# Herbal Interventions for Wound Healing-Current Status and Future Perspective

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#### Abstract:

A number of pharmaceutical formulations loaded with synthetically manufactured therapeutics are available for treatment of burn wounds. However, over the past few years researchers have ventured into exploring herbal alternatives for treatment of burn wounds due to their safety profile. The present review provides an insight into different types of wounds besides providing a compilation of the various herbal interventions which have been proved to be effective in wound healing. The review also provides a consolidation of the various formulations developed and explored by various researchers for the treatment of wounds along with a discussion on the future perspective of using herbal interventions for wound healing.

Keywords: Wound, healing, Herbal, Interventions

# **INTRODUCTION**

Wounds are described as a disturbance of the cell-cell and functional constancy of a tissue, along with or without bacterial infection. They may occur due to any disaster or injury by the pointed object.<sup>29</sup> If timely and appropriate treatment is not given to wound then it leads to ache, irritation, microbial contamination, and occasionally organ dysfunction<sup>28</sup>.

Wound healing takes place by three different phases i.e., inflammatory phase, proliferative phase, and remodelling phase.<sup>10</sup> Wound healing involves the interactivity of complicated cascade of cellcell and biochemical activity which leads to repairing and retrieval of the damaged tissues. Wound healing embraces constant interactivity between cell-cell and cell-matrix that supports the wound healing procedure which includes reduction in irritation, wound tightening, restoration of epithelium tissue, re-construction and the development of granulation tissue<sup>38</sup>.

There are a number of factors which may delay wound recovery mechanism such as, microbial contamination and interaction along blood supply, arterial stoppage & diabetes. However, the healing rate can be enhanced if one or more of the above factors could be altered by any agent<sup>12</sup>.

There are many medicinal plants which play an important and major part in wound recovery. Medicinal plants are very powerful healing agents as they support the healing of wound naturally<sup>58</sup>.

Wounds may be categorized by different methods such as based on their pathophysiology, site of wound, type of wound or the signs, intensity of wound and clinical presentation of wound. The different types of wounds are illustrated in figure 1.



Figure 1: Classification of wounds

# 1. Open wounds

Open wounds are those type of wounds in which the blood loss is seen always as blood gushes out of the body after injury. Depending on the reason which inflicts the wounds, they are classified into the following categories<sup>53</sup>.

**a.) Incised wounds:** In this type of wound there is no tissue depletion and the tissue destruction which occurs is also less. These types of wounds are caused by a pointed edged objects e.g., blade or cutter. Blood loss is abundant in these types of wounds and therefore instant care is needed.

**b.**) Laceration or tear wounds: Laceration or tear wound is a nonsurgical injury along with some kind of shock which results in tissue depletion and destruction.

**c.**) **Abrasions or superficial wounds:** Abrasion wounds occur by downward drop towards the irregular plane. In this kind of wounds, the epidermis is trimmed leading to an exposure of nerve endings which induces pain.

**d.) Puncture wounds:** These types of wounds occur by penetration of nails or needles. In these types of wounds there are more chances for microbial contamination because impurities can penetrate into skin below the wound.

Publication: 31 March 2022

**e.**) **Penetration wounds:** These types of wounds occur by an article for example cutter/blade which approach the skin and then coming out from the skin.

**f.**) **Gunshot wounds:** These types of wounds occur by rocket like objects which pass in or out from the body.

# 2. Closed wounds

In these types of wounds, the blood loss cannot be seen outside the body. These are observable in the form of blemishes. They are of lesser types as compared to open wounds, but they are as threatening as open wounds. The closed wounds can be classified as: -

**a.**) Contusion or bruises: These types of wounds occur by edgeless objects but they disrupt the tissue to bottom of the skin.

**b.)** Hematomas or blood tumor: These types of wounds are caused when the blood vessels are damaged and therefore blood starts collecting under the skin.

**c.**) **Crush injury:** These types of injuries are caused when excessive energy is put over the skin surface for a longer time interval.

# 3. Acute wounds:

Acute wounds are the injuries that usually precede by orderly and timely reformative procedures which lead to continuous renewal of structural and working character of skin. These types of wounds generally occur by cuts and the entire healing of wound occurs within anticipated period of time<sup>28</sup>.

# 4. Chronic wounds

The wounds which do not heal but enter in pathologic inflammation state are referred to as chronic wounds. They may need more time period for healing. These types of wounds are caused by bacterial infections, oxygen deficiency as well as by shock and systemic diseases e.g., diabetes, malnourishment and immune disorders<sup>39,26</sup>.

# **MECHANISM OF WOUND HEALING**

Wound recovery take place by three phases which include inflammatory phase, proliferative phase, and maturation phase (Figure 2) <sup>30,62,32,47</sup>.



Figure 2: Mechanism of wound healing

# MEDICINAL PLANTS UTILIZED FOR WOUND TREATMENT

Some examples of medicinal plants which are utilized for wound healing and treatment are listed below: -

# 1. Gingko biloba

*Gingko biloba* (Family: Gingkoaceae) and common name is "Kew tree". It was described that this plant helps in wound recovery because of its amino acid content and by mixing with vitamins it provides important supplements at the wound site which speed up the healing process<sup>7</sup>.

# 2. Centella asiatica

*Centella asiatica* (Family: Umbeliferae) is commonly known as "Brahmi". Asiaticosides and madecassosides are two active constituents which exhibit the healing activity. Asiaticoside improves epithelialization and collagen deposition and madecassoside improves collagen synthesis and angiogenesis at the wound area<sup>6</sup>.

# 3. Rubia cordifolia Linn.

*Rubia cordifolia Linn.* (Family: Rubiaceae) is commonly referred to as "Manjistha". The roots of *Rubia cordifolia Linn.* have high medicinal value. The ethanol extract of this plant shows the presence of anthraquinone glycosides, saponins, tannins and phytosterols. Tannins and anthraquinones are important phytoconstituents which may be responsible for wound healing activity<sup>40,22</sup>.

# 4. Ocimum kilimandscharicum

Journal of Coastal Life Medicine www.jclmm.com ISSN: 2309-5288(Print)/2309-6152(Online) Volume 10 No.1 (2022), Page No. 488–504 Article History: Received: 02 January 2022, Revised: 10 February 2022, Accepted: 21 February 2022, Publication: 31 March 2022 *Ocimum kilimandscharicum* belongs to the family Laminaceae. It contains tannins, flavonoids, proteins and other phytoconstituents. Flavonoids are responsible for antioxidant, wound recovery

and antimicrobial avtivity<sup>33</sup>.

# 5. Kigelia pinnata

The bark of *Kigelia pinnata* (Family: Bignoniaceae) shows the presence of some phytoconstituents such as naphthoquinones lapachol, phenyl propanoid, stigmasterol,  $\beta$ -sitosterol and small amounts of free ferlic acid, p-coumeric acid and 6- methoxymelenin. It exhibits antifungal, antiulcer, antibacterial, antioxidant activities and also possesses a wound recovery activity<sup>57</sup>.

# 6. Eucalyptus

*Eucalyptus* (Family: Myrtaceae) commonly referred to as Dinkum Oil contains cineole, also known as eucalyptol. The phytoconstituents present in eucalyptus are pinene, camphene, and phellandrene, citronellal, geranyl acetate. It is used for the treatment of burns, lesions, wounds and skin microbial contaiminations<sup>18</sup>.

# 7. Aegle marmelos

*Aegel marmelos* belongs to the family Rutaceae and its common name is "Bael fruits". It contains the phytoconstituent marmelosin and also contains carbohydrates, protein, volatile oil and tannins. It possesses a wound healing property<sup>20</sup>.

# 8. Tectona grandis Linn.

*Tectona grandis Linn*. (Family: Verabinaceae) is commonly referred to as "Indian teak" and contains carbohydrates, tannins and anthraquinone glycosides. The extract of Tectona grandis promotes the wound firmness, contraction and collegenation<sup>34</sup>.

Besides the above medicinal plants used for wound treatment, table 1 compiles a few other medicinal plants which have been used for wound treatment.

Sr.	Medicinal plant	Phytoconstituent	Herbal part used	Reference
no.				
1.	Liquorice	Glycyrrhizin, glycyrrhetinic.	Roots	3
	(Glycyrrhiza glabra)			
2.	Aloe vera	Mannose-6-phosphate	Leaf gel	24
3.	Morinda citrifolia	Saponins, tannins, triterpenes, alkaloids.	Leaves	43
4.	Lycopodium serratum	Tannins, flavonoids and triterpenoids.	Leaves	37
5.	Catharanthus roseus	-	Flower extract	41
6.	Cecropia peltata	-	Leaf	42
7.	Euphorbia hirta linn	Carbohydrates, saponins, alkaloids,	Whole plant	63

		glycosides, steroids, flavonoids, tannins.		
8.	Pterocarpus	-	Wood	9
	santalinus			
9.	Lawsonia alba	Flavonoids, steroids, tannins and	Leaves	46
		glycosides.		
10.	Erythrina	Alkaloids	Leaf	19
	senegalensis			
11.	Chenopodium botrys	α-Eudesmol, Epi-α-muurolol, and	Leaves Essential Oil	52
		Cubenol.		
12.	Napoleona			14
	imperialis			
13.	Kaempferia galanga	-	Rhizome	55
14.	Radix paeoniae	Flavonoids, glycosides, tannins, resins	Roots	35
		and terpenoids.		
15.	Rhynchosia	Tannins, Phytosterols and Flavonoids.	Leaves	54
	beddomei Baker			
16.	Tephrosia purpurea	Glycosides, Rotenoids, Flavanones.	Aerial part	31
17.	Sphaeranthus indicus	Eudesmanolide type of sesquiterpene.	Aerial parts	51
18.	Ageratum	Alkaloids, and tannins	Roots	50
	conyzoides			
19.	Hyptis Suaveolens	Sterols, alkaloids, flavanoids and	Leaves	59
		tannins		
20.	Arnebia densiflora	Naphthoquinone	Roots	1
	Ledeb.			
21.	Moringa oleifera	Proteins, Amino acids and Glycoside.	Dried pulp and seeds	48
22.	Common wireweed	Alkaloids, Steroids, Terpenoids and	Leaves	44
	(Sida acuta)	Flavonoids		
23.	Achyranthes aspera	Alkaloids, Carbohydrates, Phenolic	Leaves	16
	Linn	compounds and Tannins, Lavonoids and		
		Saponins.		
24.	Azadirachta Indica	Nimbidin and Sodium Nimbidate	Leaves	13
25.	Ficus religiosa	Tannins, Triterpenoids, Alkaloids and	Leaves	17
		Steroids		
26.	Indigofera	Alkaloids, Flavonoids, Saponins,	Whole plant	60
	enneaphylla Linn	Steroids.		
27.	Jasminum	Mucopolysaccharides and Collagen	Leaves	49
	grandiflorum	content.		
28.	Leea macrophylla	Polyphenols mainly Chlorogenic acid	Root tuber	21

29.	Sesamum indicum	Alkaloids,	Flavonoids,	Glycosides,	Seeds	25
		Phenols, Anthraquinones, Tannins.				

# Different formulations of medicinal plants used in wound healing

# 1. Gingko biloba

Bardaa, S. et al., developed a cream of Ginkgo biloba extract and evaluated its potential for wound healing. The cream consisted of 1% to 5% as a Ginkgo biloba aqueous extract. The authors concluded that the prepared formulation exhibited a good physicochemical property with uniform size distribution and remained stable. During the experimental trial, it was shown that the animals receiving the Ginkgo biloba extract cream exhibited a great improvement in wound healing as compared to control group and standard group. The authors concluded that the Ginkgo biloba extract cream could be a novel formulation for the management of acute diabetic wounds<sup>8</sup>.

# 2. Centella asiatica

Taher, M., et al., developed a Asiaticoside-rich hydrogel for accelerating the wound healing and evaluated its efficacy in rabbits. Asiaticoside is an active constituent of Centella asiatica. Asiaticoside rich fraction was incorporated in a polyvinyl alcohol/polyethylene glycol hydrogel. *In vivo* incision model was utilized for the investigation. The results showed that the prepared formulation was not only safe on the animal skin but it also exhibited a 15% faster wound healing effect as compared to the standard formulation and 40% faster effect as compared to the undressed wound. The authors concluded that the asiaticoside-rich hydrogel was efficient in increasing the rate of wound healing<sup>62</sup>.

Manisha, V. et al., developed a bio-degradable film utilising plant extract of Centella asiatica and evaluated it for wound healing properties. The results of different studies conducted revealed that the film had transparent appearance and pleasant odour with satisfactory thickness, folding endurance and tensile strength. *In vivo* studies indicated that the optimal formulation gave better results as compared to control & standard. The authors concluded that the biodegradable film delivered the drug in a controlled manner for a longer duration and improved its bioavailability<sup>36</sup>.

# 3. Rubia cordifolia Linn.

Karodi, R., et al., evaluated the wound healing activity of Rubia cordifolia. The alcoholic extract of Rubia cordifolia and the hydrogel formulation was investigated for its healing activity. Wound area and histopathology were evaluated. The results indicated that there was a decrease in wound area and tissue restoration at the wound place and histopathological features were significant (p < 0.01) in treated group<sup>22</sup>.

Charde R. M., et al., evaluated the wound healing activity of plant *Rubia cordifolia*. The wound healing activity was evaluated using different animal models and the granuloma tissue was also evaluated to estimate hydroxyproline content. The results showed a significant improvement in wound closure, skin and granuloma disrupting strength and the hydroxyproline matter was also increased with the reduction in scar area. It was concluded that *Rubia cordifolia* extract has wound healing properties because of some terpenoids and antimicrobial agents which are present in plant<sup>11</sup>.

#### 4. Ocimum kilimandscharicum

Paschapur M. S. et al., evaluated the wound healing potential of Ocimum kilimandscharicum plant. Different types of wound models were used. The results indicated that there was an improvement in skin and granuloma disrupting strength, and increase in rate of wound closure with a reduction in epithelization period. The authors concluded that the plant has healing activity due to free radical scavenging action and due to the antimicrobial properties of active constituents<sup>45</sup>.

# 5. Kigelia pinnata Sausage

Kaushik, P et al., screened the aerial part of Kigelia Pinnata plant for wound healing, and antibacterial properties. Different wound models were used for wound healing activity. Different tests were conducted to check the wound healing activity. It was observed that there was a significant increase in tissue tensile strength and wound contraction at the wound site and complete healing was also observed as compared to control and the standard group. The authors also evaluated the antibacterial activity and antifungal activity. The results of antibacterial study showed that the *Kigelia pinnta* methanolic extract only prohibited the *E. coli* strain and the results of antifungal study showed that all the fungal strains were inhibited by methanolic extract of *Kigelia pinnta*<sup>23</sup>.

# 6. Eucalyptus

Alam, P. et al., developed a nanoemulsion of *Eucalyptus* oil and evaluated its wound healing activity in animal model. Aqueous phase titration method was used for the preparation of nanoemulsion. The nanoemulsion was evaluated for different tests and the optimal formulation was used for testing wound healing activity. The results showed that the optimized nanoemulsion had a significant wound healing action as compared to pure eucalyptus oil and there was an improvement in collagen content. Histopathological studies didn't show any inflammation at the wound site which revealed the safety and non-toxicity of the nanoemulsion formulations. The research suggested that the prepared formulation had a potential to improve the wound healing action after oral administration<sup>2</sup>.

Kubera Sampath Kumar S. et al., prepared the leaf extracts of *Calotropis gigantean, Eucalyptus globulus* and buds of *Syzygium aromaticum* and covered them on natural fibres for wound bandage. SEM was used for the morphology study of prepared samples to know the pore sizes. Both gram positive strain and gram-negative strain of microbes were used for antimicrobial studies. The healing efficacy was evaluated by *in vivo* method. The study was conducted on second degree wound. The prepared bandage was applied over the wound and further study was conducted. The antimicrobial test showed the formation of zone of inhibition which indicated the antimicrobial activity of the bandage against the *E. coli* and *S. aureus. In vivo* study confirmed an appropriate rate of wound contraction<sup>27</sup>.

# 7. Aegle marmelos

Azmi, L. et al., investigated the *in vitro* wound healing activity of active constituents of *Aegle marmelos* flower extract. In this study author used a full thickness wound. Cutaneal wound healing

activity was carried out for the determination of various parameters. Results showed that treatment with flower extract resulted in a reduction in wound area with enhancement of epithelisation<sup>5</sup>.

Gautam M. K. et al., evaluated the wound healing activity of Aegle marmelos fruit pulp extract on different types of wound models. The results showed that there was a reduction in mean epithelization time and wound area and improvement in a wound breaking strength after application of fruit pulp extract. It was observed that the granulation tissues show raised levels of antioxidants (13 to 38.8%) and collagen determinants (33.7 % to 64.4%) with decrease in oxidative stress (55% to 55.6%) and myeloperoxidase markers (21.3%). The authors concluded that the A. marmelos promotes wound healing by increasing the connective tissue production with reduction in free radicals and myeloperoxidase<sup>15</sup>.

Arunachalam, K. D. *et al.*, evaluated the wound healing activity of this plant. For this study the methanolic extract of leaves was used. The authors used a standard method for evaluating the phytochemical nature, antioxidant property, wound healing potential and antigenotoxicity properties. The results showed the existence of steroid, terpenoids, saponins, tannins, lignin and flavonoids. The antioxidant study shows that methonolic leaf extracts possess good antioxidant activity for the healing of wounds as compared to the providine iodide which was used as a standard formulation. From the results obtained the authors concluded that the extracts of leaves were found to be antigenotoxicant<sup>4</sup>.

Sharma, G. N et al., investigated the wound healing properties of aegle marmelos seeds. For this study author prepared an ointment containing methanolic and aqueous extract, in two different concentrations. Different types of wound models were used. The results showed a significant improvement in rate of wound contraction, tissue tensile strength at wound site and reduction in time of epithelialization after application of the ointment containing extract<sup>56</sup>.

# 8. Tectona grandis (TG) Linn.

Varma, S. B. *et al.*, determined the wound healing properties of leaves extract of this plant. Two types of wound models were used and two concentrations of ointment were formulated. Wound closure rate was evaluated in excision model and tissue tensile strength was evaluated in incision wound model. The results indicated that both the concentrations of formulation showed a decrease in wound area and enhancement in the tissue tensile strength as compared to control group. The authors concluded that the leaves extract of this plant showed a significant wound healing action<sup>64</sup>. Table 2 compiles the different formulations containing herbal actives for wound healing.

Sr.	Medicinal	Formulation	Route of	Inference	Reference
No.	plant		administration		

#### Table 2: Herbal formulations used for wound healing

1.	Liquorice (Glycyrrhiza	Gel	Topical	Promotes wound healing.	3
	glabra)				
2.	Aloe vera	Gel	Topical	Increased wound healing.	24
3.	Morinda	Ethanolic	Oral	Improved wound closure,	43
	citrifolia	extract		reduced period of	
				epithelialization and enhanced	
				hydroxyproline content.	
4.	Lycopodium	Ointment/	Topical/ Oral	Reduced epithelialisation time,	37
	serratum	Suspension		enhanced wound closure and	
				skin and granuloma tissue	
	~			breaking strength.	
5.	Catharanthus	Ethanolic	Topical and oral	Improved wound closure rate,	41
	roseus	extract		tensile strength and expanded	
				nydroxyproline content as well	
6	Caarania	A guaque and	Topical and oral	as exhibits antibacterial action.	42
0.	neltata	Aqueous and		causes a reduction in would	42
	penala	extracts			
7	Euphorbia	Ethanolic	Oral and Topical	Promotes healing of wounds	63
/.	hirta linn	extract and	orar and ropical		
		Ointment			
8.	Pterocarpus	Ointment	Topical	Wounds healed significantly	9
	santalinus		_	faster	
9.	Lawsonia	Ethanol	Oral	Better wound healing activity	46
	alba	extract and		and breaking strength.	
		petroleum			
		ether extract			
10.	Erythrina	Ointment	Topical	Reduction of wound size and	19
	senegalensis			epithelialisation time.	
11	Change lines	<b>F</b>	Teniel		50
11.	botrus	Essential off	Topical	increase in epithelialization and	52
	000198			formation	
12	Napoleona	Ointment	Topical	Progressive decrease in wound	14
12.	imperialis	Ommont		area with time.	1 T

1		aren 2022			
13.	Kaempferia galanga	Suspension	Oral	Reduction in epithelialization period and enhancement in tissue breaking strength and increase in rate of wound	55
				contraction.	
14.	Radix	Aqueous	Oral	Decrease in wound area and	35
	paeoniae	extract		increase in tensile strength.	
15.	Rhynchosia	Aqueous and	Topical and Oral	Reduced rate of epithelialization,	54
	beddomei	Ethanol		enhanced rate of wound closure	
	Baker	extracts		and skin breaking strength of	
		(Suspension)		healed wound.	
16.	Tephrosia	Ointment	Topical	Encouraged wound closure and	31
	purpurea			improved tensile strength.	
17.	Sphaeranthus indicus	Cream	Topical	Improved wound contraction and time of epithelialization.	51
18.	Ageratum	Ointment	Topical	Stimulates the wound healing	50
	conyzoides			process and improved breaking	
				strength of wound.	
19.	Hyptis	Alcoholic,	Oral	Promotes wound healing and	59
	Suaveolens	Petroleum		increased collegenation.	
		ether and			
		Aqueous			
		extract			
20.	Arnebia	Ointment	Topical	Remarkable wound healing	1
	densiflora			activity	
	Ledeb.				
21.	Moringa	Aqueous	Oral	Enhanced wound closure, skin	48
	oleifera	extract		and granuloma breaking	
				strength, reduce scar area.	
22.	Common	Methanolic	Topical	Improved epithelialization and	44
	wireweed	extract		wound contraction.	
	(Sida acuta)	(Ointment)			
23.	Achyranthes	Aqueous and	Topical	Enhanced wound contraction	16
	aspera Linn	Ethanolic		and Healing.	
		extract			
		Ointment			
24.	Azadirachta	Leaves	Topical	Decreased wound area.	13
	Indica	extract			

25.	Ficus	Methanolic	Topical	Significant reduction of wound	17
	religiosa	extract		contraction area and rapid	
		Ointment		epithelialization	
26.	Indigofera	Ointment	Topical	Improved wound contraction	60
	enneaphylla			and tensile strength.	
	Linn				
27.	Jasminum	Paste	Topical	Improved wound healing and	49
	grandiflorum			Increased collagen formation.	
28.	Leea	Bioadhesive	Topical/ Oral	Promoted wound healing	21
	macrophylla	gel/ Ethanolic			
		extract			
29.	Sesamum	Gel	Topical	Promotes wound healing	25
	indicum				

# **FUTURE PROSPECTIVE**

Wound healing is a complex process that starts with the pain, stress, irritation and end with spot formation. Topical herbal preparations are a promising therapy for the management of wounds. There have been several studies, that confirm the benefits of medicinal plants in the recovery of wounds. The mixture of traditional and synthetic drugs can be used for the development of an excellent wound healing agent with lesser drawbacks which may be a beneficial practice for the management of wound. There is a need to develop a reliable procedure for the standardization of medicinal plants to improve the efficacy of formulations developed using them.

#### CONCLUSION

Plant constituents are potential wound healing agents which heal the wound in natural ways. Plants contains many active constituents which act by various mechanisms a few of which include antimicrobial, anti-inflammatory, antioxidant etc. for healing wounds. The active constituents and the extracts of plants regulate different stages of wound healing and therefore have a great potential for the care and prevention of wounds.

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