ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Ancient and Modern View of Wound Healing: Therapeutic Treatments

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INTRODUCTION

Medicinal plants are a source of great economic value in the Indian subcontinent. Nature has best owed on us a very rich botanical wealth and a large number of diverse types of plants grow in different parts of the country. India is rich in all the 3 levels of biodiversity, namely species diversity, genetic diversity and habitat diversity. In India thousands of species are known to have medicinal value and the use of different parts of several medicinal plants to cure specific ailments has been in vogue since ancient times. Herbal medicine is still the mainstay of about 75-80% of the whole population, mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and fewer side effects. However, the last few years have seen a major increase in their use in the developed world [1]. In developed countries, there is a growing interest in the use of medicinal plants for treating health conditions. However, information is lacking about mechanisms of action and possible differences between related species of plants [2].

In modern western medicine, approximately 50 % of drugs are in clinical use are derived from natural sources and these half are plant based. It recognized and considered to be much safe than the synthetic drugs and price wise within the search of common man. Indigenous drugs can definitely open up new vistas in therapy and purified natural compounds may serve as template for synthesis of new generation drugs which in turn may have low toxicity and better therapeutic index [3]. Chemical medicines indeed have a more powerful effect than medicinal herbs, although they present a higher degree of side effects and risks. On the other hand, plants act on the body by regulating and balancing its vital processes, rather than stopping or combating certain symptoms. Herbal medicines appear relatively safe, but there is limited human research or prospective data concerning adverse effects and herbal-drug interactions. They are generally less potent than their pure drug relatives because they contain a mixture of many chemicals in small quantities. Even so, herbal products are not free of risk but, the recent popularity of herbal medicines means that many patients need reliable information on using these substances appropriately. Most botanical products, vitamins, minerals, amino acids and mammalian tissue abstracts are currently regulated only under the federal dietary supplement Health& Education act of 1994. This act limits the FDA's authority to require proof of efficacy, safety and quality before these products are sold commercially [4].

Ancient and modern view of wound healing

Ayurveda is composed of several hypotheses based on observations, speculations, inferences, generalizations and idealism. It is very rich in concepts, without any rationale for their origin and these have not been proved by rigorous scientific experimentation [5]. Ayurveda like the Hindu religion developed in India gradually over several thousands of years. The Indus Valley civilization with its city-states like Harappa and Mohanjodaro is believed to have originated between 5000-3000 BC. These original dark skinned people were called Dravidians, had writing of their own and constructed magnificent public baths. Around 3000-2500 BC, they were overrun by lighter skinned Aryans, who came from Central Asia (Iran). Their language Sanskrit, the language of the elite, evolved in India and is considered as the mother of Indo-European languages. With the Aryans starts the Vedic Period. The Vedas (Veda = wisdom) comprise four sacred books in Sanskrit, which originated due to divine inspiration. Originally the four Vedas were transmitted by the word of mouth from teachers to students. The written forms of Vedas appeared probably sometime between 2500-1500 BC. The oldest of these, Rigveda mentions drugs and diseases. Atharva Veda deals with guiding principles for preservation of health and medicinal effects of health. The Hindu priests considered life as an illusion, a very small step to reincarnation and nirvana. Materialistic things like record keeping, history, and biographies were part of human vanity and their destructions happened in total indifference [6]. Rig Veda mentions that medicine men with pockets full of medicinal herbs, accompanied moving Aryans tribes. They operated on the wounded, took the arrows out of the flesh. They amputated the seriously wounded and infected, treated the stump and made artificial eyes and prosthesis. Soma was used to control pain. Snakebites, a common and frequent occurrence during that period were treated. The opening of the bladder with a sharp instrument is mentioned to overcome blocked urinary canal due to kidney stones [7].

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ISSN: 0975-8585

The human body like everything else in the Universe is composed of five elements earth, fire, air, water and ether (space). All human beings have mind, body, senses and soul. The five human sense organs ears, nose, eyes, skin and tongue help us in our perceptions. All living matter has the three doshas: vata, pitta and kapha. These doshas arise out of the five elements and regulate all physiological and psychological process in the living organism [8].

According to ayurveda, Vrana (wounds or ulcers) is the discontinuation of lining membrane that after healing leaves a scar for life closely resembling the modern definition. Similarly, inflammation is considered to be an early phase in the pathogenesis of wounds termed Vranashotha. Anything that brings sadness and grief to humans is defined as disease. Any imbalance in the three doshas results in diseases, which can be recognized by a variety of signs and symptoms. Vata- controls the nervous system, respiration and elimination. Pitta- governs digestion, catabolism, metabolism and perception. Kapha- is responsible for biological strength, body structure and resistance. Different types of wounds as mentioned in Ayurveda may be endogenous in origin due to a defect in human functional units, such as Vata (nerve impulses), Pitta (enzymes and hormones), and Kapha (body fluids), or exogenous due to trauma, such as Chinna (cut wound), Bhinna (perforated wound), Viddha (punctured wound), Kshata (lacerated wound), Picchita (contusion), and Ghrista (abrasion wound) [9].

Pathology of wound in modern views

Wound healing is a complex phenomenon, involving a number of well-orchestrated processes, including regeneration of parenchyma cells, migration and proliferation of both parenchymal and connective tissue cells, synthesis of ECM (extracellular matrix) proteins, remodeling of C.T.and parenchymatous components and collagenisation and acquisition of wound strength [10].

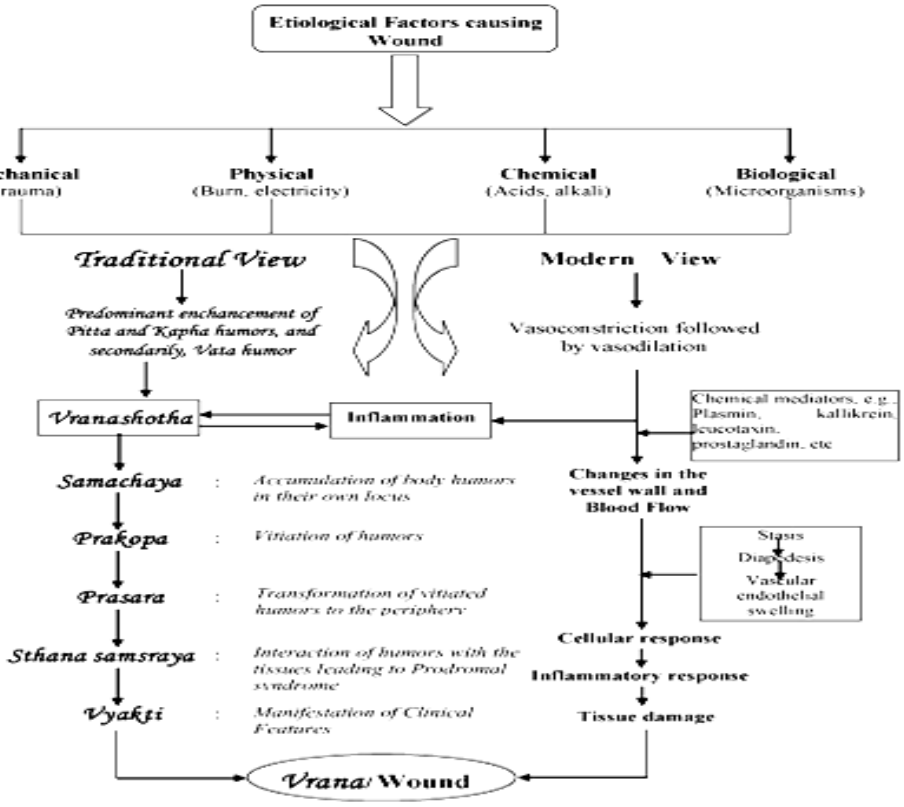

Fig 1: Comparitive representation of pathogenesis of wound repair in Ayurveda and Modern days

Based on the nature and depth wounds can be classified as:

(a) Closed wounds: i.e. contusions, abrasions, and hematoma
(b) Open wounds: i.e. incised, lacerated, penetrating and crushed

Depending on the intensity of the wound they can be termed as:

ISSN: 0975-8585

(a) simple wound : here the damage is only to the skin.
(b) Complex wound: the wound involves the underlying tissues , tendons etc.

General procedure for wound repair

Wound healing is essentially a survival mechanism and represents an attempt to maintain the normal anatomical structure and function.

Wound repair involves two distinct processes i.e.

1) Regeneration of the injured tissues by parenchymal cell, which includes cell migration and cell multiplication.
2) Wound contraction and Replacement of connective tissue.

The healing wound is a dynamic and changing process, which consists of inflammation (Inflammatory phase 0-5 days) which starts at the moment of injury, this is followed by stage of fibroplasias (proliferative phase 3-14 days) which is followed by tissue remodeling (maturation phase day7-1year) and scar formation, which is the final product of healing process. Collagen is a major protein of the matrix and contributes to wound healing. Breakdown of collagen leads to liberation of free hydroxyproline [11].

HEALING OF WOUND CAN OCCUR BY:

First or Primary Intention

This is seen when the wound is a clean incised wound. Healing proceeds rapidly with early closure of wound. There are several overlapping stages in the repair process.

Inflammation: the cut surfaces become inflamed and blood clot and cell debris fill the gap between them in the first few hours. Phagocytes and fibroblasts migrate in to the blood clot:

- Phagocytes begin to remove the clot and cell debris stimulating fibroblast activity
- Fibroblasts secrete collagen fibres which begin to bind the surface together.

Proliferation: there is proliferation of epithelial cells across the wound, through the clot. The epidermis meets and grows upwards until the full thickness is restored. The clot above the new tissue becomes the scab and separates after 3 to 10 days. *Granulation tissue,* consisting of new capillary buds, phagocytes and fibroblasts, develops, invading the clot and restoring the blood supply to the wound. Fibroblasts continue to secrete collagen fibres as the clot and any bacteria removed by phagocytosis

Maturation: The granulation tissue is replaced by fibrous scar tissue. Rearrangement of collagen fibres occurs and the strength of the wound increases. In time the scar becomes less vascular, appearing after a few months as a fine line. The channels left when stitches are removed heal by the same process.

Secondary intention

This is in the case where the wound edges are separate and there is tissue loss and sometimes the wound may be infected. Rapid closure of the wound is not possible
Therefore this leads to an ugly scar and sometimes may cause limitation of movement.

Inflammation: This develops on the surface of the healthy tissue and separation of necrotic tissue begins, due mainly to the action of phagocytes in the inflammatory exudate.

Proliferation: This begins as granulation tissue, consisting of capillary buds, phagocytes and fibroblasts, develops at the base of the cavity. It grows toward the surface, probably stimulated by macrophages. Phagocytes in the plentiful blood supply tend to prevent infection of the wound by ingestion of bacteria after separation of the slough. Some fibroblasts in the wound develop a limited ability to contract, reducing the size of the wound and healing time. When granulation tissue reaches the level of the dermis, epithelial cells at the edges proliferate and towards centre.

Maturation: This occurs as scar tissue replaces granulation tissue, usually over several months until the full thickness of the skin is restored. The fibrous scar tissue is shiny and does not contain sweat glands, hair follicles or sebaceous glands [12].

Table 1: Indian plants with wound healing activity with their models: [13-65]

SL.NO	PLANT NAME	PART AND EXTRACT USED	MODEL STUDIED	REFERNCES
1	Ageratum conyzoides	Root, alcohol	Excision wound model	[13]
2	Acalypha langiana	Leaf ,Aqueous	Excision	[14]
3	Andrographis paniculata	Leaf, alcohol, pet ether& aqueous	Excision, incision, dead space	[15]
4	Butea monosperma	Bark,alcohol	Excision	[16]

5	Bryophyllum pinnatum	Leaf, alcohol	Excision	[17]
6	Calotropis gigantea	Latex	Excision and incision	[18]
7	Centella asiatica	Plant	Excision	[19]
8	Colutea cilicia	Fruit &leaf, aqueous	Excision and incision	[20]
9	Crotalaria verrucosain	Aqueous	Excision, incision , dead space	[21]
10	Colebrookea oppositifola	Leaf, alcohol	Excision and incision	[22]
11	Cordia dichotoma	Fruit, alcohol	Excision, incision ,dead space	[23]
12	Datura alba	Leaf, alcohol	Burn wound	[24]
13	Dissotis theifolia	Stem, methanol	Excision model	[25]
14	Elaeis guineensis	Leaf, methanol	Excision model	[26]
15	Euphorbia heterophylla	Leaf ,ethanol	Excision wound model	[27]
16	*Eucalyptus globulus*	Leaf, ethanol	Excision , incision ,dead space	[28]
17	Euphorbia neriifolia	Latex, aqueous	Excision	[29]
18	Echinops echinatus	Root, petroleum ether, chloroform, ethanol and distilled water	Excision, incision, dead space	[30]
19	Elephantopus scaber	Whole plant, ethanol& aqueous	Excision, incision, dead space	[31]
20	Ficus religiosa	Leaf, hydro alcohol	Excision and incision	[32]
21	Flaveria trinerva	Methanol	Excision and incision	[33]
22	Ficus deltoidea	Whole plant, aqueous	Excision model	[34]
23	Glycyrrhiza glabra	Root, ethanol	Excision	[35]
24	Gentiana lutea	Rhizomes, alcohol and petroleum ether	Excision, incision, dead space	[36]
25	Glycosmis pentaphylla	Leaf, methanol	Excision	[37]
26	Hemigraphis colorata	Leaf paste	Excision,	[38]
27	Hippophae rhamnoides	Leaf, aqueous	Excision	[39]
28	Heliotropium indicum	Whole plant , ethanol	Excision and incision	[40]
29	Indigofera enneaphylla	Aerial parts, alcoholic	Excision and incision	[41]
30	Ixora coccinea	Flower, alcohol	Dead space	[42]
31	Jatropha curcas	Bark,	Excision, incision, dead space	[43]
32	Kalanchoe pinnata	Leaf, ethanol	Excision wound model	[44]
33	Lantana camara	Leaf, ethanolic extract	Burn wound	[45]
34	Limonia acidissima	Fruit pulp, hexane	Excision, incision, dead space	[46]
35	Laura nobilis	Aqueous	Excision and incision model	[47]
36	Lawsonia alba	Leaf	Excision and incision	[48]
37	Leucas lavandulaefolia	Maethanol	Excision and incision	[49]
38	Momardica balsamina	Fruit pulp, hexane & methanol	Excision	[50]
39	Moringa olifera	Leaf, aqueous	Excision, incision, dead space	[51]
40	Morinda citrifolia	Leaf, ethanol	Excision, dead space wound	[52]
41	Madhuca longifera	Leaf, chloroform and ether	Excision and incision wound model	[53]
42	Napoleona imperialis	Leaf, methanol	Excision model	[54]
43	Nelumbo nucifera	Rhizomes, methanol	Excision, incision, dead space	[55]
44	Ocimum sanctum	Leaves, alcoholic and aqueous	Excision, incision, dead space	[56]
45	Plantain banana	Fruit, aqueous & methanol	Excision, incision, dead space	[57]
46	Quercus infectoria	Leaf,ethanol	Excision, incision, dead space	[58]
47	Rubia cardifolia	Roots, alcoholic extract	Excision wound model	[59]
48	Rubus sanctus	n-hexane, chloroform, ethyl acetate and methanol	Excision and incision	[60]
49	Solanu xanthocarpum	Fruit, methanol	Excision and incision	[61]
50	Sambucus ebulus	Leaf, methanol	Excision and incision	[62]
51	Thespesia populnea	Fruit, aqueous	Excision and incision	[63]
52	Vinca rosea	Leaf,ethanol	Excision model	[64]
53	Wedelia calendulaceae	Aqueous extract	Incision and excision	[65]

Drugs that impair wound healing

A number of drugs ranging from analgesics to chemotherapeutic agents, which have been used in the management of wounds act in different ways.

Steroids are a group of drugs widely used for a number of indications. These would include the various forms of cortisone such as prednisolone and prednisone. Corticosteroids inhibit fibroplasia and the formulation of granulation tissue. Low doses may interfere by causing mild anorexia and high doses have a major effect on wound healing because of their interference with fibroplasia, vascular proliferation and the effect of delaying epithelialisation. They also delay wound contraction and increase the susceptibility to infection.

Anti-cancer drugs are cytotoxic but not cancer cell-specific. There are many different classes but most act on rapidly replicating cancer cells. Specific points about antineoplastics include haematological changes that may affect healing:

- They reduce most red and white blood cells.
- They cause myelosupression and may be neurotoxic (cis-platinum, Vinblastine, Vincristine, Carboplatin, Vindesine and Hexamethylamine.
- Hydroxyurea *(Hydrea)* is also known to be responsible for ulcer development in patients on long term use of the drug or on high doses.
- They damage basal keratinocytes leading to dermal atrophy and causes platelet mediated inflammatory response leading to micro-thrombi formation.

Anti-platelet drugs include aspirin and other NSAIDs. The effect is dose dependant. COX-1 could increase the local ischaemia and hypoxia associated with chronic venous ulcers. There is some evidence that the COX-II inhibitors delay healing. They have been shown to reduce scar formation without disrupting epithelialisation in the early phase of wound healing, and inhibition of angiogenesis. Antibiotics are overused in the treatment of acute and chronic wounds. Antibiotics by their nature kill bacteria but do not improve wound healing. They are an important agent in the treatment of wound infection; however they play no role in a non-infected wound. Penicillin interferes with the tensile strength of the wound by affecting the cross-linking of collagen tetracyclines. Erythromycin demonstrates anti-inflammatory properties through the inhibition of leukocyte chemotaxis. An exception may be doxycycline, a tetracycline antibiotic. Colchicine is used in the treatment of gout. It has a number of negative effects on wounds. It reduces granulocyte migration and cytokine release. Anti-coagulants drugs are used to reduce blood viscosity and include warfarin and heparin. They inhibit proper coagulation and can adversely affect wounds by increasing the risk of haematomas and seroma formation. Vasoconstricting drugs like Adrenaline, nicotine and cocaine can cause tissue hypoxia affecting microcirculation and tissue formation, i.e. some local anaesthetics have vasoconstriction properties and care should be taken if used as a pain reliever (e.g. lignocaine).Immunosuppressants drugs other than corticosteroids show no evidence of significant inhibition of healing. They facilitate healing in wounds related to auto-immune diseases and vasculitis. However, these drugs increase the risk of infection in the patient. There is some evidence that some immunosuppressive drugs improved wound healing.

Drugs that improve healing

Pentoxifylline used to improve healing by changing the flow characteristics of blood by reducing platelet aggregation, leukocyte adhesion and increasing red blood cell membrane flexibility. It has been used to treat PVD – intermittent claudication. Hormones like Oestrogen plays a role in wound healing, particularly in post menopausal women who are known to have reduced dermal collagen and dermal thickness. There are some case studies of the application of topical oestrogen to non healing leg ulcers in post menopausal women that have improved wound healing. Phenytoin, a drug used to treat seizures, when given orally is known to cause gingival hyperplasia. Some studies have been published on the topical application resulting in a decrease in inflammatory response, an increase in collagen synthesis and an increase in new blood vessel formation. Prostacyclin analogues are used in the treatment of intermittent claudication; severe limb ischaemia; prevention of imminent gangrene and to reduce pain; and the clinical symptoms associated with Raynaud's disease. They can be used to promote healing in arterial and vasculitic ulcers. Drugs such as diltiazem and nifedipine are useful in treating vasculitic ulcers. They help improve blood flow to the digits and are helpful in preventing necrosis in the extremities. Vitamin A has been known to stimulate both humeral and cell mediated immune mechanisms. There have been some studies to show that it can reverse the effects of oral corticosteroids in the way they delay wound healing. Vitamin C is one of the most important agents in wound healing. It is involved in the stimulation of fibroplasia. It is required for the hydroxylation of lysine and proline during the pathway in the synthesis of collagen, most critically important for tensile strength of a wound. Vitamin C influences resistance to infection, it is essential for both neutrophil and fibroblast function and it strengthens and promotes new blood vessel formation. Zinc is important to wound healing because of its part in the structural integrity of protein. It is essential for the functioning of at least 200 enzymes in the body and plays a vital role in vitamin A metabolism. It is involved in the cross-bonding of collagen and is known to promote re-epithelialisation. Thus the management of wound healing is a complicated and expensive program.

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