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Chapter 21

Alternative Approaches to Wound Healing

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Additional information is available at the end of the chapter

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Abstract

The history of wound healing across the globe abounds with usage of various herbs for treating simple cuts and bruises to serious burns. Wound healing is a complex and dynamic process and, moreover, depends a lot on the wound bearing person's immunity and mental status. Synthetic medicine may give rise to side effects of allergy and resistance with usually higher cost of treatment. Whereas the alternative and complementary medicine such as Ayurveda, Siddha, Unani, Chinese medicine, and ozone therapy can lessen these side effects considerably and offer treatment at lower costs, thus elevating the overall quality of life of the patient. In today's times the patient is more demanding and has the ability to partake in treatment decisions. It is then the moral responsibility of the scientists to apply modern up-to-date scientific acumen to provide evidenced-based concept to alternative therapies of wound healing to ensure that these practices are safe and efficacious.

Keywords: wound healing, alternative therapies, Ayurveda, Siddha, Unani, Traditional Chinese Medicine, ozone therapy

1. Introduction

Wound healing continues to pose a challenging clinical problem despite scientific developments in the field. A correct and efficient wound management is essential. Emphasis is required on new and alternative therapeutic approaches and development of technologies for acute and chronic wound management. A wound can be defined as a damage or a disruption to the normal anatomical structure and function [1]. This can range from a simple break in the epithelial integrity of the skin or it can be deeper, extending into subcutaneous tissue with damage to other structures such as tendons, muscles, vessels, nerves, parenchymal organs, and even bones [2]. Depending on the time of repair, wounds can be divided as acute, chronic,

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and complicated. Wound healing is a natural, complex, dynamic yet continuous process, and is initiated as any injury occurs and continues till the entire repair of the wound and tissue remodelling is complete. The process can be randomly divided into (i) coagulation and haemostasis, (ii) inflammation, (iii) proliferation, and (iv) wound remodelling with scar tissue formation. If the wound healing is interrupted by any infection, tissue hypoxia, edema, growth factor imbalance or nutritional, and metabolic status of the host, then the wound may take extended time for repair. Normal wound healing is a dynamic and complex process involving a series of coordinated events including bleeding, coagulation, initiation of an acute inflammatory response to the initial injury, regeneration, migration, and proliferation of connective tissue and parenchyma cells, as well as synthesis of extracellular matrix proteins, remodelling of new parenchyma, connective tissue, and collagen deposition [3–7]. Modern synthetic allopathy-based medicines have their share of limitations of allergy, resistance, cost, etc., which has prompted the scientists and wound care professionals to consider alternative approaches to wound healing and validating their use using modern technology. The perception toward alternative medicine such as Ayurveda, Siddha, Unani, and Chinese has changed. The World Health Organisation (WHO) defines traditional medicine as "the sum total of the knowledge, skills, ands practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" [8]. Each of the above-mentioned systems of medical practice offers a variety of medicines for wound management and has been traditionally practiced since ancient times in few parts of the world and is fast getting acceptance in rest of the globe. Ayurveda or Indian traditional and Chinese medicine have rich abundance of knowledge and have been well known as ethnopharmacological and folklore-based systems. Siddha also has origin in south of India, Tamilnadu, which aims in providing ultimate cure to both mind and body systems. "Food as medicine" is the principle behind Siddha treatment. Unani system of medicine has its origin in Iran and also has documented evidences of antimicrobial herbs possessing wound healing properties. Ozone therapy has been in use since World War I times and offers remarkable bactericidal action. The abovementioned alternative therapies offer an economical approach to wound healing. Besides this benefit, they have significant lesser side effects thus increasing patient compatibility as compared to modern medicine.

2. Alternative approaches in wound healing

2.1. Ayurvedic products

A rich heritage of knowledge on preventive and curative medicines is available in ancient scholastic work included in the Atharvaveda (an Indian religious book), Ayurveda (Indian traditional system of medicine), etc. Many Ayurvedic plants have a very important role in the process of healing of wounds (*vrana*). Plants are more potent healers because they promote the repair mechanisms in the natural way. Plant-based therapy not only accelerate healing process, moreover, also maintain the esthetics. More than 70% of wound healing Ayurveda-based pharma products are plant-based, 20% are mineral-based, and remaining contain animal

products as their base material. The plant-based materials are used as first aid—antiseptic coagulants and wound wash [9]. Different Ayurvedic preparations are made and used topically for healing of wounds. Ghee is used in many Ayurvedic traditional preparations and also finds use as an ointment base. It is rich source of essential fatty acids (EFAs), which regulate prostaglandin synthesis and hence induce wound healing. Cow ghee (*Goghrita*) specifically possesses regenerative properties promoting the growth of healthy cells and is clinically proven. *Bhasma* is a calcined preparation in which the gem or metal is converted into ash. *Grithas*, also called as *neyyu*, are medicated clarified butter. *Taila* or medicated oil is manufactured by steeping powdered medicinal substances, water, vegetable drugs in paste form and fragrance-producing materials such as cardamon, saffron, sandalwood, camphor. *Malam* (Cream) too is applied topically and has been documented in ancient ayurvedic texts for its helpfulness in wound healing. Some of the herbal drugs that are mentioned in Ayurvedic texts which have been specifically studied for their wound healing properties (*vranaropaka*) are mentioned below.

2.1.1. Aloe vera

A. vera finds a mention in Ayurvedic practice since centuries regarding its wound healing property. A study carried out by Yadav *et al.* [10] in 2012 provides the scientific rationale for the traditional use of *A. vera* gel for management of wound using wound excision model in experimental rats. The effect produced by *A. vera* gel with reference to wound contraction, wound closure, decrease in surface area of wound, tissue regeneration at the wound site, and histopathological characteristics were significant in treated rats. The effect of *A. vera* gel on biochemical studies revealed significant increase in collagen and decreased hexosamine content and malondialdehyde levels when compared with control. The authors concluded that *A. vera* gel is very effective on open wounds and a promising herbal drug. It also had a marked influence on the collagen level which is the precursor protein for wound healing mechanism. *A. vera* gel reportedly accelerated epithelialization, neovascularization, and increased wound contraction in the later stage of the wound healing process.

2.1.2. Cleome rutidosperma DC.

A study [11] justifies the use of folklore plant *C. rutidosperma* for the treatment of wounds. Petroleum ether, chloroform, methanol, and aqueous extracts of *C. rutidosperma* (Family: Capparidaceae) roots were evaluated for their wound healing activities in rats using excision and incision wound models, respectively. The effects of wound healing were assessed by the rate of wound closure, period of epithelialization, and wound breaking strength. Nitrofurazone (0.2% w/w) in simple ointment IP was used as reference standard for the activity comparison. The authors concluded that the animals treated with methanol and aqueous extracts of *C. rutidosperma* showed faster rate of wound healing compared with other extracts under study. The wound healing property of the roots can be attributed to the presence of flavonoids, triterpenoids, and tannins which possess the antimicrobial and astringent properties which seem to be responsible for wound contraction and increased rate of epithelialization.

2.1.3. Kshatantak Malam

It is a combination of *Acyranthes aspera*, *Allium cepa*, and *Cannabis sativa* also known as *Baharer nani* has been traditionally reported by Bengal School of Ayurvedic Physicians as external healer for open cuts, complicated wounds and burns but still a scientific document proving its quality was not available. Gangopadhyay *et al*. [12] reported its pharmacological evaluation and chemical standardization for its wound healing activity in rats. The test drug was applied topically on a 8 mm diameter full thickness punch in Wistar rats. Framycetin and povidone-iodine ointment were used as standard comparators. Parameters such as wound contraction size (mm^2), wound index, healing period (days), tensile strength (g), DNA (mg/g), RNA (mg/g), total protein (mg/g), hydroxyproline (mg/g), PAGE study, and histological analysis were carried out for analysing the effects of the malam. Out of the three constituents, *A. aspera* specifically possesses potent wound healing activity, *A. cepa* owns antimicrobial activity, and *C. sativa* is capable of tissue repair by virtue of its anti-inflammatory property.

2.1.4. Katupila (Securinega leucopyrus) (Willd.)

Another plant used since ancient times in Saurashtra region of India and Srilanka is known as *Katupila* in Srilanka and *Humari* in India. It is mentioned as one of the 60 measures for wound healing by *Acharya Sushruta* (Ancient spiritual Hindu teacher). *Katupila* leaves act as antiseptic, and the paste is capable of removing extraneous material from the wounds without the need of surgery [13].

2.1.5. Ayurvedic polyherbal formulation

Rawat and Gupta [14] reported wound healing activity of a prepared ayurvedic formulation containing *Jasad Bhasma*, *Gandhak*, *Tankankhar*, *and Ras Kapoor*. *J*. (*Yashad*) *Bhasma* is ash containing zinc. *Gandhak or Gandhaka Rasayan* is an ayurvedic mineral-based medicine, which contains detoxified sulfur processed with herbal juice as a main ingredient. *Gandhak Rasayan* is a great antibacterial, antiviral, and antimicrobial ayurvedic medicine. *Tankankhar* is borax applied topically for its analgesic property. Ras Kapoor are pills made out of camphor (*karpoora/ kapoor*), mercury compound (*Shuddha Hingula*), purified opium (*Papaver somniferum*), nutgrass (*Musta/ Cypeus rotundus*), Connessi seed (*Indrayava/ Holarrhena antidysenterica*), and Nutmeg (*Jatiphala/ Myristica fragrans*). The preparation was studied on excision and incision wound models in rats. The preparation exhibited remarkable wound healing in rats and the authors suggest further mechanism-based probing to prove the effectiveness of the constituents to be utilised in humans.

Few more folklore plants which were validated by means of preclinical wound healing studies are mentioned below in **Table 1**. Almost all the plants are shown to be wound healers by applying their extracts topically on wounds created by punches on rats. Their subsequent effect on wound healing models such as excision, incision, and dead space wound models in rats corroborate their wound healing properties. These plants ultimately are reported to stimulate wound contraction, increase hydroxyproline and eventually collagen content thus strengthening the wound area, increase the wound closure rate, reduce scar area, and epithelialization

period. Few plants such as *A. cepa*, *Ageratum conyzoides*, and *Heliotropium indicum* are known to specifically heal the wounds by benefit of their antioxidant property. Dexamethasone is a potent anti-inflammatory glucocorticoid which is used in skin allografts but is known to delay wound healing. Plants such as *Ocimum sanctum*, *Gossypium herbaceum*, *Ficus hispida*, *Pyrus communis*, and *Tetrapleura tetraptera* have been specifically shown to promote dexamethasone suppressed wound healing tested in wound healing models (**Table 1**). *Alafia multiflora* is found to be one of the plants which contains retinoids and have shown marked interaction with steroids like dexamethasone and was reported to further delay the healing of dexamethasone-suppressed wounds. Thus, vitamin A even if known to hasten the process of wound healing is shown to interact with steroids and thus concomitant application should be avoided in dexamethasone suppressed wounds. Few plants such as *Echinacea* species, Vitamins such as A and E found in plants, Bromelain, and Grape seed extract have demonstrated few interactions with conventional therapies used for wound healing (**Table 1**).

No.	Name	Wound healing activity
Plants effective on acute wounds in rats		
1.	*Mimusops Elengi* (*Linn*.) (Sapotaceae)	The methanolic extract ointment of *M. elengi* in rats effectively stimulated wound contraction; increased tensile strength of incision and dead space wounds as compared to control group [15]
2.	*Carica papaya* (Caricaceae)	Contains a mixture of cysteine endopeptidases such as papain. Chympopapain A and B, papaya endopeptidase-II, papaya endopeptidase-IV, omega endopeptidase, chinitase, protease-inhibitors, and proteins. Papaya fruits possess wound healing properties; papaya latex was applied to the burn wound using hydrogel as a vehicle system [16]
3.	*Tephrosia purpurea* (*Linn*.) (Leguminosea)	Contains glycosides, rotenoids, isoflavones, flavones, chalcones, flavonoids and sterols. It is used in the treatment leprous wound and the juice is used for the eruption on skin [17]
4.	*Adhatoda vasica* (*Linn*.) (Acanthaceae)	Leaves and stems of the plant have been reported to contain an alkaloid mimosine, leaves also contain mucilage and root contains tannins. The methanolic, chloroform and Diethyl ether extract ointment (10% w/w) of *A. vasica* has significant wound healing activity. In both extract ointment, the methanolic extract ointment (10% w/w) showed significant effect when compare to standard drug and other two extract in excision wound model [18]
5.	*Piper betle* (Piperaceae)	In Indian folkloric medicine, betel leaf is popular as an antiseptic and is commonly applied on wounds and lesions for its healing effects. This particular property has paved way for further experimental studies, which have established pan extract to have antimicrobial and anti-leshmian properties. Fresh juice of betel leaves is also used in many Ayurvedic preparations [19]
6.	*Moringa oleifera* (*Linn*.) (Moringaceae)	It has anti-inflammatory, antibacterial and counter irritant action, which helps in wound healing. The aqueous extract was studied and it was found that there was

No.	Name	Wound healing activity
		significant increase in wound closure rate, skin-breaking strength, granuloma breaking strength, hydroxyproline content, granuloma dry weight and decrease in scar area was observed [20]
7.	*Eucalyptus globules* (Myrtaceae)	It is used for cuts, wounds and to boost the immune system [21]
8.	*Terminalia Chebula* (Combretaceae)	Traditionally, fruit pulp is used to stop bleeding. Recent studies showed that various aqueous and organic extracts increased cell proliferation and reduced free radical production thus promoting wound healing. Significant utility of the plant is in cases where ammonia accumulation is a limiting factor [22]
9.	*Aegel marmelos* (Bael) (Rutaceae)	Methanolic extract was found to heal wounds faster when tested in wound healing models in rats. *A. marmelos* treated wounds were reported to epithelialize faster and rate of wound contraction was higher as compared to control group of rats [23]
10.	*Alternanthera sessilis* (*Linn*.) (Amaranthaceae)	Consist of chemical constituents like α and β-spinosterols lupeal isolated from roots. The leaves are used for cuts and wounds. The wound healing property of *A. sessilis* (*Linn*.) attributed to sterols present in the plant [24]
11.	*Mussaenda frondosa*. (*Linn*.) (Rubiaceae)	The leaves extract was tested on wound healing models in rats. *M. frondosa* treated rats displayed Increased wound concentration and tensile strength, augmented hydroxyproline content along with antibacterial activity [25]
12.	*Aristolochia bracteata* (Aristolochiaceae) and *Cassia tora* (Leguminosae)	Wound contracting ability of the extracts was significantly greater than that of the control, which was comparable to that of the reference standard 0.02%w/w nitrofurazone ointment [26]
13.	*Mimosa pudica* (Mimosaceae)	Used in folklore medicine for arresting bleeding and in skin diseases. *M. pudica* has been reported to contain mimosine (an alkaloid), free amino acids, sitosterol, linoleic acid and oleic acid. The wound healing studies on roots indicated that phenols constituents/tannins play an important role in wound healing process. The result of excision wound model is indicating that significant increase in wound contraction compared with standard group, revealing that the extract has ability to induce cellular proliferation. The increase in tensile strength of wounded skin indicates the promotion of collagen fibers [27]
14.	*Anthocephalus Cadamba* (Rubiaceae)	The potent wound healing capacity was shown from the wound contraction and increased tensile strength has thus validated the ethno therapeutic claim [28]
15.	*Lantana camara* (*Linn*.) (Verbenaceae)	Showed considerable signs of dermal healing and significantly decrease mean wound healing time and reduced scarring at the wound enclosure [29]
16.	*Carapa guianensis* (Meliaceae)	The ethanolic leaf extract of *C. guianensis* showed increase in the rate of wound contraction, skin breaking strength, the rate of epithelialization [30]
17.	*Curcuma longa* (*Linn*.) (Zingiberaceae)	Curcumin has potent anti-inflammatory and analgesic activities. Volatile oil isolated from *C. longa* also exhibits antibacterial and potent anti-inflammatory activity. *C. longa* also contains protein, fats, vitamins (A, B, C, etc) all of which have an important role

No.	Name	Wound healing activity
		in would healing and regeneration. Turmeric has been used for treating the wounds in the rats. The presence of vitamin A and proteins in turmeric result in the early synthesis of collagen fibers by mimicking fibroblastic activity. Juice of the fresh rhizome is commonly applied to recent wounds, bruises and leech bites [31]
18.	*Tecomaria capensis* (Bignoniaceae)	*T. capensis* significantly stimulated wound contraction. The breaking strength of the treated incision wounds increased in *T. capensis* extract when treated groups compared with the control group [32]
19.	*Hyptis suaveolens* (*Linn.*) (Lamiaceae)	Aqueous, alcoholic and petroleum ether extracts were tested in rats in wound healing models. Petroleum ether extract was found to show enhanced wound healing activity compared to other extracts. Period of epithelialization, granulation strength, hydroxyproline content was found to be increased in petroleum ether extract as compared to other extracts. Histopathological study of this extract too revealed more collagen and macrophages as compared to other extracts [33]
20.	*Arnebia densiflora* (*Ledeb.*) (Boraginaceae)	Rats treated with *A. densiflora* showed rapid healing than the control group. Wound closure and collagen production were faster and healing occurred on the 14th day after wounding [34]
Plants possessing anti-oxidant property contributing to wound healing activity		
21.	*Allium cepa* (Liliaceae)	It contains kampferol, β-sitosterol, ferulic acid, myritic acid, prostaglandins. Flavonoids have been documented which is believed to be one of the most important components of wound healing. The enhanced wound healing in rats when *A. cepa* was administered orally may be due to free radical scavenging action and the antibacterial property of the phytoconstituents present in it [35]
22.	*Ageratum conyzoides* (Asteraceae)	The leaves are applied to the wounds act as septic and heel them quickly. Several Phytoconstituents like alkaloids and saponins are known to promote wound healing process due to their antioxidant anti-microbial activities. The wound healing property of *A. conyzoides* appears to be due to the presence of its active principles, which accelerate the healing process and confers breaking strength to the healed wound [36]
23.	*Heliotropium Indicum* (Boraginaceace)	Various extracts of *H. indicum* were tested in wound healing models in rats. The methanolic and aqueous extracts were shown to be working better than petroleum ether extract. Increase in the granulation tissue weight, hydroxyproline content, and increased activity of superoxide dismutase and catalase level was reported to be contributing factors for better wound healing of *H. indicum* as compared to 0.2% w/w nitrofurazone ointment [37]
Plants reported to improve dexamethasone suppressed wound healing		
24.	*Ocimum sanctum* (*Linn.*) (Labiaceae)	Ethanolic extract of *O. sanctum* significantly decreased the anti-healing effect of dexamethasone in all wound models like incision, excision and dead space wound model. It was reported that the plant has various actions like free radical scavenging effect, metal chelation and immune modulation [38]

No.	Name	Wound healing activity
25.	*Gossypium herbaceum* (*Linn*.) (Malvaceae)	Ethanol and ethyl ether fractions of *G. herbaceum* were tested in wound models to test the effect of the plant on diabetes and dexamethasone delayed wounds. The plant displayed significant increased wound contraction, breaking strength and decreased epithelization period. Hydroxyproline and collagen content was increased [39]
26.	*Ficus hispida* (*Linn*.) (Moraceae)	Ethanolic extract of roots of *F. hispida* was investigated in normal and dexamethasone depressed healing conditions, using incision, excision and dead space wound models in albino rats. Collagen and hydroxyproline content was increased thus proving the pro-healing effect of the plant [40]
27.	*Pyrus communis* (Rosaceae)	Ethanol and ethyl acetate extracts of *P. communis* were tested in dexamethasone delayed wound healing model in rats. The study reported that plant treated wounds displayed fast healing of infectious wound, in immunosuppressed and disease condition like diabetes [41]
28.	*Tetrapleura tetraptera* (Mimosaceae)	The stem bark aqueous extract was studied for effect on dexamethasone delayed wounds in excision and incision wound models in rats. The authors reported excellent potential of the plant related to epithelialization, contraction and tensile strength improvement [42]
Plant reported to display interaction with dexamethasone and further delay wound healing (drug–herb interaction)		
29.	*Alafia multiflora* (*Stapf*.) (*Apocynaceae*)	The study on *A. multiflora* highlights the drug-herb interaction. Aqueous extract of the plant was studied for its effect on normal and dexamethasone delayed wounds in rats utilizing excision and incision wound models. It showed beneficial effects in normal rats. But in dexamethasone delayed wounds, the plant extract further deteriorated the wound healing. This proved the known interaction between retinoids occurring in the plant and the steroid but also indicated at involvement of some other constituent contributing to the delayed wound healing [43]
Plants with interactions with conventional therapies and reported side effects		
30.	*Echinacea* species (*Echinacea purpurea*, *Echinacea pallida*, *Echinacea angustifolia*) (Asteraceae)	Risk of poor wound healing in chronic users [44]
31.	Vitamin A (Retinoic acid)	Interaction with steroids to further delay wound healing [45]
32.	Bromelain (Protein extract from pineapple, *Ananas sativus*)	Can improve wound healing but carries risk of bleeding. Recommended to stop its usage 2 weeks before surgery [46]
33.	Vitamin E	Can improve wound healing owing to its antioxidant property but carries risk of bleeding. Recommended to stop its usage 2 weeks before surgery [47]
34.	Grape seed extract	Possesses antioxidant activity owing to the presence of active proanthocyanidin content. Proanthocyanidin is a bioflavonoid that acts as a strong antioxidant, protecting DNA from harmful free radicals. Additionally, grape seed extract has been

No.	Name	Wound healing activity
		reported to reduce inflammation, stabilize collagen and elastin, act as a natural antihistamine, and protect and heal connective tissue. It seems safe overall with no studies pertaining to its interactions were found to be reported. Seems safe overall [48]

Table 1. Ayurvedic plants with reported wound healing activity.

2.2. Siddha medicines

Siddha is the traditional system of medicine practiced in Tamilnadu, South India, and Tamil speaking areas of the world. The Siddhars' (founders of Siddha medicine) used lots of herbs to treat cardiac and respiratory conditions, heal wounds, treat snake and scorpion bites, dreaded diseases like cancer, and documented them in the form of palm leaf manuscripts, stone, and copper scriptures, etc. The claim of the Siddha physicians is that the medicinal plants are commonly identifiable, easily available throughout the year, cost effective, and with lesser adverse effects [49]. The Siddha system of medicine aims at offering complete cure to mind and body. It follows the principle of "Food as medicine" [50]. The Siddhars have documented many oils (*Tailam*) and ointments (*Kalimbu*) effective in wound healing. There are few plants mentioned in Siddha system of traditional medicine which have been evaluated preclinically for their wound healing activity.

Few noteworthy studies using Siddha medicines are mentioned below.

2.2.1. Siddha polyherbal oils

Siddha medicine has used *Kayathirumeniennai*, *punguthailam*, *and mathanthailam* as polyherbal (medicated oils) since centuries, but recently, Sabarianandh *et al*. in 2014 made efforts to scientifically validate the use of these oils on experimentally induced burn wounds in Wistar rats. The study showed wound contraction was significantly decreased; epithelialization was increased as compared to the vehicle treated group. This was even confirmed by the histopathological analysis [51].

2.2.2. Heritage Sanjeevi

Pugalendhi *et al*. demonstrated the effect of Heritage *Sanjeevi* (a Siddha combination drug) on wound healing in Wistar rats. "Heritage *Sanjeevi*" is a medication made up of *Curcuma Aromatia*, *Psoralea Corylifolia*, *Vernonia Anthemintica* (*Willd*.), *Hydnicarpus Laurifolia*, *Elettaria Cadamomum*, coconut milk, mercury, sulphur, hydrogyrum schloride calomel, "Sulphie" of lead, copper sulphate, zinc sulphate, and camphor. The mixtures of these compounds were processed in the manner that all the inorganic material is detoxified using an ancient detoxin called *Pooneer*. The extracted oil is filtered and stored in glassware. It is used for external application only, and its shelf life is six years, and it has been claimed to have excellent healing property against burns, scalds, chemical burns, acid burns, and radiation burns. The medica-

tion was tested on Wistar rats by external application till the time the wound which was created using a punch was completely healed. The study results demonstrated significant reduction in the size of the wound. The authors claimed that wound healing can be credited to one or few constituents of the medication causing collagen production and thus helping in faster wound correction [52].

2.2.3. Siddha Kalimbu

Another study revealed the wound healing ability of a polyherbal Siddha formulation, *Siddha kalimbu* consisting of 10 gm each of *Ficus spp* (*Itthi*), *Adenanthera Pavonina* (*Manjeti*), sandalwood (*Santhanam*), jasmine (*malligai*), *Symplocos racemosa* (*Roxb*.) (*Vellilothram*), *Ficus hispida* (*Atthi*), *Alstonia scholaris* (*Satvin*), and dried roots of 12.5 gm of *Curcuma longa* (*Manjal*) when mixed with 60 ml of Eal oil (muscle relaxant drug), 10 ml neem oil (*Azadirachta indica*), 20 ml of coconut oil, and 10 ml *Millettia pinnata* (*Pungai*) oil. The formulation was tested on excision and incision wound models in rats, and it was reported that the Siddha treatment significantly healed the wound by synthesizing collagen and influencing the growth hormone. The topical application of the formulation increased the wound breaking strength, wound contraction, and period of epithelialization [53].

2.2.4. Polyherbal formulation

Krishnamoorty *et al*. in 2012 reported an *in vitro* study of a polyherbal formulation comprising of extracts of *Wrightia tinctoria*, *Aloe vera*, *Curcuma longa*, and *Terminalia chebula*. They studied the impact of the formulation on fibroblast cell migration and proliferation using scratch wound assay technique. Fibroblast cell migration and proliferation were studied employing cell migration assay. Carbomer-based gel with beeswax made for a novel delivery system and the formulation proved significantly effective in management of superficial wounds and first degree burns [54].

2.2.5. Kungiliya vennai and Kalchunna thailam

Vennai (*Butter*) *and thailam* (*Balm*) are mentioned and used in Siddha medicine as wound healing bases. *Kungiliya vennai* is herbal formulation containing *Shorea robusta*, *Sesamum indicum*, and *Cocos nucifera*. It is traditionally recommended by Siddha practitioners for wound healing. *Kalchunna thailam* finds a mention in Siddha medicine for wound healing and is a preparation of limestone and coconut oil mixed in equal proportions. In an excision wound model in Sprague Dawley rats, the *Kungiliya vennai and Kalchunna thailam* treated rats showed positive outcome in the wound healing process. The preparations were comparable with the standard 2% Mupirocin ointment. The authors reported *Kungiliya vennai* has additional property of regenerating adnexal structures such as hair follicles, sweat, and sebaceous glands [55].

Few more Siddha plants which were preclinically evaluated for wound healing activity are mentioned below (**Table 2**).

No.	Plant name	Wound healing activity
1.	Banyan tree (*Ficus benghalensis*)	Ethanolic and aqueous extracts of *F. benghalensis* were evaluated in excision and incision wound models. Both extracts exhibited significant wound-healing activity, which was proven by decrease in the period of epithelialization, an increase in the rate of wound contraction and skin-breaking strength. Proteoglycans and glucosaminoglycans have been shown to play important roles in wound healing [56]
2.	Common wireweed (*Sida acuta*)	Was studied respectively on two types of wound models in rats, (i) the excision and (ii) the incision wound model. Wound contracting ability of the *S. acuta* ointment (5% w/w) significantly greater than that of the control nitrofurazone ointment (0.2% w/w) which was employed as standard comparator drug [57]
3.	Barmuda grass (*Cynodon dactylon*)	Flavanoid fraction of *C. dactylon* in Swiss albino mice demonstarted the wound healing activity, when it was applied externally daily on excised wound area for 8 days [58]
4.	Country fig (*Ficus racemosa*)	Aqueous and ethanolic extract of roots of *F. racemosa* in Wistar albino rats showed significant increase in percentage closure by enhanced epithelialization. The effect can be linked to enhanced collagen synthesis. Results showed the herb hastened the wound healing process by decreasing the surface area of the wound [59]
5.	Purging nut (*Jatropha curcas*)	Bark extract showed significant wound healing activity in albino rats. It accelerated the healing process by increasing the skin breaking strength, wound contraction, dry granulation tissue weight, and hydroxyproline levels. Epithelization period was also significantly decreased [60]
6.	Maasikkai (*Quercus infectoria*)	Ethanol extract of the shade-dried leaves of was studied in rats and it showed a positive effect on wound healing, with a significant increase in the levels of the antioxidant enzymes, superoxide dismutase and catalase, in the granuloma tissue [61]
7.	Pomegranate (*Punica granatum*)	Ethanolic extract on Wistar rat showed significant the wound healing activity. It significantly increased the rate of wound contraction and collagen turnover [62]
8.	Red silk cotton (*Bombax malabaricum*)	Alcoholic Bark extract resulted in a significant decline in the wound in rats. When compared with standard drug, nitrofurazone, it was found superior in terms of wound contracting ability, wound closure time, and tensile strength [63]
9.	Rhus olina (*Lannea coromandelica*)	Ethanol and acetone extracts of barks were applied to male Wistar rats in the form of simple ointments exhibited wound healing activity in excision and incision methods. Framycetin sulphate was taken as standard control. It displayed potent wound healing activity in terms of significant wound contraction and increased tensile strength [64]
10.	Plantain tree (*Musa paradisiaca*)	The extract of *M. Paradisia*ca holds substantial wound healing activity in rat models [65]
11.	Kino tree (*Pterocarpus marsupium*)	The effect of heart wood extract of *P. marsupium* on wound healing has been studied in diabetic and normal animals. The effect has also been compared with standard (mupirocin ointment) application. The results show that application of heart wood extract significantly increased wound healing in both normal and diabetic animals [66]

Table 2. Siddha herbs with reported wound healing activity.

2.3. Unani medicines

Unani system of medicine has its origin in Iran and also has documented evidences of antimicrobial herbs possessing wound healing properties. Like Siddha, Unani system too has a mention of cow's ghee (*Roghan-e-gao*), *Shorea robusta*, etc. Following are examples of wound healing plants or medicines (*marham*) according to Unani system of medicine.

2.3.1. Iranian wound healing plants

Pirbalouti *et al*. reported the wound healing properties of five traditional Iranian plants on alloxan-induced diabetic wounds in rats. Wound area, epithelialization time, and histopathological characteristics were studied upon treatment with *Malva sylvestris*, *Punica granatum*, *Amygdalus communis*, *Arnebia euchroma*, *and Scrophularia deserti*. The results corroborated the traditional wound healing use of the above plants [67].

2.3.2. Marham-e-Ral

Similarly, a study described the wound healing effect of a Unani formulation *Marham-e-Ral* in rats. Ingredients of this formulation are *Shorea robusta Gaertn* (*Ral*), Camphor (*Kafoor*), Catechu (*Katha*), *Roghan-e-Gao*, and Beeswax. *Marham-e-Ral* was administered topically once a day till complete epithelialization occurred. Wound contraction and epithelialization were measured. Both excision and incision wound models were developed. Rate of wound contraction was significantly enhanced so was the epithelialization period. The plant extracts have revealed presence of flavonoids, triterpenoids, and tannins which are known to contribute to wound healing. They also possess astringent, antimicrobial and antiinflammatory effects. Based on their study, the authors claimed the prohealing stroke *Marham-e-Ral* possesses [68].

2.3.3. Aloe (Elva)

Aloe is one of the oldest plants documented across the globe and also features in Unani system of medicine where it is called as *'Elva'*. Oryan *et al*. [69] reported the detailed account of wound healing activity of *A*. *vera* in rats. They demonstrated that the wound healing was 50% faster with aqueous extract of *A*. *vera* as compared to silver sulfadiazine in case of open wounds.

2.3.4. Golnar-e-farsi

Punica granatum (*Linn*.), known as *Golnar-e-farsi* in Iran, popularly known as pomegranate flowers and *Achillea kellalensis* (*Bioss*.) and *Hausskn* a well known traditional herb used in tribal medicine of Iran is locally known as *Golberrenjas or Bumadaran-e-Sabzekoh* were studied scientifically by Pirbalouti *et al*. in 2010. The authors reported their significant wound healing properties in rat excision wound model owing to their increased wound contraction ability and collagen turnover [70].

2.3.5. Shorea robusta

Shorea robusta finds a mention in both Siddha and Unani systems of medicine. A study carried out by Wani *et al*. in 2011 reported the wound healing property of *S*. *robusta Gaertn*. *f*. in excisional and incisional wound models in rats. The ethanolic extract was found to accelerate wound contraction, increased tensile strength, and hydroxyproline content thus acting as a wound healer [71].

2.4. Chinese herbs

As are Ayurveda and Siddha to India and Unani to Iran, traditional Chinese system of medicine has been practiced for ages in China. Traditional Chinese Medicine (TCM) focuses on the concept of Yin and Yang which describes two opposing yet complementary aspects of any one phenomenon. Yin is associated with poor circulation and healing and stagnation, while Yang is related with being overheated and excess of scar tissue. Thus for optimum wound healing, an ideal balance needs to be struck between Yin and Yang. Raw Chinese formulas are created specific to each patient. A raw formula means simply that the herbs in the formula are in their natural state without modification. Traditionally, raw Chinese formulas are given in their organic form, cooked for several hours, and then ingested, but it tends to have an undesirable taste. However, with wound healing, a topical application is convenient, effective, and has no or less side effects. Herbs can be utilized in their natural state and with their maximum potency. Few of the examples of wound healer herbs of TCM are as follows:

1. Tam *et al.* [72] were the first to report a combination of *Radix astragali* and *Radix rehmanniae* in the ratio of 2:1 for the treatment of diabetic foot wounds. The herb combination showed its effectiveness in treating diabetic wound healing through the actions of tissue regeneration, angiogenesis and anti-inflammation.

2. *Angelica sinensis* (AS) called as *Dang-Gui* in Chinese, was analysed in detail by Hsiao *et al*. [73] using proteomics to demonstrate range of pharmacological effects associated with AS which will prove fruitful in developing it as a wound healing herb. The authors concluded that AS extract and its active component ferulic acid (FA) participate in the modulation of wound healing process associated with fibroblasts. FA specifically acts as a ROS scavenger. Additionally, FA is also able to trigger proteins like heme oxygenase-1 (HO-1), heat shock protein 70 (HSP70), Extracellular signal-regulated kinases (ERK ½), and Protein kinase B (Akt), which help cells to respond to environmental stress thus contributing to its enhanced wound healing ability.

3. Hou *et al*. [74] recently demonstrated the wound healing property of a four-herb Chinese medicine ANBP which is a pulverized mixture of four herbs including *Agrimonia eupatoria* (A), *Nelumbo nucifera Gaertn* (N), *Boswellia carteri* (B), and *Pollen Typhae Angustifoliae* (P) explored the effect of four-herb Chinese medicine ANBP. The herb was evaluated on the basis of wound healing and scar formation in rabbit ear hypertrophic scar models of full-thickness skin defect. Compared with the control group, local ANBP treatment not only significantly improved wound healing, but also reduced scar formation. The study results demonstrated that ANBP treatment along with reducing collagen synthesis, blocked

excessive deposition of collagen and also promoted collagen maturity, thus obstructing the formation of scar. The mechanism of the effect of ANBP on collagen expression is different in the early and late stages of wound healing, which is favourable for wound closure and scar contraction. Using proteomics approach, the authors suggested that ANBP promoted wound healing and condensed scarring by bidirectional regulation of the Transforming Growth Factor β (TGF- β)-/Smad-dependent pathway.

4. Chinese medicine book, Compendium of Materia Medica proclaims *Lucilia sericata* known as *'WuGuChong'* in Chinese for treating superficial purulent diseases like carbuncle. Zhang *et al.* reported that fatty acid extracts of *Lucilia sericata* can promote murine cutaneous wound healing by virtue of its remarkable angiogenic activity. Wound excision model in rats followed by Vascular Endothelial Growth factor (VEGF) expression analysis by western blotting, RT-PCR and immunohistochemistry strongly suggested the mechanism involved in wound healing property of the herb [75].

5. Chak *et al*. [76] demonstrated the effect of another Chinese medicine *Shiunko* consisting of sesame oil, *Lithospermi radix*, (*LR; Lithospermum erythrorhizon Sieb. et Zucc.*), *A. sinensis*, lard, and beeswax. The authors reported that *Shiunko*-treated fibroblasts induced range of biochemical events engaged in the wound healing process, including cell proliferation and anti-apoptosis, anti-oxidant activity, secretion of collagen, and cell mobility. It was also noted that Stathmin, a differentiation marker was greatly induced by *Shiunko*, which is a sign of good healing process. Proteomics suggested peroxiredoxin and glutathione S-transferase were involved in antioxidantion offered by *Shiunko*. Also, superoxide dismutase was enhanced after *Shiunko* treatment which again contributed to its wound healing property. TGF-β was upregulated on *Shiunko* treatment which happens to be upstream regulator of collagen expression and an indispensable factor for wound healing.

6. *Terminalia chebula* is mentioned in other systems of medicine like Ayurveda for its wound healing ability. Likewise, it was proven by Li *et al*. [77] that tannin extracts from immature *Terminalia chebula* fruits helps in cutaneous wound healing in rats. The immunohistochemical, transcriptional and translational levels of VEGF analysed in the study helped the authors conclude that the wound healing property was by the virtue of anti-angiogenic effects. Also, the proliferation of bacteria like *Staphylococcus aureaus* and *Klebsiella pneumonia* were inhibited by the extract thus conferring the much needed antibacterial effect beneficial for faster wound healing. Thus the study concluded that tannin extracts from immature fruits of *Terminalia chebula Fructus* (*Retz.*) stimulated cutaneous wound healing in rats.

2.5. Ozone therapy

Ozone therapy dates back to the year 1914 when it was used during World War I for the treatment of gas gangrene. Ozone has multiple therapeutic effects in wound healing due to the property of releasing nascent oxygen, which has been shown to have bactericidal capabilities and to stimulate antioxidant enzymes. There are few randomized clinical trials to verify the use of ozone therapy in the early stages of wound healing. To verify the same, Zhang *et al*. [78] recently carried out a study assessing the use of ozone therapy in the early stages of

diabetic foot ulcer by estimating the expression of VEGF, TGF-β, and Platelet derived growth factor (PDGF). The authors claimed that the oxygen-ozone therapy increased the levels of all the above three endogenous growth factors which contributed to its enhanced wound healing ability. Similarly, Wainstain *et al*. [79] demonstarted that oxygen–ozone therapy along with conventional therapy for 24 weeks hastened the healing of diabetic foot ulcer. The theory that ozonated oil has wound healing property was investigated at our laboratory in an excision wound model using Sprague Dawley rats. The animals were divided into four groups, which were treated with sesame oil (vehicle), framycetin (standard), or two doses of ozonated sesame oil (peroxide values 500 and 700 mEq/1000 g, respectively). The formulations were topically applied on the excision wounds once daily for 11 consecutive days, and the animals were euthanized on the 12th day. Ozonated oil treated wounds had significantly higher tensile strength, collagen content, and superoxide dismutase activity than that of the vehicle treated wounds. Histopathological analysis of skin of the excised wound area treated with ozonated oil revealed better healing activity in comparison with the vehicle-treated wounds. Thus it was concluded that ozonated oil can be of potential remedial use for healing wounds [80]. Another animal study was carried out by Kim *et al.* [81] to evaluate the therapeutic effects of ozonated olive oil in guinea pigs in acute cutaneous wound healing model. Full thickness punch wound was created on the back of guinea pigs and ozonated olive oil treatment was compared with pure olive oil and no treatment control group. The immunohistopathological results demonstrated that topical application of ozonated olive oil increased the levels of VEGF, TGF-β, and PDGF thus accelerating acute cutaneous wound healing. A study conducted by Travagli *et al*. [82] reported a deleterious effect of ozone treatment on aged mice. The authors claimed that ozone therapy in 8-week mice enhanced wound healing, while when administered to 18-week mice, the full thickness excisional wound displayed delayed healing. This may also be attributed to reduced bacterial infection and/or increased O_2 tension by O_3 contact in wound area in younger population.

3. Clinical studies supporting the folklore use of alternative therapies

Scientists advocate more clinical studies to be conducted to provide robust proof-of-concept of folklore wound healing property of the herbs mentioned in alternative therapies. Few of the clinical studies carried out are documented subsequently.

3.1. Ayurveda-based clinical studies

3.1.1. Katupila study

A case study of diabetic wound of a 55-year-old female patient wherein *Katupila* paste [(*Securinega leucopyrus*) (*Willd*.)] was applied daily and after a month the wound was reported to have healed completely leaving a minimal scar. The healing properties of *Katupila* were attributed to its antimicrobial, antiseptic, and wormicidal qualities. Also it was shown to possess abundant quantities of flavonoids and tannins which offer the antioxidant effects [13].

3.1.2. Manjishthadi Gritha

A clinical study employing *Manjishthadi Gritha* was carried out by Baria *et al*. The *Gritha* was prepared using seven herbs namely, *Manjishtha* (*R. cordifolia Linn*.), *Daruharidra* (*B. aristata DC*.), *Mocharasa* (*Salmalia malabaricum*), *Dhatakipushpa* (*Woodfordia fruticosa* (*Linn*.) *Kurz*.), *madhuka* (*Madhuca indica J. F. Gmel*), *Lodhra* (*Symplocos racemosa Roxb*.) *and Rasanjana* (*Extractum berberis*). The *Gritha* was applied topically on wounds mostly from anorectal cases twice a day for 21 days. The observation period of 1 month recorded the results of the study. Out of 45 patients, 24 were treated with the *Gritha* and 21 with povidone iodine ointment. The *Gritha*-treated patients showed better wound healing, no left-over scar, no excess pigmentation, and absence of adverse effects. The authors reported *Manjishthadi Gritha* as an economical and effective wound healing combination [83].

3.1.3. Honey: A pilot study

Vijaya *et al*. [84] reported a pilot study using honey for healing the cutaneous wounds of 10 randomly selected patients of both sexes. Honey collected locally was applied daily for 20 days and the size of the wound was measured on day 7, 15, 20, and after complete wound healing. The authors concluded that honey was remarkable in healing the wounds and can be very effectively used as first aid dressing material. A case study [85] was reported employing honey for the cure of a chronic infected wound on the right lower limb of a 70-year-old female. Every morning the wound was cleaned with neem bark decoction, and Dabur® honey was applied on the wound. Along with the local application, following drugs were administered orally every 12 hours: *Glycerrhiza glabra* (*Linn*.), *Asparagus racemosus* (*Willd*.), *Tribulus terrestris*, *Tinispora cordifolia* (*Willd*). At the end of fifth week, the authors reported a complete healing of the wound leaving a minimal scar. Sushruta Samhita has mentioned *honey* (*madhu*) as a wound healer centuries ago. The above case study practically proved the effectiveness of honey. It is hyperosmolar so confers antibacterial effect. It has high viscosity so acts as physical barrier. Presence of enzyme catalase in honey gives it antioxidant properties. The four drugs given orally possess antioxidant, adaptogenic, and immunomodulatory activities. Clinical studies employing honey with bigger population although would yield more authentic conclusions.

3.2. Unani medicine-based study

3.2.1. Dragon's blood cream

Namjoyan *et al*. [86] reported a clinical study using Dragon's blood cream, a deep red resin obtained from four different sources, *Croton spp*., *Dracaena spp*., *Daemonorops spp*., and *Pterocarpus spp*. 60 patients referred to remove their skin tags were included in this randomized clinical trial to receive either Dragon's blood cream or placebo cream. Wound measurement and process of healing was checked on 3rd, 5th, 7th, 10th, 14th, and 20th day of the trial. The patients receiving Dragon's blood cream showed significant wound healing. The phenolic compounds present in Dragon's blood cream reportedly contribute to its effective wound healing property.

3.3. Clinical study on ozone therapy

3.3.1. Adjuvant ozone therapy

Shah *et al*. [87] presented a case study of a 59-year-old female patient with an extensively infected wound and exposed tibia to about $^{4}/_{5}$th of its extent. Topical ozone therapy twice a day and ozone hemotherapy once a day along with daily dressings and parenteral antibiotics showed significant improvement in 15 days in the patient. After a follow-up of 20 months, the patient was able to walk with minimal disability. Ozone disintegrates into reactive oxygen species which further lead to increased growth factors contributing to faster wound healing. The study stated that oxidative injury is a possible side effect of ozone therapy but at therapeutic doses oxygen radicals are removed by the blood antioxidants and thus side effects are rare and only observed in overdose or compromised anti-oxidant system.

4. Conclusion

The folklore knowledge is abundant with mention of various herbs and medicines as wound healers across different civilizations and systems of medicines. Modern medicine is fast attempting to explore the ancestral data and test its effectiveness using current experimental methods. The focus is on analyzing the molecular basis of the effectiveness of the concerned plants. Proteomic and genomic-based evidences using robust markers blended with traditional knowledge can provide relevant answers and solutions for healing of wounds which affect the largest organ of human body. Although more randomized clinical trials are the need of the day to validate the ancient claims.

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