1 (IL-1) which are activated by elastase and collagenase that are formed by neutrophils [17]. Monocytes reach the wound site and are modified into macrophages. They remove the dead cells and remains of debris and also the infectious part of the cell matrix and plays a role in secretion of TGF-β and VEGF cytokines [18]. Macrophages allow the cell engulfing process in which and also releases different factors like PDGF, β-FGF, TGF-β, TNF-α, IL-1 and IL-6 which are in the proliferative phase. Lymphocyte cells are the important factor for producing IL-2 this may be helpful in recruiting fibroblasts [12]. Repairing of wound area processed by forming epithelial layer on skin surface in which keratinocyte cells migrate, multiply and transform to restore the newer epithelial layer with the help of stem cells of remaining hair follicle rhizome [19]. This process is being triggered with the help of keratinocyte growth factor, EGF and TGF-α [17]. Further growth and development is forwarded in a systematic way which includes resettling or migration, multiplication, arrangement and anatomical lumen formation of endothelial cells that germinated from preexisting parent ducts to other new one. This process is known as angiogenesis and it utilizes the angiogenic mediators like VEGF and PDGF[19]. At the last remodeling phase in which the inflammatory cell part remains silent and the fibrous cellular material i.e. fibroblasts assists and connects other tissues or organ parts to continue the synthesis of collagen fibers and further linking up of collagen molecules [17]. Any irregularity in wound repair results from any bacterial or microbial growth on the wound surface that interferes with wound hygiene.

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WOUND HEALING POTENTIAL OF SOME MEDICINAL PLANTS

Tea Tree Oil

Volatile essential oil of tea tree oil (*Melaleuca alternifolia*) proved to have wound restoration potential due to its antimicrobial and anti-inflammatory activity [20, 21]. Its cooling action helps to decline tissue injury and improves wound healing process experimented by using porcine model to highlight the cooling and healing potential of hydrogel of tea tree oil. The effectiveness of *Melaleuca alternifolia* showing cooling sensation on burn wounds [22].

Jojoba

Dry eternal undergrowths of jojoba (*Simmondsia chinensis*) chiefly constitute liquid wax grown in the areas of Africa and America. *In-vitro* studies on the executors of re-epithelialization i.e. keratinocytes and fibroblasts induced the synthesis of collagen 1 in fibroblasts in the presence of jojoba liquid wax. There was no interference effect being noticed with the secretion of enzymes like matrix metalloproteinase-2 and matrix metalloproteinase-9 by which it could be useful for treating wounds [21].

Olive Oil

Antioxidant potential of phenolics in olive oil is quite higher than those of vitamin E potential on lipids and oxidizing potential of DNA. This could be done by preventing any disturbance in endothelial expressions of molecules that are responsible for cell union and also enhances the production of nitric oxide**.** By the study it comes to know about the stimulatory potential of olive oil on acute skin repair in guinea pigs by applying topically ozonated olive oil which acts due to indications by PDGF, TGF-β and VEGF [13,16] .

Carica papaya Linn.

Carica papya Linn. Fruits belong to the family Caricaceae. Fruits of papaya contain chemical constituents such as alkaloids like carpaine, phytosterols, a combination of cysteine endopeptidases components like papain. It also contains chinitase, omega endopeptidases, papaya endopeptidases II and IV, chymopapain A and B, different protease inhibitors and proteins. Enzymes like papain and chymopapain helps in removal of waste debris and promotes development of newer healthy granulating tissue which proves to possess wound healing activity. In the study papaya latex in the form of hydrogel as a vehicle system was applied to treat burn wound [16]**.**

Aloe vera

Traditionally *Aloe vera* has been applied for treating burn wounds, ulcers and other surgical wounds [23]. In *Aloe vera* different bioactive components are present like cinnamic acid, lupeol, phenols, salicylic etc., oleic acid, anthraquinone derivatives, pyrocatechol, phytol, water soluble polysaccharides, acemannan, aloe-emodin, aloin etc [24]. *Aloe vera* leaves possess antibacterial potential with acetone extract was performed to state the proving effect of its activity [25]. Chemical derivatives which are responsible for antibacterial activity include dihyroxy-anthraquinones, acemannan and saponins [26]. Gram-positive bacteria are highly responsive to activity as that of gram negative bacteria [27]. Bioactive constituents of aloe vera in the form of gel formulation exhibit anti-inflammatory potential due to presence of aloe and aloe-emodin. Presence of glucomannan influences fibroblastic growth factor FGF by stimulating newer cell development**.** These chemical constituents promote inter cellular oxygen transportation, improves the skin quality, increases contraction of wound tissues and synthesis of collagen fibers as all to boost up the wound healing process by altering or remodeling of epithelial cells [28].

Citrus fruits

Chief flavonoid naringenin found in its glycosidic form is obtained from different fruits having citrus contents, tomatoes and other fruits. Naringenin is evidenced to possess different therapeutic activities like antibacterial activity, antitumour activity, antiviral activity, anti-inflammatory activity, cardio-protective action and also antioxidant potency [29]. Naringenin allows inhibition of leukocyte cell formation at the site of wound and inhibits the production of free radicals that cause anti-inflammatory action. At the time of pro-inflammatory cytokines production naringenin boosts up the antioxidant potential by activating the nuclear erythroid related factor 2 (Nrf2) acts on macrophages to suppress the action of nuclear factor-kappa B (NF-kB) and activates the heme oxygenase-1(HO-1)[30].

Curcuma longa

A rhizome of *Curcuma longa* belonging to Zingiberacecae family is a native herb broadly explored for its healthcare benefits. Widely used active constituent i.e. curcumin has been used by native individuals for its medicinal value and food flavoring activity for centuries[31]**.** Curcumin extracted from curcuma longa has been used traditionally by ayurvedic medicine practitioners for treating various skin problems, respiratory problems, inflammation, and digestive disorders, as food additive and also as a cosmeceutical [32]**.** The active constituent curcumin has proven its activity in altering the physiological and molecular changes in treating wound inflammation

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during inflammatory and generative phase [33]. Curcumin has been proved in reducing expressions of IL-1 and TNF-α that are pro-inflammatory cytokines [34]. It suppresses the activity of kinase like phosphatidylinositol-3-kinase-protein kinase B (PI3K AKT) and Ikappa-B kinase (IKK) which then inhibits the nuclear factor-kB (NF-kB). Mechanism of action of curcumin functionally helps in treatment of wound healing [35].

Centella asiatica

Traditionally, *Centella asiatica* is known for its therapeutic role in aiding many ailments like in treating skin disorders like leprosy and psoriasis, wound healing, improving mental health in different areas Asiatic countries [36]. Chiefly active constituents of the plant drug are saponins and its sugar esters like asiaticoside, madecassic and asiatic acid.These constituent significantly helpful in collagen synthesis [37]. The active constituents of the plant drug by preclinical studies has proven to treat skin disorders like scleroderma, psoriasis and scar formation and also investigates its action for treating wound healing [36,38]. Literature survey reported about asiaticoside to possess active wound healing potential for both normal and delayed wound healing models [39]. It acts by increasing growth and cellular proliferation and also elevates the collagen synthesis on injured surfaces and simultaneously also regulates the keratinization process which allows thickening of skin at the site of infection [16].

Calendula officinalis

Commonly known marigold plant different dosage forms like infusions, liquid extracts, ointments and tinctures have been used [40]. The active therapeutic activity of the plant is being shown due to the presence of different chemical constituents like triterpenoid derivatives, saponins, essential micronutrients, flavonoids and polysaccharides which possess anti-inflammatory potential, antioxidant activity and also wound healing potential [41]. An investigation has been done to illustrate the anti-inflammatory activity of marigold by using the extract of plant having a blend of carotenoids, flavones and triterpenoid that cause suppression of cytokines and macrophages that are capable of moderating acute or chronic inflammation [42].

***Moringa oleifera* Linn.**

Native plant of Indian subcontinent and also a part of Indian diet for decades. It has been reported the antioxidant, radio-protective, hypotensive and diuretic and anti-inflammatory potential of this plant. Aqueous extract of this was studied showing the significant wound or skin healing potential, increasing wound closure rate and skin breaking strength and also decreases the scar area on skin surface [43].

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Pterocarpus santalinus

Wood part of plant *Pterocarpus santalinus* Linn of family Fabaceae has been used as an astringent, tonic and also helpful in inducing perspiration. The wound healing potency was studied by using ethanolic extract of leaf and stem bark [44]. This allows the remarkable decline in the duration time of epithelialization and increases the skin breaking strength, hydroxyproline content and rate of wound contraction. Cellular pathophysiological study of granulating tissues also proved about the increasing rate of collagen synthesis w.r.t. controlled group of animals.

Euphorbia hirta

Slang cannabis of *Euphorbia hirta* belonging to family Euphorbiaceae mainly grown in the regions of tropical countries and also been traditionally beneficial for treating cough, asthma, worm infections and eye infections [45]. Inhibitory potential against platelet aggregation and therapeutic action such as anti-inflammatory, sedative, antipyretic, analgesic potential studied by using aqueous extract of plant drug. An investigation has proven the wound healing potential of *Euphorbia hirta* by using its ethanolic extract on wistar albino rats on superficial cuts, deep cuts and dead space injury [46, 47].

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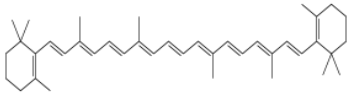
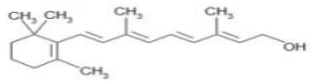
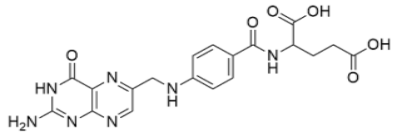
Table 1 List of some traditionally used medicinal plants with wound healing potential

Name of plant	***Part used***	**Chemical constituents**	***Formulations***	***Clinical evidence***
Achillea millefolium **Family:** Asteraceae 	Entire plant mainly flowers part, flower	Volatile oils like caryophyllene, azulene, flavonoids, α & β pinene, amino acid derivative, terpenoids, lignans	Liquid dosage forms for topical use	Possess antibacterial activity against *Shigella dysenteriae*, Yarrow plant proven to possess anti-inflammatory effect by inhibiting protease enzyme [12].
Aloe Vera **Family:** Asphodelaceae 	Mucilage from inner leaf parts	Minerals, vitamins like vit. C,vit. A, vit. E, minerals, sugar, saponins, lignin, folic acid that possess antioxidant potential  beta-carotene  Vitamin A  Folic acid	Gels and ointments for topical use	Aid in healing of wounds, helpful in curing burns and ulcers by making a protective coat above the injured surface to speed up the healing process. Its different photoactive constituents stimulate the wound healing process and posseses anti-inflammatory activity (cytokine production and enzyme inhibition) [48].

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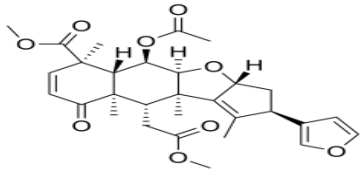
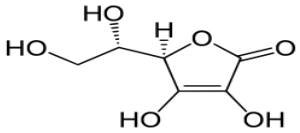
		Folic acid		
Azadirachta Indica **Family:** Meliaceae 	Seed oil, bark	Active constituent azadirachtin, and others nimbine, nimbidine, nimbidol, nimbolide, calcium, mineral, vitamin C, proteins, water insoluble agents like petrol ether, ether, ethyl acetate, dilute alcohol etc.  Nimbin  Ascorbic acid	Liquid extracts in organic solvents	Different pharmacological potential proven for neem as skin ailment, possesses antiviral, anti-inflammtory, antifungal activities. Oil of neem helpful in collagen binding and maintains the elasticity of skin [49].

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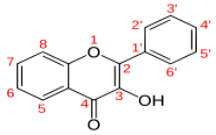
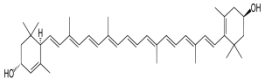
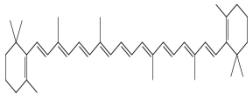
Calendula Officinalis **Family:** Asteraceae 	Flower	Triterpenes or Oleanolic acid glycosides, also triterpene alcohols like α & β amyrins, flavonoids, faradiol, its flowers rich in lutein whereas leaves contains lutein 80%, zeaxanthin 5% and also β-carotenes.  Flavonols  Lutein  beta-carotene	Liquid extracts, ointments and comminuted herbal substance	Different pharmacological potential proven for antiviral, anti-inflammatory and antiviral properties. It also facilitates poor wound healing, reduce inflammation and controls bleeding [50].
Centella asiatica **Family:** Apiaceae 	Leaves	Triterpenoid saponins like Asiatic acid, brahmic acid, centelloside and others are centellose, madecassoside, centelloside  Triterpenoids	Powder, cream for topical application act as adjuvant	Stimulates wound healing potential and also in repairing of different connective tissues [39].

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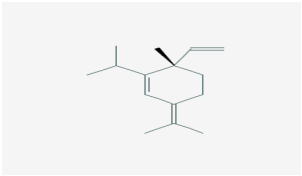
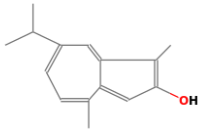
Chamomilla Recutita **Family:** Asteraceae 	Flower		Liquid extracts like tincture, oils, lotions, infusions and also in powder form	Possess antimicrobial, anti-inflammatory, antioxidant potential, wound healing and a mild astringent [51].
Commiphora Myrrha Family: Burseraceae 	Gummi-resina	Furanoeudesema-1,3-diene (34.9%), α-elemene (12.63%), lindestrene (12.9%), germacrone, β-selinene  α-elemene  7-isopropyl-1,4-dimethyl-2-azulenol	Tinctures	Possess antibacterial and antifungal action, anti-inflammatory action, analgesic and local anesthetic activity, helpful in treating minor wounds by topical application, inflammation of skin and abrasions [52].

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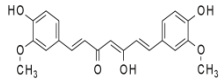
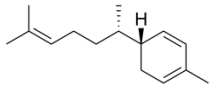
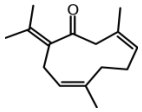
Curcuma longa **Family:** Zingiberaceae 	Rhizome	Active constituent is curcumin, 3-6% polyphenolic compounds, demethoxycurcumin, vitamin A and also some essential oils such as zingiberene, turmerone, germacrone  Curcumin  Zingiberene  Germacrone	Pastes, ointments, powder	Possess antifungal, anti-inflammatory, analgesic activity by decreasing formation of prostaglandins, helps in synthesis of collagen fibres due to the presence of vitamin A and proteins [12].

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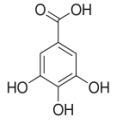
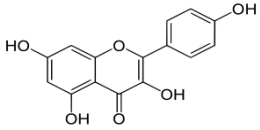
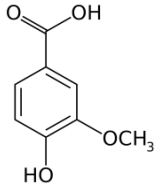
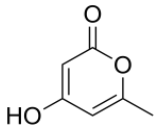
Euphorbia hirta **Family:** Euphorbiaceae 	Roots, whole plant	alkanes, triterpenes, quercitin, polyphenos, ascorbic acid, euphorbin derivatives, gallic acid, kaempferol, inositol, protocatechuic acid  Gallic Acid  Kaempferol	Aqueous and ethanol Extracts	Aqueous extract of plant shows anti-inflammatory and analgesic activity, also helpful in platelet aggregation whereas ethanol extract of herb possess wound healing activity [47].
Ginkgo biloba 	Green leaves	Two major constituents that are terpenes such as ginkgolides and lactones contains flavonol like ginkgo flavones, catechin, ascorbic acid, shikmic acid, vanillic acid, iron based superoxide  Vanilic acid  Lactone	Liquid extracts such as tinctures, glycerites	Helpful in increasing blood fluidity, as an antioxidant, membrane stabilizer, used to promote epithelization [53].

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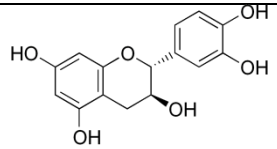
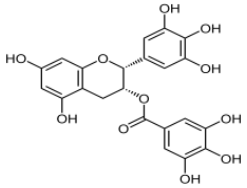
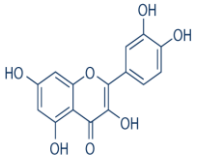
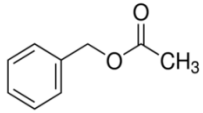
		 Catechin		
Hypericum Perforatum **Family:** Hypericaceae 	Whole plant	Active ingredients include hypericin, hyperforin, pseudohypericin, epigallocatechin, isoquericitin, ferulic acid, vitamins and carotenoids  Epigallocatechin  Quercetin	Liquid and semi-solid dosage forms	Have antibacterial, analgesic potential use to heal minor topical wounds [54].
Jasminum Grandflorum **Family:** Oleaceae	Leaves, flower	major compounds are benzyl alcohol (5.11%), linalool (8.2%), eugenol (2.5%), methyl linoleate (2.8%)  Benzyl acetate	Liquid extracts (ethanol)	Possess wound healing potential by improving tensile strength in early phases of healing [55].

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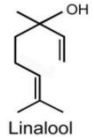
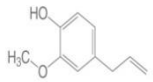
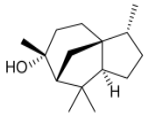
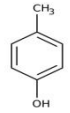
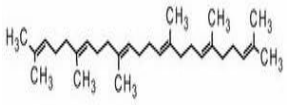
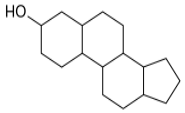
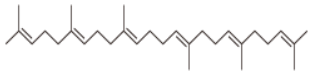
		 Linalool  Eugenol		
Pterocarpus Santalinus **Family:** Fabaceae 	Leaves, flower	Phenols, alcohol, ethers, ketone, propanoic acid, bisabolo, cedrol, propanoic acid  Cedrol  p-cresol  Squalene	Gels, ointments and ethanolic extracts	Helps to improve collagen synthesis [47].
Tridax Procumbens **Family:** Asteraceae 	Leaf juice, flower	Rich source of alkaloids, steroids, carotenoids, fatty acid, phytosterols, flavonoids like catechin, centaurin  Sterols  Triterpenes	Liquid extracts (aqueous and ethanol	Helpful in epiththelization and collagenation

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CONCLUSION

Several naturally occurring medicinal plants have proven activity for healing cutaneous wounds due to the presence of a variety of phytoconstituents having therapeutic activity. Also there is a need for systematic approach, standardization and safety analysis of traditionally used medicinal plants before recommending as ailment. Now different herbal formulations are proving satisfactory results in wound healing. The phytoconstituents show their action by acting through different mechanisms like collagenation, epithelialization and improving elasticity of tissues. The wound care management aims at lowering the risk factors that interfere with healing process and cause wound infections and allows enhancement of healing procedure. Also the use of traditional phytoconstituents with modern formulation skills leads to production of better wound healing dosage form with effective strength and minimal side effects.

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