Original Article

AN OVERVIEW ON NATURAL WOUND HEALING PROCESS WITH SOME INDIGENOUS PLANTS AS WOUND HEALER

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Abstract

Skin provides a protective barrier against any damage. Wound healing involves various cellular mechanisms. Wound is defined as the injury which may be due to physical, chemical or thermal means represents a major global health challenge as it can put financial and social stress especially on patients and their families. Wound healing process is a complex process having a series of different steps. So, a good wound healing management is required for the whole community. Historical records show the important role of medicinal in treatment of various ailments. In early 1900's the herbalism declined in Europe and the United States due to expansion of Allopathic medicine but now a days the trend again moves to Herbalism due to uneasiness caused by side effects of synthetic drugs. Herbal drugs in comparison to synthetic drugs cause minimal side effects and least resistance issues. In this review article information regarding natural wound healing process and plants possessing wound healing properties are gathered.

Keywords: Herbalism, wound healing, Polyherbal, Indigenous and epithelialization.

Introduction:

Skin is the largest organ of the body. It plays an important role in maintaining the physiological hemostasis in the human body by sensing the extrinsic stimuli. Its important function is to provide a physical, chemical and bacterial barrier and thereby aids in wound healing process. However the physiological regulation of skin wound healing is very complex process which involves various mediators and their interaction in highly sophisticated temporal sequence.[1] Wound healing is complex process which involves various steps. Various synthetic drugs are available in market such as antibiotics but due to their inadequate supply, high cost, resistance problem which led to the development of plants for treatment of various ailments. Currently various medicinal plants alone or in combinations are used to treat various diseases. Now, various polyherbal formulations are used to heal the wound. These formulations contain various chemical constituents which act by stimulating the healing process .[2-3]

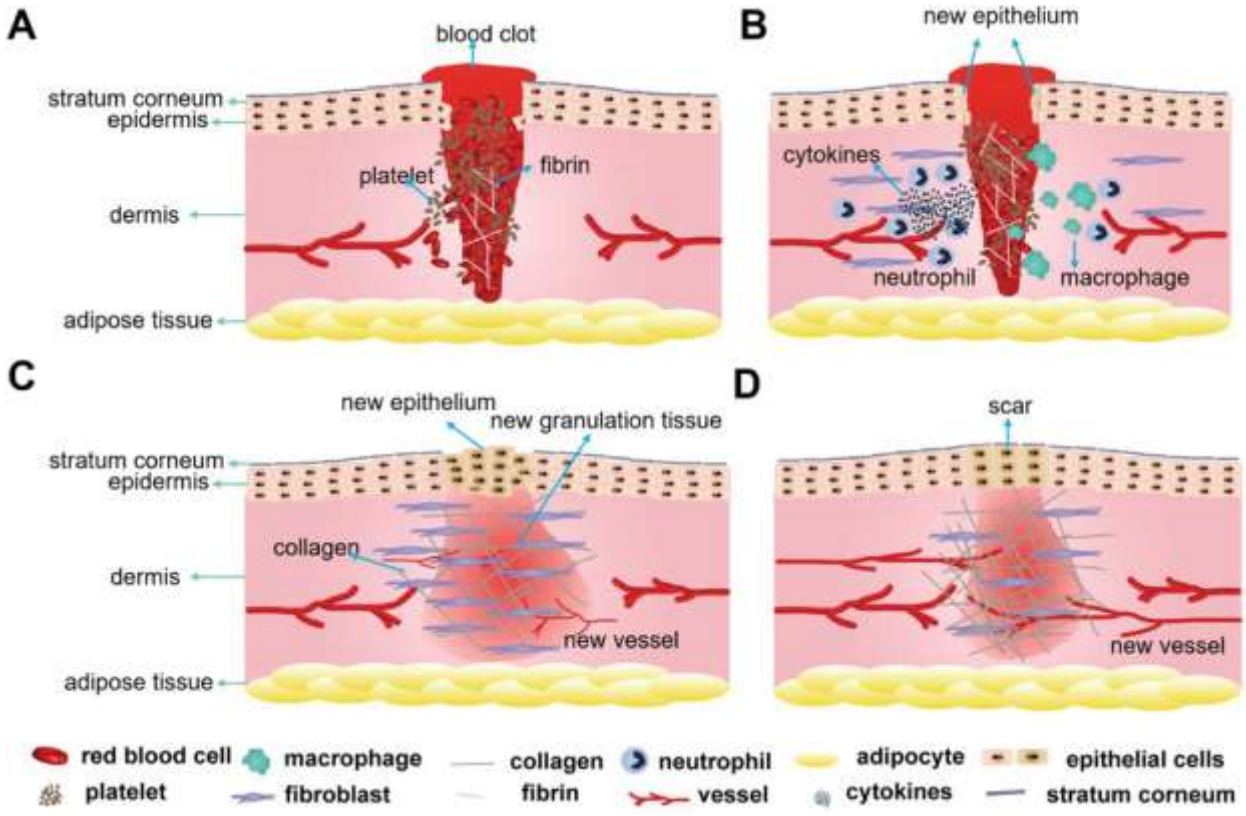
Natural Wound Healing Process

Natural wound healing process is a sequence of four major steps namely Haemostatis, Inflammation, Proliferation and Remodeling. These are describes as below:

1. Haemostatis:

Haemo means blood or statis mean stop. It is the process to prevent the blood loss or stop the bleeding after an injury. Immediately after injury blood vessels which get damaged contracts and platelets responsible for hemostasis get activated by thrombin and releases the alpha and dense bioactive molecules triggers the coagulation .[4] After that an insoluble clot is formed of fibrin, fibronectin and thrombospondin which help to stop bleeding. Alternatively lesions are formed act as shielding mechanism against bacterial invasion.[5] Platelets play an important role by directly capturing immune cells in blood clot and by releasing a secretome of chemokine attractants because platelets secretome contains certain growth factors which stimulate resident skin cells including fibroblast & keratinocytes. They express a number of tolls like receptors which regulates to produce the antimicrobial peptides. Coagulation process gets stopped once the clot is formed which prevents excessive thrombosis. The injured tissues is repaired by smooth muscles cells & endothelial cells which gets proliferate to release growth factors derived from platelet .[6-10]

Fig. 1. Different Stages of skin wound healing



A) Coagulation phase. This phase is characterized by the formation of blood clots to protect the wound. The blood clot is mainly composed of red blood cells, platelets and a cross-linked fibrin network. B) Inflammation phase. The main characteristic of this phase is the inflammatory response. In this phase, macrophages, neutrophils and lymphocytes migrate to the wound and secrete cytokines. C) Proliferation phase. Tissue regeneration is the key feature of this phase. At this time, fibroblasts, epithelial cells, and endothelial cells migrate and proliferate, and form the new epithelium, granulation tissue and vessels. [D) Remodeling phase. This phase involving wound contraction and remodeling may cause scars.[11]

2. Inflammation:

It involves the primary defense mechanism against the pathogens or bacterial infection. Inflammation can be triggered by external & internal factors. External factors include microbial & non microbial. Non microbial

means allergens, irritants etc. whereas microbial factors means pathogenic associated molecular patterns. Internal factors released when cell plasma injured or cell dies .[12,13]

Our immune system recognizes internal and external factors and thereby can trigger an inflammatory response against them. Pathogen associated molecular patterns and damage associated molecular patterns are recognized by pattern recognition receptors present on cell surface of leukocytes and activates immune cells like mast cells, lengerhans cells, T cells and macrophages .[14,15]

Also, a proinflammatory cytokines & chemokines attract the leukocytes to the site of injury. These pro-inflammatory molecules stimulate vasodilation which increases the vascular permeability, along with endothelial cells express more adhesion proteins such as selectins & facilitates the neutrophil & monocyte adhesion .[16]

Neutrophils are first leukocytes recruited during the acute inflammatory process & attracts by tumor necrosis factor alpha (TNF-α), chemoattractants such as interleukins-1 (IL-1), & bacterial endotoxins such as lipopolysaccharide (LPS). Neutrophils and other wound cells have their own cytokines. Neutrophils remove the necrotic tissue & pathogens through phagocytosis (i.e eating the pathogens & damaged cells) .[17-19]Neutrophils engulf the pathogens & destroying themselves & release the reactive oxygen species, antimicrobial peptides, eicosanoids & proteolytic enzymes. They trap the pathogens in DNA web coated with antimicrobial peptides .[20,21]

Uncontrolled & excessive inflammation may cause severe condition may promotes tissue injured & delays healing. If there is no infection after wound then neutrophils get destroyed within a few days of injury onset.[22]Most of the neutrophils are comes out from the injury site & adhere to fibrin scab and out of these some neutrophils get removed by innate clearance mechanism. Remaining neutrophils are cleared by other mechanism such as apoptosis, necrosis & phagocytosis which ultimately leaves the inflamed tissue. Monotypes which are the types of leckocytes enter the injured tissue in response to local milieu & gets differentiate into macrophages. Macrophages act as master effector cells in tissue repair & show both versatility & plasticity. They reach peak wound infilteration 7days post injury in humans. Macrophages can also engulf the cell debris or pathogens & also exhibit morphological changes in response to cytokines. Later stage inflammation can be characterized by a transition to alternative activation through neo differentiation of newly recruited monocytes along with switching of existing macrophages insitu to an anti inflammatory phenotype. Alternatively activated macrophages express proresolutory cytokines & also arginase is aslo the main factor of repairing of wound. Anti-inflammatory macrophages also release a number of growth factors which facilitates fibroplsia, angiogenesis and re-epthelization .[22-26]

3. Proliferation:

The proliferative phase of healing causes the activation of keratinocytes, macrophages and endothelial cells for performing wound closure, matrix deposition and angiogenesis. At the time of 12 h post injury, keratinocytes gets activated by changes in mechanical tension, electrical gradients due to exposure to H_2O_2, pathogens, growth factors and cytokines. This activation of keratinocytes at the wound edge causes partial epithelial mesenchymal transition, where they form more invasive and migratory phenotype .[27,28]

This phase starts within 48 hours of injury. It mainly consist of a series of fewer events namely angiogenesis, formation of granular tissues, wound contraction and epithelialization. In first event (angiogenesis) new blood vessel are formed and angioblasts grow outward into the affected area and join with other buds to form new capillaries .[29,30] This process causes the transportation of nutrition to affected area and side by side removal of waste products. As the time passes these buds grows well and aid in providing the healthy wound bed of pink to rosy red color. After angiogenesis matrix metalloproteases which are formed during healing process breakdown the debris which is collected during inflammation phase. Then fibroblasts convert into myofibroblasts which decreases the size of wound.[31,32]

4. Remodelling:

Remodelling is the final phase of the healing process which began about 21 days of post injury and lasts for 1 year or 2 years or sometimes more than 2 years depending upon the severity of wound.

In remodeling phase granulation tissue matures into scar with reduction in the number of capillaries via aggregation into larger vessels, decrease in the amount of glycosaminoglycans and the water associated with the glycosaminoglycans (GAGs) and proteoglycans .[33] This process also involves the increase in tissue tensile strength. First of all type III collagen was synthesized at high levels, which was then replaced by type I collagen known as the dominant fibrillar collagen in skin. Remodelling of the extracellular matrix proteins occurs through the actions of matrix metallioproteinases(MMP) and serine proteinases enzymes. Specific MMP proteases such as collagenases, the gelatinases and the stromelysins are necessary for wound healing. The healed tissue is not so much strong as that of normal tissue because of less tensile strength. But as the time progresses for several months or more, the collagen level in the repaired tissue gets slowly increased the tensile strength to a maximum of about 80% of normal tissue .[34,35]

Indigenous Plants as Wound Healers

Centella asiatica urban (Gotu Kala)

It is a tropical medicinal plant belongs to family *Apiaceae* which can be commonly seen along the banks of rivers, streams and ponds. It is a culinary vegetable as well as medicinal plant. .[36]

Pharmacological Impacts: Anticancer, Antiulcer, wound healing, anti-inflammatory, Memory booster and antioxidants. Centella asiatica herbal tea possesses excellent antioxidant property .[37]

Centella asiatica act as wound healer by promoting the fibroblast proliferation, stimulating the collagen deposition as well as collagen remodeling. It also improves the tensile strength of newly formed skin and also inhibiting the inflammatory phase of scars and keloids .[38,39]

Bryophyllum Pinnatum Kurtz

It is a perennial herb grows belongs to family *Crassulaceae and grows* all over India especially in hot and moist climates.

Pharmacological Impacts: Astringent, anti-allergic, antihypertensive, antiemetic, carminative, antiulcer and anti-inflammatory.

Its wound healing activity is due to the high saponin content. Saponin aid in precipitation and coagulation of red blood cells thereby stop the bleeding. It also contain tannins which stimulate healing of wounds.[40,41.42]

Jatropha Curcas Linn.

It is a multifunctional plant belongs to family *Euphorbiaceae* which is a rich source of phenolic compounds, flavonoids, saponin and alkaloids.

Pharmacological Impacts: Anticancer, Anti inflammatory, antioxidants and anticancer.

Its wound healing activity is due to its high saponin content. Saponins aid in precipitation and coagulation of red blood cells thereby stop bleeding. It also contain tannins which stimulates the haeling of wounds .[43]

Lantana Camara L.

It is a perennial shrub belongs to family *Verbenaceae.*

Its wound healing action is processed by enhanced fibroblast proliferation, collagen regeneration and increased wound contraction ability .[44]

Pharmacological Impacts: Antipyretic, antimicrobial, antimutagenic, fungicidal and insecticidal.

Its wound healing action is assess by increased rate of epitheliazation, increased content of hydroxyproline and also the increase collagen production .[45]

Lawsonia Innermis inn.

It is multibranched deciduous shrub effectively use in treatment of headache, dysuria, herpes infection, syphilitic, dysentery, gonorrhea, smallpox etc .[46]

Pharmacological Impacts: It is very popular for its hypoglycemic activity, antioxidant activity, wound healing activity, anticancer and hepatoprotective activity.

It shows the excellent wound healing property by producing thick keratinization, proliferation of epithelial layer and formation of new blood vessels. It also act by induction of large amount of collagen which are responsible for providing the strength to tissue thereby help in hemostasis and thereafter epithelization occurs .[47,48]

Aloe vera

It is a plant which is stems less or very short stemmed, belongs to Liliaceae Family.

Its leaves are green to grey green, thick and fleshy .[49]

Pharmacology Impacts: The Bioactive compounds of aloe vera is very effective in various treatments such as allergic conditions, diabetes, dysentery, ulcer, skin diseases etc

Its wound healing property is due to the presence of a compound glucomannan which contains high percentage of mannose, a polysacchardides. This glucomannan stimulates the production, secretion of collagen and transverse connections among collagen bands, results in accelerate the wound healing process. Its wound healing property is also due to the presence of Vitamin E, C and different amino acids. Vitamin C increases the collagen level whereas Vitamin E acts as strong antioxidant. It increases the tensile strength of wound by proliferation of cells .[50-52]

Ocimum sanctum

It is commonly known as holy basil, Tulsi which is widely spread throughout India. It is a small herb around 18 inch tall which grows into low bush.[53]

Pharmacology Impacts: Different parts of Ocimum sanctum such as roots, stem, leaves, stem, flower etc. used mainly for their analgesic, antimicrobial, anti inflammatory and immunostimulatory properties. Tusli extract is very beneficial in common colds, heart disease and inflammation .[54]

It is the main constituent of various herbal formulations such as anistress, antihypertensive, antiemetic, anticancer, antiasthamatic etc.


It also possesses wound healing property. It increases the rate of epithelizaton and wound contraction. It contains fixed oil and linolenic acid which have the ability to block cyclooxygenase and lipoxgenase pathways of arachiodonic acid metabolism and thereby possesses anti inflammatory property .[55]

Table 1: Chemical Constituents Present in Indigenous plants showing wound healing property

Plant	**Chemical constituents**	
Centella Asiatica[37]	Glycosides	Asiaticosside, madecassoside, madecassic acid
	Triterpenic acid	Asiatic acid, madasiatic acid, brahmic acid, thankunic acid, terminolic acid.
	Phytosterols	Stigmasterols, Campesterols, Beta- sitosterols.
	Other constituents	Glutamic acid, alanine, glycine, aspartic acid, glutamine acid.
Bryophyllum Pinnatum Kurtz [41,42]	Triterpenoids and Steroids	Bryophollenone, taraxerol, pseudo taraxasterol, friedelin, glutinol, bryophyllol, bryophynol, peposterol, codisterol, 22-dihydrobrassicasterol
	Phenols, Flavonoid	Astragalin, quercetin, Kaemferol, luteolin, O-β-D-glucopyranoside
	Fatty acids, Minerals and Others	Palmitic acid, stearic acid, oxalic acid, citric acid, malic acid, ascorbic acid, riboflavin, thiamine, niacin, glycine, phenylalanine, glucose, galactose.
Jatropha Curcas Linn. [43]	Fatty acids	Stearic acid, arachidic acid, oleic acid, linoleic acid, palmitic acid.
Lantana Camara L. [45]	Triterpenoids	Camaryolic acid, methylcamaralate, camangeloyl acid, camarinin.
	Flavonoids	Linaroside and Lantanoside
	Pentacyclic Triterpenes	Lantadene A,Lantadene Band icterogenin
Lawsonia Inermis [47,48]	Flavonoids	Apigenin, Pectolinarigenin, Pectolinarin, Luteolin
	Sterols	Lawsaritol (24β-ethycholest-4-en-3β-ol), Stigmasterol and β-sitosterol

	Terpenoids	Hennadiol, botulin, betulinic acid, lawnermis acid.
	Alkaloids	Harmine, Harmaline
	Coumarins	Lacoumarin (5-allyoxy-7-hydroxycoumarin)
Aloe vera[50,51]	Anthraquinones	Barbolin, Isobarbolin, Chromones, Anthracin-C-glycosides.
	Sugars	Glucose, Fructose, Polymannose, glocomannose.
	Minerals	Sodium, Calcium, Zinc, Chromium, Maganese and copper.
	Enzymes	Amylases, Lipases, Alkaline Phosphases, Catalases and peroxidases.
	Other constituents	Amino acids, sterols and salicylic acid
	Harmones	Auxins and gibberellins.
	Vitamins	Vitamin A,C, E,B12 and folic acid.
Ocimum Sanctum[55]	Flavonoids	Quercetin, kaemferol, genistein
	Vitamins	Vitamin A,C, E and K.
	Enzymes	Glucose-6- Phospahe, glutathione reductase, glutathiones peroxidase.
	Phenoilc Acids	Hydroxy cinnamic acids, Hydroxy Benzoic acids.
	Minerals	Zn and Se

Conflict of Interest:

The authors declare no conflict of interest.

Conclusion:

Wounds are of various aetiology and different classification. Wounds are the major cause of deformity and even death. Severity of wound depends upon different factors such as age, stress, chronic disease, infection etc. Immediately after wound, healing mechanism starts which is further facilitated by combination of series of steps: Hemostasis, inflammation, proliferation and remodeling. Plants have huge potential in wound healing care as there is a possibility to produce different topical formulations using various plants parts. In India traditional medical system is very popular since ancient time but with time this traditional system needs some advancement. In this article various indigenous plants which are responsible for wound healing are discussed. Combination of traditional and modern knowledge seems to be the best approach to formulate novel therapeutic herbal formulation for wound healing.

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