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"PHRAGMITES *KARKA EXTRACT*" TO TREAT WOUNDS HEALING REVIEW

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ABSTRACT:

This complex network has been organized in three sequential and overlapping steps. The first step of the inflammatory phase is an immediate response to injury; primary sensory neurons sense injury and send danger signals to the brain, to stop bleeding and start inflammation. The following target of the inflammatory phase, led by the peripheral blood mononuclear cells, is to eliminate the pathogens and clean the wound. Once this is completed, the inflammatory phase is resolved and homeostasis is restored. Phytochemical studies carried out on the Phragmites karka plants have demonstrated a wide variety of the biomolecules present in the plants which may be responsible for their use in traditional medicine. Through various bioassays, different biologically active compounds were identified. Since bioautography was used to monitor the wound healing activity of the extract, this shows that bioassays can be used as a guide during isolation. Although a p-coumaric acid compound isolated in this study was not identified due to a contaminant, this study shows that there is a biologically active compound belonging to the phenolic derivative. Which may be unique Further work is required to identify the specific phenolic and to determine if it is indeed unique and a good candidate for the treatment of infected wounds.

Keywords: Skin infection, Wound healing, Dermal Wound Repair, Hemostasis, Ischemic mechanisms.

INTRODUCTION

The skin is the largest organ of the body. The skin and its derivatives (hair, nails, sweat and oil glands) make up the integumentary system. One of the main functions of the skin is protection. It protects the body from external factors such as bacteria, chemicals, and temperature. The skin contains secretions that can kill bacteria and the pigment melanin provides a chemical pigment defense against ultraviolet light that can damage skin cells. The primary function of the skin is to serve as a protective barrier against the environment.[1] Loss of the integrity of large portions of this barrier -as a result of injury or disease- may lead to major complications or even death. The ability of the skin to repair any wound is therefore a main skin "duty" in order to keep a proper homeostasis. Wound healing represents therefore a major organ functional ability of the skin in humans as well as in mammals.[2] Skin repair is a multistep complex biological process that requires a close interaction of multiple cell types in a highly coordinated program. It involves hemostasis, inflammation, angiogenesis, migration and proliferation of progenitor cells, as well as production and remodelling of the extracellular matrix (ECM). As a peculiar example recent studies have allowed a better understanding of the intervention of distant stem cells derived from distant tissues such as bone marrow in order to allow cutaneous healing. Abnormalities of wound healing are very common.[3] Skin wound healing is a fascinating mechanism and represents an evolutionary advantage not only for mammals. Due to its vital functions as a physical, chemical and bacterial barrier, skin wound healing is an important step for survival finalizing in wound closure.[4] Despite a great body of literature with regard to wound healing mechanisms, there are still many questions. Physiological regulation of skin wound healing is a complex process, which is dependent on many cell types and mediators interacting in a highly sophisticated temporal sequence. Although some interactions during the healing process are crucial, redundancy is high and other cells or mediators can adopt functions or signaling without major complications. The purpose of the following update on skin wound healing is to focus on the different phases briefing the reader on actual knowledge and new insights. At the end, this update will briefly focus on 3 topics of high interest, i.e., scarring, tissue engineering in skin wound repair, and plasma application in skin wound healing. One of the main reasons for skin wound healing seems to be the restoration of the barrier function in order to prevent further damage or infection. This requires the distinct interplay and crosstalk of a multitude of cells and mediators from the very onset.[5] However, prolonged wound healing phases or excessive responses of the organism to the injury impede normal wound healing and might be associated with scarring. In this context, the transition from the inflammatory to the proliferative stage of wound repair is a topic of intensive current research. First of all, skin cells are exposed to acute phase signals such as damage- associated molecular patterns or pathogen-specific molecular patterns, which are recognized on their parts by toll-like receptors initiating and perpetuating inflammation. Leukocytes, especially neutrophil granulocytes, transmigrate alongside an increasing gradient of chemokines until arrival at the site of injury. In addition, neutrophils secrete many pro-inflammatory cytokines and thereby amplify the inflammatory response. The influence of

cytokines and chemokines in wound repair has been extensively reviewed elsewhere. Activated regulatory T cells are part of the adaptive immunesystem. Aside from leukocytes, regulatory T cells are able to regulate tissue inflammation via the attenuation of the interferon-γ production and the accumulation of pro-inflammatory macrophages. It is assumed that this effect is mediated by the epidermal growth factor receptor pathway, which is coopted for the facilitation of skin wound repair.

Skin Wound Healing

Normal wound healing is a dynamic and complex process involving a series of co-ordinated 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 andconnective tissue and collagen deposition. Despite the fact that the processes of repair begin immediately after an injury in all tissues and that all wounds go through similar phases of healing, specialized tissues such as liver, skeletal tissue and the eye have distinctive forms of regeneration and repair and follow separate pathways. Cutaneous wounds close by epithelial resurfacing and wound contraction.[6] Dependent on the species, one or the other process dominates the progress of wound repair. For example, rodents heal mainly by contraction, whereas in humans, reepithelialization accounts for up to 80% of wound closure. Skin wound epithelialization is reliant on the wound specifics such as the location, the depth, the size, microbial contamination as well as patient-related health conditions, genetics and epigenetics. Partial thickness wounds that involve the epidermis and partially the dermis usually heal by primary intention with intact skin appendages, i.e., hair, nails, and sebaceous and sweat glands.In contrast, full-thickness wounds are characterized by complete destruction of the epidermis and dermis as well as deeper structures. Repair of tissue loss is initiated by the formation of granulation tissue that replaces the defect before epithelial covering can occur. This form of wound repair is called healing by secondary intention.[7] Healing by third intention is related to complex cases, e.g., septic conditions when wounds areleft intentionally but temporarily open in order to be closed after regression of the highly inflammatory and often life-threatening situation. When the patient is stable and wounds are well-conditioned, wound closure is accomplished by sutures or by plastic surgical reconstruction.[8]

Processes and Characteristics of Dermal Wound Repair

Wound repair is a normal and complex biological process in the human body occurring in all tissues and organs. It depends on the type of injury, the underlying disease,systemic mediators, and local wound factors. Dermal wound repair is ahighly dynamic process involving interaction between epidermal and dermal cells, controlled angiogenesis, the extracellular matrix, and plasma-derived proteins (coordinated by cytokinesand growth factors) The many biological mechanisms overlapping during the progression of the skin wound repair reaction can describe the loss of consensus on the number of phases involved in this reaction. However, all researchers maintain that these phases are interrelated, and suggest that the wound repair

process is a continuum.[9]Theimmediate aim of repair is to achieve tissue homeostasis and integrity in order to accomplish this aim as the repair process consisting of three phases: inflammation, proliferation, and tissue remodeling. These phases and their physiological functions occur in a regulated and precise manner since discontinuities, aberrancies, or lengthening in the process can lead to delayed wound repair or a non-repair chronic wound.[10]

Inflammation

Inflammation occurs immediately after tissue damage, and the key aim of this phase is to prevent infection. Since the mechanical barrier as the frontline against exceeding microorganisms is no longer intact. The inflammatory phase is separated vascular response (hemostasis) and cellular response (inflammation).[11] The vascular response consists of platelet activation leading to the formation of a fibrin clot and repair of the vascular system of the injured tissue. The fibrin clot is made of platelets, collagen, fibronectin, and thrombin. The fibrin clot provides a scaffold for using monocytes, neutrophils, endothelial cells, and fibroblasts. The inflammatory response begins with the release of cytokines such as transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and interleukin 8 (IL8/CXCL-8) from the fibrin clot and directly from the damaged tissue. These work as strong chemotactic signals to recruit neutrophils to the wound. Neutrophils have various mechanisms for removing bacteria, foreign particles, and damaged tissue. They have the phagocytotic activity foringesting and destroying foreign particles.[12]They can also degranulate and release various toxic substances (i.e., eicosanoids, cationic peptides, and proteinases, i.e., elastase, proteinase 3, cathepsin G, and an urokinase-type plasminogen activator), which will remove bacteria and dead host tissue. Oxygen-derived free radical species have bactericidal properties produced as a by-product of neutrophil activity. Approximately 3days after injury, neutrophils decrease innumber and are replaced with macrophages. They have many tasks such as promotion and resolution of inflammation, host defense, removal of apoptotic cells, and support of cell proliferation and tissue restoration.[13]

Proliferation

The proliferative stage of healing arises approximately 2–10days after wounding and is determined through interaction between different cell types. Initially, keratinocytes are called to the injured dermis and then the angiogenesis occurs. During angiogenesis, capillary sprouts accompanied by fibroblasts and macrophages replace the fibrin clot, which is termed as granulation tissue. Various factors are involved in this process among which vascular endothelial growth factor (VEGF) and FGF play a focal role in the regulation. Furthermore, angiogenesis is triggered by stimulation of the bone marrow and endothelial progenitors at normal concentrations of oxygen. In the final stage, fibroblasts derived around a wound or bone marrow motivated through macrophages are transformed into my of broblasts. Myofibroblasts are identified as

contractile cells and play a remarkable role in the closure of the wound.[14] Both fibroblasts and myoblasts synthesize and deposit ECM proteins,predominantly in the form of collagen that eventually forms a scar. It is crucial to maintain a balance between ECM protein deposition and degradation, since the disruption of this process causes abnormalities in scarring.[15]

Re modelling

The final phase of healing consists of remodeling, which begins 2-3weeks after injury and continue up to 2 years or more. The main goal of the remodeling stage is to extend new epithelium and apoptosis of unneeded blood vessels, fibroblasts, and inflammatory cells, resulting in maturation of scar. During this stage, the composition of matrix alters, and type IIIcollagen is eradicated and replaced with type I collagen, which is performed by matrix metalloproteinase (MMP) produced by fibroblasts, macrophages, and endothelial cells to strengthen the scar.[16]

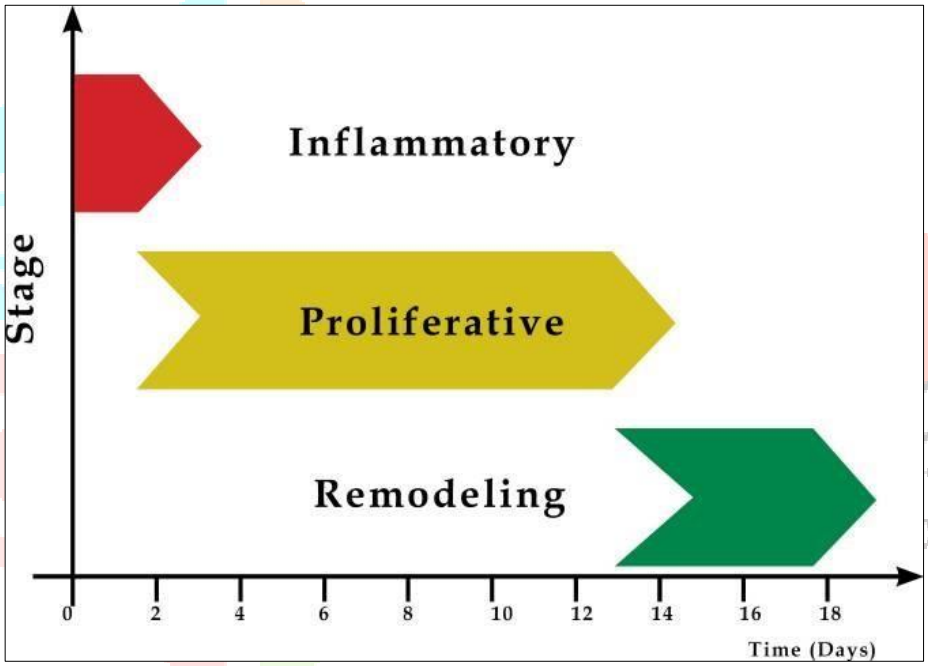

Figure: 1 Healing steps.

Wounds can be classified as:

Time is an important factor in injury management and wound repair. Thus, wounds can be clinically categorized as acute and chronic according to their time frame of healing.[17]

Acute wounds

Wounds that repair themselves and that proceed normally by following a timely and orderly healing pathway, with the end result of both functional and anatomical restoration, areclassified as acute wounds.[18] The time course of healing usually ranges from 5 to 10 days, or within 30 days. Acute wounds can be acquired as a result of traumatic loss of tissue or a surgicalprocedure**.**

Complicated wounds

A complicated wound is a special entity and is defined as a combination of an infection and a tissue defect. The cause of the defect, in contrast, evolves due to the traumatic or post-infectious aetiology, or a wide tissue resection (e.g., in tumour management). Every wound is contaminatedirrespective of the cause, size, location and management.[19] Whether or not a manifest infection develops depends on the virulence, number and type of microorganisms, as well as on the local blood supply and the patient's inherent resistance. Typical characteristics of infection are the five signs and symptoms that have been well documented: redness, heat, pain, oedema and lossor limited function in the affected part. The frequency of wound infections depends on the typeor surgical technique and the location of the wound.[20]

According to the degree of contamination, wounds are classified into three groups as follows:

(i) aseptic wounds (bone and joint operations);
(ii) contaminated wounds (abdominal and lung operations); and
(iii) Septic wounds (abscesses, bowel operations, etc).

Chronic wounds

Chronic wounds are those that fail to progress through the normal stages of healing and they cannot be repaired in an orderly and timely manner. Chronic wounds are wounds that have failed to progress through the normal stages of healing leading to a prolongedloss of substance. In the human setting, chronic wounds are usually defined by a persistence ofan unhealed wound for at least 3 months. In Western countries, the most common causes of chronic ulcers are vascular diseases that are responsible for up to 70% affected patients. The vascular disorders causing chronic wounds can either derive from large diameter vessels diseases or in contrast small diameter vessels diseases. Disorders of lower limbs large diameter arteries or veins can indeed lead to ischemia. Once ischemia having led to tissue necrosis, a complete wound repair cannot occur because of the same ischemic mechanisms.[21]

Causes of lower limbs atheroma are mainly

(a) Tobacco intake,
(b) Overweight,
(c) Elevated cholesterol levels,
(d) Diabetes,
(e) Hypertension.

Causes of venous insufficiency are

(a) Genetic background,
(b) Repeated pregnancies in females
(c) Overweight,
(d) Prolongedstanding at work.

Cutaneous wound healing

Cutaneous wound healing is an essential physiological process consisting of the collaborationof many cell strains and their products. Attempts to restore the lesion induced by a local aggression begin very early on in the inflammatory stage.[22]In the end, they result in repair, which consists of the substitution of specialized structures brought about by the deposition of collagen, and regeneration, which corresponds to the process of cell proliferation and posterior differentiation through preexistingcells in the tissue and/or stem cells**.**

Wound healing

Wound healing is a complex process of recovering the forms and functions of injured tissues. The process is tightly regulated by multiple growth factors and cytokines released at the wound site. Any alterations that disrupt the healing processes would worsen the tissue damage and prolong repair process.[23] Various conditions may contribute to impaired wound healing, including infections, underlying diseases and medications. Numerous studies on the potential of natural products with anti-inflammatory, antioxidant, antibacterial and pro-collagen synthesis properties as wound healing agents have been performed.

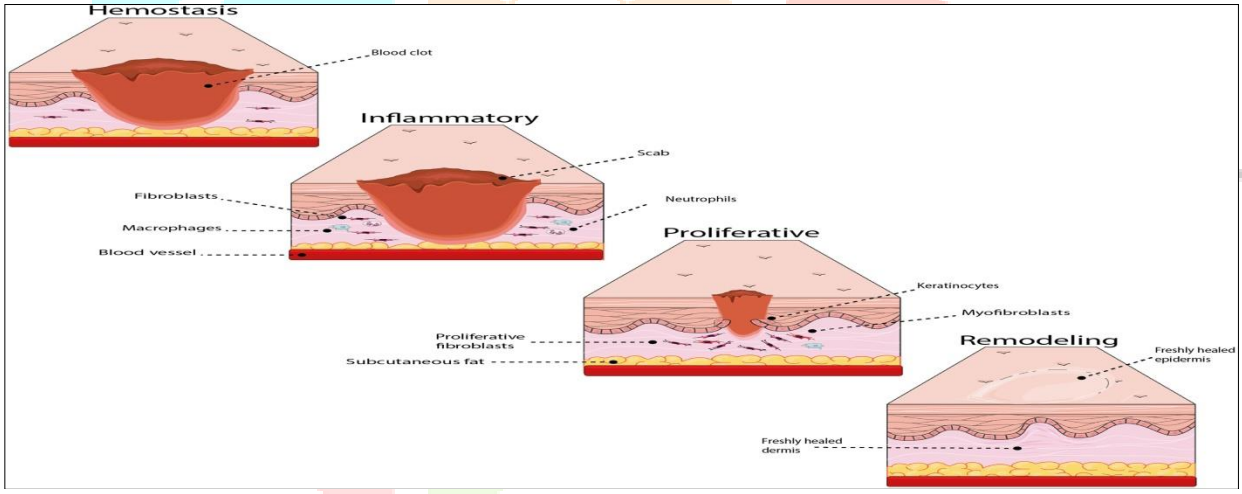

Figure 2: Wound healing

WOUND INFECTIONS

The most common preventable challenge to wound healing is possible infection, and topical antimicrobials have long been used empirically to attempt to prevent wound infection. While bacteria are a normal part of the skin flora and thus wounds, a critical threshold of 105 bacteria has been proposed as the delineation between colonization and a clinically relevant infection that may impede wound healing. It is also necessary to distinguish between an incidental positive culture and a true pathogen affecting a wound. Repeat surface cultures in a wound are of limited use, neither confirming nor ruling out a continued infection; rather, clinical diagnosis of an infected wound remains of primary importance. Deep tissue cultures are somewhat more controversial. While they have better sensitivity and specificity in isolating a causative organism in an infected wound, it is still not perfect; isolates

from different parts of the same wound have even been shown to have different organisms.[24] Additionally, the practitioner is, in essence, exacerbating the initial wound with an even deeper wound, but this may still be a worthwhile trade-off if it guarantees appropriate antimicrobial coverage. There are many approaches towards both

treatment and prevention of wound infections. Silver has been used as adjunct in wound care for over 2000 years and remains a popular wound care ingredient today. It has a broad spectrum of activity and is available in numerous forms. Newer advances in using silver for wound healing have focused on allowing for sustained release of silver in high enough concentrations to allow for retained efficacy. Nanocrystalline silver dressings were developed with this in mind and help to address the shortcoming that silver nitrate has—to work properly, it would have to be administered 12 times a day. Furthermore, a recent review found no convincing evidence that silver sulfadiazine has any effect on wound healing overall, despite its common use among practitioners. Similarly, iodine-containing compounds have long been used in wound healing but there have been some concerns with toxicity of iodine-containing compounds, especially over large wound areas. For limited wounds, though, cadexomer iodine (iodine within a starch lattice formed into microbeads) has a good deal of data supporting its use as a cost-effective adjuvant for wound healing.[25]

Scarless healing of fetal wounds

Fetal wound scarless healing is known as an ideal method of healing. This method is completed by some combined actions within cells such as adhesion molecules, cytokines under the precise control of genes, and the ECM**.** ECM synthesis and remodeling are essential for wound healing; recent studies have focused on the differences between fetal and adult fibroblasts and have revealed that in collagen gels in compression with adult fibroblasts, fetal fibroblasts have a greater migratory capacity, more hyaluronate receptors, and different growth factor profiles. Studies into dermal matrices containing fetal and adult fibroblasts have indicated that dermal matrices containing fetal fibroblasts could promote scar less repair. A number of up regulated anti-fibrotic genes and down regulated fibrotic genes have been detected in the fetal dermal matrix. The results obtained by Hu et al. revealed that in keratinocytes and fibroblasts between scar less and scarring wound, 546 genes had differential expression. They also identified more than 60 differential pathway regulations in scar less and scarring skin cells in fetal murine. Owing to high expansion capacity under simple culture conditions, engineering of fetal tissue has high potential for the treatment of human skin wounds.

Biology of Wound Healing, Chronic Wounds, and Aging

The complex process of wound healing occurs in overlapping phases, including inflammation,proliferation, angiogenesis, epidermal restoration, and wound contraction and remodeling Important cell types in this process include platelets, which recruit inflammatory cells and form a provisional matrix, and macrophages, which include several phenotypes and regulate the cytokine environment in the wound, which influences proliferative, responses and wound closure. Matrix metalloproteinases (MMPs) are active throughout wound healing, aiding in phagocytosis, angiogenesis, cell migration during epidermal restoration, and tissue remodeling.

Conflicts of Interest

The author has no conflicts of interest to declare.

CONCLUSION

Wound healing is a multiphase process involving well-calibrated and synchronized responses to an injury to the skin. Alterations in any of these phases can promote chronic wound development and may impede wound healing. Identification and optimization of modifiable risk factors play a critical role in wound management.

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