Review Article

Burn wound: Pathophysiology and its management by herbal plants

Abstract

In human body, wound healing is a normal biological phenomenon. Burns may be acute or chronic depending upon the source and its time of exposure. Burn wounds may be superficial, partial or full thickness wounds. When skin comes in contact with higher temperature, protein denaturation takes place due to which the plasma membrane integrity is lost. When skin is burned, a number of inflammatory mediators and releasing agents such as histamine, nitric oxide, oxygen free radicals, eicosanoid products, tumor necrosis factors, and interleukins etc., are released at the site. For wound healing mechanism, the keratinocytes has to move from uninjured site to the burned area. For deeper burns this process takes a long time. By some unknown mechanisms, burn wounds may convert from one form to another form. So burn wound depth must be accurately measured before starting the treatment to prevent the complications. Burns can be induced in experimental animals by using different models. Many treatments such as herbal drugs, topical agents, gene therapy, volume therapy, and rehabilitation can be employed. This review article mainly deals with the theoretical and practical aspects of burn wound healing. Some burn wound healing plants with their chemical constituents, plant part used, uses and animal models are described here.

Key words:
Burn, herbal plants, management, wound healing

Introduction

Any discontinuity or break into the surface of epithelium due to any physical, chemical or biological source is known as wound.[1] A wound is also known as cellular disruption or functional discontinuity of a living tissue. A wound can be open or close depending upon the type of injury. Open wounds are caused by cut or torn. Close wound occurs when a blunt force trauma causes a contusion. There is another type of wound known as burn wound, which is caused by fire, heat, radiations or electricity.[2] There are some phases of wound healing such as inflammation, proliferation, and tissue remodeling.[3] For burn wound healing these phases must take place in an orderly manner and must continue for a specific duration. There are a number of factors that affect wound healing process. These factors can affect the wound healing phases, which lead to impaired tissue repair. Some of these factors are oxygenation, infections, age, stress, diabetes, medications, and smoking etc.[4] Burns are classified on the basis of following characteristics:

1. On the basis of increasing depth[5] or number of skin layers and area of skin effected:[6]
   a. Epidermal wounds
   b. Superficial partial wounds
   c. Deep partial wounds
   d. Full thickness wounds.

2. On the basis of nature of the repair process:[7]
   a. Acute wounds
   b. Chronic wounds.

Pathophysiology

Denaturation of proteins occurs after a prolonged exposure of temperature higher than 40°C, due to which their plasma membrane integrity is lost. When temperature is higher than 60°C, this process speed up and takes only a

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Dhirender Kaushik, Shiwani Kamboj, Pawan Kaushik, Shivkant Sharma, A. C. Rana[1]
Department of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, [1]Rayat College of Pharmacy, Ropar, Punjab, India

Address for correspondence:
Mr. Pawan Kaushik,
Institute of Pharmaceutical Sciences, Kurukshetra University,
Kurukshetra - 136 119, Haryana, India.
E-mail: pwn.kaushik1@gmail.com

second. Higher temperature and prolonged contact cause a more deep burn.[8] The molecular structures get altered and many antigens and immune modulating agents get released, which cause burn shock pathophysiology. These releasing agents include histamine, nitric oxide, oxygen free radicals, eicosanoid products, tumor necrosis factors, and interleukins etc., Histamine is seen only after burn and it is known that in the pathophysiology of burn, histamine get interaction with xanthine oxidase and oxygen radicals.[9]

Burn wound conversion is a process in which one type of wound gets converted into another type of wound by some unknown mechanism. There are three types of zones present in the pathogenesis of burn wound conversion:[10]

1. Zone of coagulation, whose damage is non-recoverable. It is deepest among the three zones
2. Zone of stasis, which is present in the middle
3. Zone of hyperemia.[10]

Zone of coagulation consists of devitalized tissues. Zone of hyperemia is characterized by vasodilation and inflammatory changes without structural damage. Zone of stasis presents a part of vascular stasis and ischemia.[11] Burn wounds of more superficial type can convert into deeper wounds. So burn wound depth must be accurately measured to prevent the effects of burn wound conversion.[12]

Wound Healing Mechanism

Epidermis has the capability to integrate. In case of deep dermal burn wounds, healing is slow because in this case, the keratinocytes has to move to the burn area from an uninjured site.[13] After a major injury due to burn, there is acute influx of inflammatory mediators and growth factors for a long time at the burn wound site. Various types of cells such as platelets, neutrophils, lymphocytes, macrophages, and fibroblasts are involved in burn wounds.[14] Macrophages are also important for wound healing.[4] There are some principle molecular regulators such as vascular epithelial growth factors, platelets derived growth factors, and transdermal growth factor-β (TGF-β), which are involved in evolution of burn wounds. During the initial stage of wound healing, for the activation and proliferation of fibroblasts, TGF-β is a pre-requisite. Prolonged activity of TGF-β leads to wound contraction.[14]

Models for Initiating Burns in Experimental Animals

Superficial partial thickness burn wound model

Remove the hairs from the abdomen of male Wistar rats by applying a depilatory cream and wash-off the remaining hairs with tap water. In this model, a 2 cm × 2 cm and 3 mm thick piece of lint cloth is immersed in boiling water (100°C) and then places it on the right half of each anesthetized animal's ventrum within the boundaries of the rat epigastric flap. Application of the cloth for 4 s causes a superficial partial-thickness burn injury extending to the superficial dermis.[15]

Deep partial-thickness burn wound model

For preparation of rat models with burn wounds, remove hairs from the back of male sprague dawley rats. An aluminum cylinder (3.76 cm in diameter, 3.78 cm in high) heated to 75°C in the attemperator for 1 h is placed onto the right back of anesthetized rats for 10 s to cause deep partial-thickness burn wound sized as 3.5 cm × 3.5 cm. In order to confirm the degree of burn, the wound tissues are used to prepare the pathological sections, which are to be examined by special pathologists.[16]

Full-thickness burn wound model

On the day of wounding, place the female Sprague Dawley rats in a ventral position and immobilize on their abdomen for the surgery. Shave the dorsum of each rat. Immediately before operation, anesthetize rats with an intramuscular injection of 35.0 mg/kg ketamine and 5.0 mg/kg xylazine in the gluteal area. When fully anaesthetized, the shaved areas are cleaned with povidone iodine and alcohol. Isolate the operation site with a sterile towel. Wounds are created by using the sterile technique on the dorsum of each rat using hot metal heated at a temperature of 100°C for 30 s with a burner.[17]

Assessment of Burn Wound Healing

The animals have to be inspected daily and the healing is observed by estimating the parameters such as epithelialization period, wound contraction, and histopathological analysis.[18]

Wound contraction

Wound contraction helps in wound closure and it is expressed as the reduction in percentage of the original wound size beginning from 1st day until complete epithelialization takes place. Epithelialization period is the time in days required for falling of eschar without any residual raw wound. The progressive changes in the wound area are assessed accordingly. The day of wounding is not included. After every 2 days, the size of wound is recorded by tracing on a paper throughout the monitoring period.[19] By transferring the tracings on 1 mm^2 graph sheet, the wound surface area is calculated.[20] Then, the percentage wound contraction is calculated by using the following formula:

% wound closure = ([initial area of wound- nth day area of wound]/initial area of wound) ×100

Therapeutic Strategies and Clinical Treatment

It includes the following:

1. Volume therapy
2. Nutrition and rehabilitation
3. Skin grafting

4. Gene therapy
5. Drug therapy and topical agents
6. Herbal drugs

Volume therapy

It includes lipofilling into scar which improves functions and appearance. When histological examination was performed the new collagen deposition, local hypervascularity, and dermal hyperplasia were observed in the context of new tissues.[21]

Nutrition and rehabilitation

In case of emergency treatment, special attention to the airway for ensuring oxygenation, ventilation and circulation should be given. Renal failure and mortality may increase if there is a delay in fluid re-suscitation. For this purpose, volume restoration formula is given by Parkland, which indicates to give 4 ml of lactated Ringer's solution/kg of body weight per % total body surface area, during the first 24 h.[22]

Skin grafting

Skin grafting provides an immediate barrier to invasion of micro-organisms. For skin graft, a minimal of new tissue synthesis is required.[23] This technique involves the removal of a piece of skin by surgical method after choosing a donor site. Harvesting is also performed in which the skin graft is removed by a dermatome that shaves a piece of skin from the donor site. The piece can be 10/1000 of an inch thick. Then, surgeon places this piece on surgically cleaned wound. The area of graft is not moved for 5 days to help the graft healing. Two type of skin grafting is done:

Temporary skin grafting

It is necessary until a definitive cover is achieved. The use of this type of skin graft was popularized by James Barrette Brown in 1942.

Permanent skin grafting

This type of skin grafting is used to cover the wound permanently. The skin is taken from the body of burnt patient.[24] The cryopreserved cultured epidermal allografts have the following advantages:

1. Frozen stored that can be used anytime in necessity
2. Gives early wound closure
3. Can be applied repeatedly
4. Sheet grafts and meshed grafts can be used for permanent wound closure.[25]

Gene therapy

It is a new technique for wound healing, which involves gene manipulation. Gene transfer is a powerful tool for transferring important proteins at wound environment site.[26] Gene therapy is used to maintain or regulate the amount of growth factors during the wound healing.[27] For the treatment of chronic wounds, gene transfer is a good way.[28]

Drug therapy and topical agents

Wounds are susceptible to bacterial infections. For this reason, drugs such as antibiotics and topical agents are employed for wound healing purpose. Various bacterias such as *Streptococcus faecalis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Clostridium tetani*, *Clostridium perfringens*, *Ecsherichia coli*, *Klebsilla* and *Pseudomonas* etc., are involved in bacterial infection.[29]

1. For treating gram positive bacterial infection: Benzyl penicillin.
2. For entereobacterial infection: Amoxicillin/ampicillin.
3. For entereobacterial with klebsellial infection: Mezlocillin and ozlocillin.
4. For treating gram negative bacterial infection: Gentamycin and tobramycin.
5. For anaerobic bacterial infection: Imidazoles.[29]

The aim of clinical treatment for burn wounds is to provide healing of the wound as soon as possible in order to prevent infections.[30] This topical application helped in improving the patient survival with major burns and minimize the incidence of burn wound sepsis.[31] Silver sulfadiazine (SSD), mafenide cream, and silver nitrate are used as topical agents.[29] SSD is widely used topically and many burn dressings contain SSD.[32] It was introduced by Fox in 1970.[33] It comes in the market as a topical agent in pseudomonal infections of burn, but now it is recognized as a broad spectrum antibacterial agent,[34] antifungal,[35] and antiviral agent.[36]

Herbal drugs

With the aim of finding drugs with maximum therapeutic activity and least toxicity, a number of medicinal plants have been evaluated. Compared to modern drugs, about one-third drugs are for treating skin disorders.[37] Wound healing Ayurvedic drugs of plant origin constitute about 70%, from mineral origin 205 drugs and the remaining 10% are from animal origin, which are used for some other ailments such as vrana (wounds/ulcers), Nadivrana (sinuses), upadamsha (syphilitic ulcers), Vranjakrimi (maggots in wounds), Dustavrana (septic wounds), Vranashotha (inflammatory changes of wounds), Ugravrana (purulative ulcer), Netravrana (hordeolum or stye sepsis), Pramehapidaka (diabetic carbuncle), and Bhagandara (fistula-in-ano) etc.[38] Some herbal plants having wound healing properties are described in Table 1.

Conclusion and Future Perspectives

Burn wounds may cause serious complications if not treated at the right time. So, the factors effecting wound healing should be considered accordingly. Topical agents can be employed to protect wounds from bacterial infections. In case of serious injuries, the effective drug therapy must be taken. A large number of topical agents and antibiotics are

Table 1: Herbal plants having wound healing activity

Plant (family)	Part used	Chemical constituents	Uses	Burn wound models	References
Acalypha indica (Euphorbiaceae)	Leaves	Tanins, saponins, steroids, cardiac glycosides, alkaloids, and phenols	Pneumonia, asthma, rheumatism, contraceptives, wound healing, and antiseptic	Excision and incision wounds	[35,39,40]
Achyranthes aspera (Amaranthaceae)	Leaves	Flavonoids, alkaloids, oleanolic acid and oleanolic acid based saponins	Antimicrobial, larvicidal, antifertility, immunostimulant, hypoglycemic, antioxidant, diuretic, cardiac stimulant, antihypertensive and antipyretic	Excision and incision wounds	[41-43]
Allamanda cathartica (Apocyanaceae)	Leaves	Flavonoids and triterpenoids	Malaria and jaundice	Excision and incision wounds	[44]
Aloe vera (Liliaceae)	Leaves	Anthraquinones, vitamins, enzymes, lignin, saponins, salicylic acid, and amino acids	Cuts, burns, insect stings, bruises, acne, poisoning, welts, skin lesions, sunburns, antiviral, and anti-tumor	Third degree burns	[45-47]
Anacardium occidentale (Anacardiaceae)	Shoots	Polyphenols, tannins, moderate saponins and trace of free reducing sugars	Fever, conserve stomach, anti-inflammatory, and antidiarrheal	Excision wounds	[35,48,49]
Areca catechu (Arecaceae)	Areca powder	Catechin, tannins, gallic acid, arecoline, arecaine, arecaidine, guvacoline, guvacine, and choline	Leg ulcers, extensive burns and healing of donor area in skin graft surgery	Incision, excision and dead space wounds	[41,50,51]
Borassica juncea (Brassicaceae)	Leaves	Flavonoids, tannins, alkaloids, phenolic compounds, volatile oils and terpenoids	Anti-nociceptive, antihyperglyce-mic activity and hematological studies	Excision wounds	[41,52,53]
Bryophyllm calycinum (Crassulaceae)	Leaf	Alkaloids, triterpenes, glycosides, flavonoids, cardienolides, steroids, bufadienolide and lipids	CNS depressant, analgesic, antimicrobial, antiallergic, antitumorous, antiulcerous, antifungal, antiviral, gastroprotective, insecticidal, muscle relaxant and sedative	Not mentioned	[41,54,55]
Calendula officinilis (Asteraceae)	Crushed flowers	Cartenoids, flavonoids, glycosides, steroids, sterols, quinines, volatile oil and amino acids	Analgesic, antidiabetic, anti-inflammatory. gynecological and eye diseases, skin injuries and in some cases of burns	Thermal burns	[41,56-58]
Calotropis gigantean (Asclepiadaceae)	Drops of stem latex	Cardiac glycosides, calotopin, uscharin, calotoxin, calactin, uscharidin, and gigantin	Expectorant, depilatory, anthelmintic, ringworm of the scalp, piles, asthma, dropsy and in painful joint swellings	Excision and incision wounds	[41,59,60]
Carica papaya (caricaceae)	Fruits	Vitamins (B_{12}, A, C), flavonoids, tannins, saponins, glycosides, alkaloids and folic acid	Antimicrobial, anti-inflammatory and antioxidant	Excision and dead space wounds	[61-64]
Centella asiatica (Umbelliferae)	Leaves	Triterpenes, amino acids, fatty acids, sesquiterpenes, alkaloids, sterols, carotenoids, tannin, chlorophyll, and pectin	Wounds healing, mental disorders, atherosclerosis, fungicidal, antibacterial, antioxidant, and anticancer purposes	Incision, excision, and dead space wounds	[65-71]
Cleome viscose (Cleomaceae)	Paste of leaf	Coumarino-lignans, cleomiscosin A, B, C, and D	Anti-inflammatory, antiseptic, malarial fevers, blood diseases, wounds, ulcers, analgesics, antimicrobial and antipyretic	Full thickness excision wounds	[72-75]
Crocus sativus (Iridaceae)	Pollens	Crocetin, crocin, gentiobioside, glucoside, anthocyanins, flavonoids, vitamins (especially riboflavin and thiamine) and amino acids	Aphrodiasic, antispasmodic, expectorant, depression, insomnia, cholera, tonic for heart and nervous system, measles, and jaundice	Second-degree burns	[76-79]
Curcuma longa (Zingiberaceae)	Rhizome	Curcumin, turmeric oil, 1,7-bis, 6-hepta-diene-3, 5-dione, proteins, fats, vitamin A, B, and C	Antibacterial, antifungal, and anti-inflammatory	Partial thickness burns	[41,19,80]

Contd...

Table 1: Contd...

Plant (family)	Part used	Chemical constituents	Uses	Burn wound models	References
Ficus religiosa (Moraceae)	Leaf extract	Tannins, saponins, flavonoids, steroids, terpenoids, and cardiac glycosides	Wound healing, anti-inflammatory, analgesic and anti lipidperoxi-dation activity	Excision and incision wounds	[41,81,82]
Hyptis suaveolens (Lamiaceae)	Leaves	Steroids, alkaloids, carbohydrates, proteins, flavonoids, tannins, and glycosides	Stimulant, carminative, sudorific, galactogogue, parasitic cutaneous disease, anti-inflammatory, and antifertility	Incision, excision and dead space wounds	[72,83]
Kalanchoe pinnata (Crassulaceae)	Leaves	Secondary plant products such as cardiac glycosides and flavonoids	Anti-inflammat-ory, infections, anthelmintic, hepatoprotective, antimicrobial, antinociceptive, rheumatism, and immune suppressant	Excision wounds	[84-86]
Laurus nobilis (Lauraceae)	Leaves	Alkaloids and mono-terpenoids	Astringent, carminative, diaphoretic, digestive, diuretic, Emetic, stomachic and for healing purpose	Excision and incision wounds	[44]
Morinda pubescens (Rubiaceae)	Fruit extract	Phenols and alkaloids	Antimicrobial activity, wound healing, arthritis, diabetes, muscle aches, menstrual difficulties, heart disease, cancer and gastric ulcers	Excision wounds	[35,87,88]
Nigella sativa (Ranunculaceae)	Seeds	Fixed oil, sugars, resins, alkaloids, flavonoids, sterols, tannins, saponins and essential oils	Asthma, hypertension, diabetes, inflammation, bronchitis, headache, eczema, fever, dizziness, gastro intestinal disturbances and for wounds	Full-thickness and second-degree burns	[89-92]
Pongamia pinnata (Fabaceae)	Seed oil	Carbohydrates, alkaloids, flavonoids, glycosides, steroids, tannins, and saponins	In enteric infections, anthelmintic, abdominal enlargement, diseases of the eye, skin and vagina, itch, piles, tumors, ulcers, and wounds	Not mentioned	[93,94,35]
Rubia cordifolia Linn.(Rubiaceae)	Roots	Anthraquinone glycosides, saponins, tannins and phytosterols	Blood purifier, immunomodulator, anti-inflamematory and antioxidant	Excision wounds	[41,95-98]
Scoparia dulcis (Scrophulariaceae)	Root extract	Tannins, scoparic acid A and B, scopadulin, alkaloids, saponins, flavanoids and amino acids	Stomach troubles, HT, diabetics, bronchitis, analgesic and antipyretic	Incision, excision and dead space wounds	[35,99,100]
Terminalia arjuna (Combertaceae)	Stem bark	Tannins, arjunolic acid, arjunin, tri-terpinoids and flavonoids	Antioxidant properties, cardiotonic, diuretic, cardioprotective, hypotensive and antibacterial	Incision and excision wounds	[101,102]
Terminalia chebula (Combertaceae)	Fruits	Tannins, tannic acid, gallic acid, ellagic acid, glucose and sorbitol	Astringent, antiseptic, rejuvenative, tonic, anthelm-intic, laxative, piles and stomatitis	Excision and incision wounds	[41]
Thespesia populnea (Malvaceae)	Leaves	Quinones, sesquiterpene quininones, mansonone (D, E, F, G, M) and thespisone	Insect bite, warts, scabies, gonorrhea, migraine, headache, fistula, psoriasis, and laxative	Open wounds and reconstructed incision wounds	[41,103,104]
Tridax procumbens (Asteraceae)	Whole plant	Flavonoids, alkaloids, carotenoids, flavonoids (catechins and flavones), saponins, and tannins	Antibacterial, immunomodulatory, anti-inflammatory, and antimicrobial activities	Excision wound model	[41,105]
Vernonia arborea Buch (Asteraceae)	Aqueous and metha-nolic extracts of bark	Flavonoids, tannins, saponins, glycosides, triterpinoids, and sesqui-terpines	Wound healing, jaundice pain and rheumatic fever	Excision, incision and dead space wounds	[106,107]

CNS – Central nervous system; HT – Hypertension

present in the market for their wound healing properties. Many complications may be there due to genes involved in burn injury. So in case of burn injury, genetic dissection should be carried out on the global context. *Pseudomonas* bacteria's are largely involved in acute and chronic nosocomial infections. Understanding the genetic programs underlying infection is necessary for the treatment of burn wound infections.

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