MS.ID-IJPBS-2550
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2023) 13 (2): 137-148
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

A Mechanistic Approach and Overview of Medicinal Plants on Wound Healing

Partha Pratim Das, Aishwarya Das, Osman SK and Soma Das*
Department of Pharmaceutical Sciences, School of Medical Sciences, Adamas University, Barasat, Barrackpore Road, West Bengal, India – 700126.

Received: 14 Jan 2023 / Accepted: 12 March 2023/ Published online: 01 April 2023
***Corresponding Author Email:** somapharma@gmail.com

Abstract
In everyday pathology, wound occupies a prominent place. Healing of wound plays a key physiological action to support the integrity of skin following trauma, either by accident or by intent procedure. Wound healing is the task of tissue repair to replace back to its normal structural architecture and function occurred due to injury. The scar formation is the product of wound healing that is a dense connective tissue made up of collagen. Traditional medicinal system plays amazing role in the mainstay of wound care for millions of people worldwide. There is expanding interest to use the medicinal plants in wound healing due to the existence of fewer side effects and management of wounds over the years. Medicinal plants are considered potent healers as they facilitate the repair mechanism naturally. Plants due to presence of certain valuable active phytoconstituents have enormous potential for management and treatment of wounds over the years The main aim of the review is to highlight and emphasize the mechanistic insight of wound healing process and application of traditional medicines with wound healing properties that have been used for over a thousand years to treat wounds of various types due to burns, scars, pressure, diabetes, gastric and duodenal ulcers. The synthesis of conventional and new expertise through application of medicinal plants will generate powerful medicines for wound healing to fabricate a cost-effective, logical, steady, and sustainable delivery means for the control of wounds.

Keywords
Wound, Wound Healing, Traditional Medicinal System, Mechanistic insight.

*****

INTRODUCTION:
Most important body tissue organ is skin when it is rupture by some injuries, violence or slow down the continuity called wound. There are such a process or specific mechanism by which body can repair our own wound called wound healing. Wound healing is basically a most complex biological process[1].

Our body always maintain a proper physical and chemical balance throughout every intra cellular and inter cellularly and maintain the tissue integrity. After an injury if both are recovered shortly, numerous pathways of intracellular and intercellular pathways must be turned on and reciprocated each other which result the activation of coagulation cascade, inflammatory pathways, immune system, and cell proliferation. Numerous cell types like neutrophils, monocytes, lymphocytes, and dendritic cells, endothelial cells, keratinocytes, and fibroblasts, go through significant phenotypic and gene expression alterations that result in cell proliferation, differentiation, and migration [2.] These mechanisms come to a halt in a certain order in the following days as recovery advances if this response is effective and the harm does not cause the organism to perish. Given how difficult it is to heal a wound, it is amazing that it rarely goes out of control and that malignant

transformation rarely occurs in a wound environment. For the majority of injuries, the once-functional tissue is replaced by a patch of cells (mostly fibroblasts) and disorganised extracellular matrix known as a scar[3]. Amazingly, the mechanism of regeneration in some eukaryotic creatures allows the body's response to harm to perfectly recreate the original tissue architecture. This skill is present in humans during prenatal development, but it disappears after adulthood. It is still unknown how regeneration takes place and why humans lose this capacity [4-6] Traditional medicinal system is widely distributed in India. In this review an attempt to highlight the mechanistic approach of wound healing and studies on various plants with medicinal value that are emerging as effective in the treatment of wounds. Though wounds heal in stage, the role of medicinal plants play extensive role in wound management. Many plant-based medications and its ayurvedic properties may blend well with the natural metabolic activity of human tissue. Plant based medical treatment have been in practise for more than thousands of years.

Burden of fibrous tissue:

Practically all tissues go through the process of healing a wound after being exposed to almost any harmful stimuli. Thus, despite the numerous types of insult and the various organs involved, the series of events that follow cardiac attack, for instance, is strikingly close to that which follows a burn, a spinal cord injury, or a bullet wound. The development of scars during wound healing also generally causes tissue malfunction wherever it occurs. Congestive heart failure and/or irregular heart rhythms are hypothesised to originate from the development of myocardial scar tissue in the case of myocardial infarction (arrhythmias)[7]. Additionally, fibrotic reactions to toxin-mediated damage are thought to cause the development of liver cirrhosis and some types of lung fibrosis [8,9.] It's interesting to note that, under certain conditions, the liver is among the few bodily organs that can recover up to 70% of its own without creating scar tissue. Uncertainty surrounds why the liver's capacity for regeneration appears in some situations but not others. Due to the immaturity of the immune systems in human embryos, which recover without scarring, it is a leading theory that the involvement of the immune response is in the transition between regenerative and fibrotic healing[10]. Public health is severely hampered when healing occurs through fibrosis rather than regeneration. Although it is challenging to estimate with accuracy, the overall financial effect of diseases brought on by fibrosis is in the hundreds of billions of dollars[11] Importantly, improper healing frequently results in permanent impairment, which has a big financial effect [2]. Therefore, it would greatly benefit human health if chronic inflammatory healing processes could be changed into regeneration processes, in which the underlying tissues are restored.

Wound healing throughout heredity:

All multicellular creatures have the inherent capacity to react to damage and repair tissue. But there is a lot of variation in the way this procedure takes place. Our understanding of human wound repair may be improved by studying wound repair in different phyla. This research may also point to molecules or pathways that might be targeted to regain lost regeneration potential. The sponge is the earliest type of multicellular organism and the parent of all contemporary multicellular species. Even though sponge wound healing has not received much attention, current research on cellular pattern in these creatures has shed light on the origins of embryonic pattern in metazoans. For tissue regeneration, patterning the three-dimensional arrangement of cells within an organism—is probably necessary. It is typically not believed to play a role in scarring-induced tissue healing. Simple organisms, sponges lack a body axis, several cell layers, and tissues [12–14] The patterning of embryonic sponge cells depends on soluble factors called wingless related integrated site (Wnt) proteins and converting growth factor- (TGF-), and a hedgehog-like cell-surface signal called hedging [15] is also generated in overlapped patterns with the Wnt proteins and TGF. In parallel, developmental morphological events in Drosophila melanogaster, like tracheal fusion [17] and dorsal closure[16], bear a striking visual resemblance to human wound healing. D.melanogaster possesses a complicated craniocaudal asymmetry in the adult form, unlike sponges. Additionally, the very same molecular machinery is employed in similar morphological developmental processes in D.melanogaster embryos as well as to seal an epithelium gap in a wound [18]. In other complex organisms, including humans, these intracellular signal transduction and cell-adhesion pathways are present after injury and their components are highly conserved across species, which suggests that in the wound area in adults patterning cues for multicellular organisation exists and not fully functional[19.] Morphogenetic processes involving tissue mobility have been employed as model of wound repair to more clearly understand the role of expression patterns in this process. For successful closure[20], along with stringent regulation of the related cell division and cell-cell adhesion, Jun N-terminal kinase (JNK)

triggering and the signalling pathway of the transcription factor activator protein 1 (AP1) in leading-edge epithelial cells in D. melanogaster appear to be crucial .This process corresponds to the re-epithelialization (the reproduction of an unbroken keratinocyte layer) of mammalian wounds, as will be detailed later, further underscoring the shared basis of tissue repair across phylogeny. Due to their amazing capacity to regrow amputated limbs through the production of a blastema, that is a mass of unicellular organism proficient in regeneration, and because of their near resemblance to mammals, frogs' ability to heal wounds has recently attracted much attention. To develop into a variety of cell types, upcoming injury, differentiated cells in the adult tissues that encompass the severed area differentiate into mononuclear blastemal cells, that can multiply and possess the capacity to develop into a variety of cell types[21, 22]. These cells then repair the limb in a manner like that of an embryo. The preservation of this regenerative state requires nerve stimulation [23]. The anterior-gradient protein, formed by the schwann cells of transacted nerves, has recently been displayed To assist the proliferation of blastemal cells in salamanders, the anterior-gradient protein, organized by the schwann cells of transacted nerves, has recently been exhibited [24] Similar to planarians, which are basic creatures without sophisticated organ systems, they are also efficient of entirely regenerating an whole organism from a little portion of the original organism—as little as 1/289—of the organism. Ablastema, which may repair organ systems and tissues [25], is created when undifferentiated cells (also known as neoblasts) assemble at the site of the injury. Till 20% of all cells in planarians are assumed to be devoted to the restoration of adult tissues. In spite of the fact mammals still possess a significant portion of the cellular mechanism used by creatures like salamanders, they have a restricted capacity for regeneration. This appears to be partially caused by the quick intervention of fibrous tissue, which inhibits ensuing tissue regeneration. For instance, when a mouse's spinal cord is wounded, neurons start to regenerate, but glial cells at the lesion site encourage the production of scar tissue, impeding healing. The neurons reattach, nevertheless, if indeed the mouse spinal cord is severed in a way that prevents scar formation [26,27.] By stopping infectious microbes from entering the wound and by halting the continuous mechanical deformation of bigger tissues, this quick interposition of scar tissue likely gives a survival benefit (a process that could compound the initial insult). It will likely be necessary to be able to decrease the quick fibrotic reaction such that numerous potent cells like stem or progenitor cells may promote tissue regeneration instead of scar formation in order to manage the wound healing process in mammals such that it turns towards regeneration.

Various steps of wound healing process:

Inflammation, new tissue development, and remodelling are the three overlapping but separate stages of the typical mammalian response to damage in all organ systems. Inflammation, the first step of wound healing, happens as soon as tissue injury occurs. To pause further loss of blood and fluid, eliminate damaged and devitalized (dying) tissues, and avoid infection, components of the immune system, inflammatory pathways, and coagulation cascade are necessary. The creation of a blood clot, followed by the development of a fibrin matrix, which serves as the framework for engulfing cells, results in haemostasis. Then, in response to platelet degranulation, complement activation, and the by-products of bacterial breakdown, neutrophils are drawn to the wound [28]. Monocytes start to emerge in the wound after two to three days and then develop into macrophages. Although neutrophils and macrophages are assumed to be important for coordinating subsequent steps in the body's reaction to injury, their role in wound healing is not fully known. However, recent research suggests that the duplication in the inflammatory process can make up for a lack of either cell type[29] Minor wounds may still be repaired even when neither cell type is present, nor scarring is even lessened [30]. New tissue development, the second phase of wound healing, takes place two-ten days after damage and is characterised by cellular migration and proliferation of various types of cells. The keratinocytes' migration over the damaged dermis (the skin's inner layer) is the first thing to happen. The formation of new blood vessels, followed by the sprouting of capillaries linked to fibroblasts and macrophages, causes the fibrin matrix to be replaced by granulation tissue, which creates a fresh surface for keratinocyte migration later in the repair process. The fibroblast growth factors, and Vascular endothelial growth factor A (VEGFA) have major positive significant regulators of angiogenesis [31] The fibroblast growth factors (FGF2) also known as basic fibroblast growth factor (bFGF). The model of diabetes in animal where wound repair is dysregulated, for instance, the administration of VEGFA alone to wounds can heal [32] At least in non-ischaemic wounds the recruitment of bone mesenchyme endothelial progenitor cells can also lead to angiogenesis, however the amount of this allowance is minimal, [33].Later in this stage,

macrophages encourage fibroblasts drawn from the outline of the wound or from the bone marrow, and some of these cells develop into myofibroblasts [34].Contractile cells called myofibroblasts gradually converge the margins of a wound over time. Interactions between fibroblasts and myofibroblasts result in the production of extracellular matrix, primarily in the form of collagen, which in turn constitutes the majority of the mature scar [35]. Remodelling, juhytr4 the third phase of wound healing, starts two to four weeks following damage and seems to last for at least a year longer. All the after-injury-activated processes wind down and end during this phase. The larger part of endothelial cells, macrophages, and myofibroblasts either experience programmed cell death (apoptsis) or quit from the wound, leaving a mass made primarily of collagen as well as other extracellular matrix proteins and containing few cells (Fig. 1c). Skin integrity and homeostasis are likely continuously regulated by epithelial-mesenchymal interactions [36]. Additionally, the acellular matrix actively remodels itself over a period of 6 to 12 months from one with a backbone predominately made of collagen type 3 to one with collagen type 1 [37]. The tissue, however, never regains the characteristics of healthy skin [38]. It's interesting to note that neither of these collagen types are produced by vertebrates like zebrafish (Danio rerio) and C. elegans, whose extracellular matrix is exclusively made up of type VI and type XVIII collagens [39]. This discovery raises the possibility of an evolutionary adaptability not seen in the initial phases of wound healing.

Mechanism of action of wound healing procedure:

DNA-microarray investigations were conducted to discover such genes across the genome [40,41]Genes that are functionally significant for the process of wound repair are those that are altered in response to skin injury. These studies demonstrated the significance of functional genomics investigations for the study of cancer and wound healing by demonstrating how the pattern of expression of gene of mending wounds on skin closely imitates that of extremely malignant tumours [42]. Interpretation of the functions of a number of genes controlled during wound repair was made possible through the creation and study of genetically altered mice [28]The movements of cell that take place in dorsal closure in D. melanogaster embryos as well as the repair of skin of mammalians have also been found to be similar. The genetically tractable D. melanogaster system has been utilised to discover and functionally characterise the molecules associated with wound healing, particularly in re epithelialization, thanks to wounds and the development of wound - healing models in D.melanogaster [20]. In a recent review[43] the roles of these proteins in wound repair were discussed. We concentrate on the function of these proteins and their downstream effects in the heal of the wounded epidermis (the outermost skin layer) and dermis. Growth factors and hormones are other proteins which are known to be involved.

Factor 1: Peptide growth: To construct the new epithelial tissues on the wounded cell, Hepatocyte Growth Factor (HGF), plays a vital role by activate the tyrosine kinase MET [31, 44]. It is interesting to note that mice with the MET gene deleted from keratinocytes responded to skin wounds with significantly delayed re-epithelialization, and it was discovered that the cells which ultimately protected the wounds in these mice had avoided the recombination event that resulted in Met's deletion and continued to express MET [44]. Although it is obvious that other growth factors cannot make up for a deficiency in HGF-mediated signalling, this discovery was unexpected given that regeneration of epithelial tissues are associated with other growth factors. Components of the FGF family are additional growth factors that favourably govern re-epithelialization. TGF is one of the peptide growth factors which have the inhibition role of regeneration of epithelial tissues. FGF receptor 2 formed form FGF family proteins IIIb has a major application in the process of wound healing. This is demonstrated by the significant delay in re-epithelialization seen in transgenic mice that express FGFR2-IIIb mutants that are dominant-negative in keratinocytes. Despite binding to FGF, the mutant receptor is unable to transmit the signal [45]. The most significant ligands for FGFR2-IIIb, whose activities were lost in these mice, are probably FGF7 and FGF10 [46]. The main sources of FGF7 and FGF10 are selected form mice which have minimul number of epidermal T cells. These leads the keratinocytic cell proliferation and wound healing damage which lends credence to this theory [47].

After skin damage, the expression of several ligands for the EGF receptor (EGFR) increases, and one of them, heparin binding EGF, has been demonstrated to play a vital role in re-epithelialization [48]. Research on mice with the EGFR gene knocked out specifically in keratinocytes would be required to ascertain how the EGF family contributes to the wound healing process. Nonetheless, functional redundancy is probably possible because EGFR ligands are abundant at the wound site. These pro-re-epithelialization factors (HGF, FGFs and EGFs) are receptor tyrosine kinases' ligands, and their activation frequently induces keratinocyte migration, proliferation and survival. Members of the AP1 family and STAT3, another transcription factor,

mediate several of these activities. Those factors are activated in reaction to cytokine-receptor activation as well as signalling via different receptor tyrosine kinases. In D. melanogaster, Dorsal closure and wound healing are compromised by the absence of AP1 proteins [20, 49] or AP1 components. Recent studies show that AP1 proteins[49] have a similar role in mammalian wound repair[50], despite the fact that some of their actions are probably veiled by redundancy across the several members of the mammalian AP1 family [49]. However, it was discovered that mice with epidermis specific Stat3 deletion delayed epithelial healing after injury [51, 52, 53] indicating that STAT3 is certainly engaged in re-epithelialization. TGF- is a negative regulator of wound re-epithelialization in contrast to these mitogenic growth factors. Re-epithelialization has been shown to be greatly accelerated in mice with dominant-negative TGF- receptors in the epidermis and in mice lacking the transcriptional regulator SMAD3, one of the main targets of TGF-mediated signalling. Unexpectedly, the TGF-family member activin, which also interacts with SMAD3, promotes keratinocyte development at the site of the lesion instead of inhibiting it. This effect, nevertheless, is probably mesenchyme-mediated[54], highlighting the importance of interactions between epithelial and mesenchymal cells in the healing of wounds.

Factor 2: Hormones and others: A number of low-molecular-mass mediators, in addition to peptide growth factors are regulators of wound re-epithelialization. As an illustration, keratinocytes produce the hormone acetylcholine and its receptors, resulting in an autocrine loop that regulates migration both positively and negatively (via M4 subtype muscarinic acetylcholine receptors). Additionally, catecholamine hormones (including adrenaline) and their receptors are produced by keratinocytes, which inhibits re-epithelialization in an autocrine manner[55, 56]. Unexpectedly, it has been discovered that polyunsaturated fatty acids and their PPAR-activating derivatives play a key role in regulating re-epithelialization. Following skin damage, keratinocytes express more PPAR- and PPAR- (also known as PPAR-) molecules[57]. Pro-inflammatory cytokines operate to upregulate the expression of the PPAR- gene and of as-yet undiscovered ligands, which in turn trigger the stress-activated protein-kinase signalling cascade, activating the AP1 proteins. This has functional significance because mice with the PPAR- gene knocked out had a much lower rate of re-epithelialization, which was caused by keratinocytes' decreased migration and higher apoptosis [58]. By increasing the expression of the genes for integrin-linked kinase and 3-phosphoinositide-dependent protein kinase 1, which phosphorylate and activate the anti-apoptotic protein AKT [59], PPAR- improves cell survival. Last but not least, a surprising recent discovery is that electrical impulses also control wound re-epithelialization [60]. A lateral endogenous electric field is produced when an epithelial layer is disrupted, as is well known. This field was discovered to represent a crucial directional cue for keratinocyte migration in response to in vitro monolayer injury. The phosphatases PTEN, EGFR, α-6-β-4-integrin, phosphatidylinositol-3-OH kinase, and others have been implicated as receptors and signalling molecules [43, 60]. This system controls corneal wound healing and may have a comparable role in skin wound healing [43, 60]. It follows that a variety of circumstances, including physical ones, can cause the intracellular signalling pathways to become active, which in turn controls how the wound re-epithelialization process progresses through its many stages.

Epithelial stem Biology:

The ability of stem cells to develop into mature, adult cells and their propensity for long-term self-renewal (such as cancer stem cells) are what distinguish them from other types of cells. Multipotent or pluripotent stem cells (capable of producing all body cell types, including germ cells) are two different types of stem cells (capable of forming many cell types). Similar to haematopoiesis, the distinction between multipotent epithelial stem cells and multipotent progenitor cells can only be made using a combination of clonal analysis and serial long-term transplantation techniques[61]. The bulge or niche, also known as the upper permanent portion of the hair follicle below the sebaceous glands, has been clearly demonstrated by this method to include multipotent progenitor cells[62, 63].

The same experimental approach has also conclusively shown that multipotent stem cells exist outside the bulge, supporting earlier findings that stem cells are found there[64]. In response to physiological stimuli or traumas, tissue stem cells can also increase their capacity to create different lineages, a feature that holds enormous promise for regenerative medicine techniques. One hypothesis states that the epidermis is rebuilt by multipotent progenitor cells or stem cells that are formed in and migrate from the hair follicle bulge[62-64]. Unquestionably, multipotent stem cells from the bulge can aid in the healing of the epidermis[61, 65].

In fact, the infundibulum has discrete epidermal and hair-follicle domains and can extend deep into the dermis, in human hair follicles, up to several hundred micrometres. In addition, genetic investigations have

demonstrated that the epidermis is self-renewing and independent of cells derived from multipotent hair follicle stem cells[65, 66]. The belief that epidermal renewal depends on a hierarchy of stem cells and transient amplifying cells has been contested by lineage-tracing studies in mice[67], which support the notion that during normal homeostasis, epidermal renewal depends on a single independent population of proliferative cells. Another factor to take into account is the fact that the characteristics of stem cells are still up for debate, which affects the design and interpretation of experiments.

Quiescence has long been considered a crucial characteristic of all stem cells, therefore maintaining a label (which shows that cells are not actively dividing) has been a necessary need for identifying epithelial stem cells[68]. The ability of stem cells to divide quickly in some organs but not others is now supported by solid evidence. The expression of Lgr5, a transmembrane protein that codes for the leucine-rich-repeat–containing G-protein–coupled receptor 5 that is downstream of the WNT–mediated signalling pathway, recently served as a demonstration that intestinal stem cells cycle quickly. These findings, together with the finding that haematopoietic stem cells don't always retain label, have led some researchers to rethink quiescence as a crucial aspect of "stemness"[70]. As a result, the presence of stem cells in a tissue is not ruled out by the absence of label-retaining cells, as is the case for the expression of differentiation markers. In the end, the only reliable indicator of stemness is function. The transitional zone between the juncture of the conjunctiva and the cornea, which is thought to contain the corneal stem cells[71], is absent in the absence of the limbus. Future approaches to tissue regeneration and wound healing will undoubtedly be influenced by the identification of all cells with stem cell potential. Additionally, the ex vivo repair of skin appendages is made possible by the ability to massively increase multipotent epithelial stem cells in culture and a clearer understanding of the interconnections between epithelial and mesenchymal cells that control hair follicle formation [75, 76]. In this context, a recent study of spontaneous hair follicle production in the healing skin of adult mice highlights the significance of WNT mediated signalling for skin morphogenesis and repair [77] and offers hope for the possibility of hair follicle regeneration. De novo hair-follicle morphogenesis, however, has never been seen in humans despite the fact that it is known to happen in some species (for instance, in deer during the formation of their antlers). Dermal papilla cells have an inductive role in the development of hair follicles and are connected to the neural crest[78–80].

Dermal papilla cells have the ability to create spheres that resemble neurospheres and express markers for adipogenic, chondrogenic, and osteogenic differentiation (which, when cultured in the proper conditions, express hallmarks of neural differentiation). As a result, mesenchymal cells separated from other tissues and dermal papilla cells appear to have functional similarities (for instance, the bone marrow or adipose tissue). The development of novel wound healing strategies, such as those that encourage stem cell migration, stimulate the development of epidermal appendages (such as hair follicles and sweat glands), and lessen scarring, will be made possible by understanding the molecular mechanisms governing epithelial and mesenchymal stem cell fate[75, 76, 81].

The development of regenerative technologies in one therapeutic area may be applied to wound healing due to sufficient similarities in cell pathways and processes. Because to the accessibility and structure of skin, the regenerative nature of healing, the dearth of effective limb salvage treatments, and the present usage of cell therapies, wound healing is a suitable target for regenerative medicine. Regenerative medicine provides a number of opportunities for accelerating and promoting wound healing.

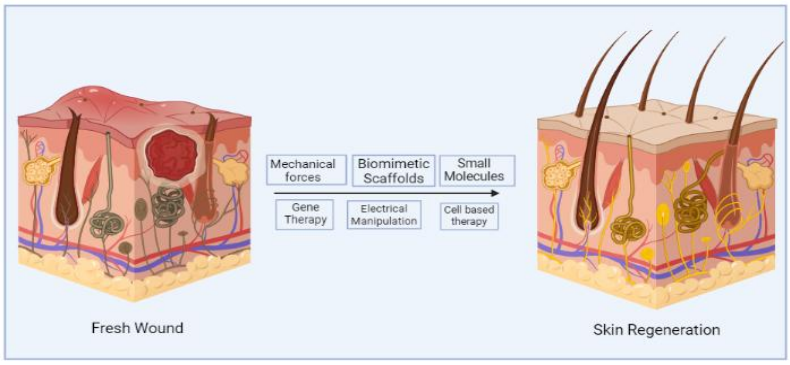

Fig: 1: Regenerative medicine

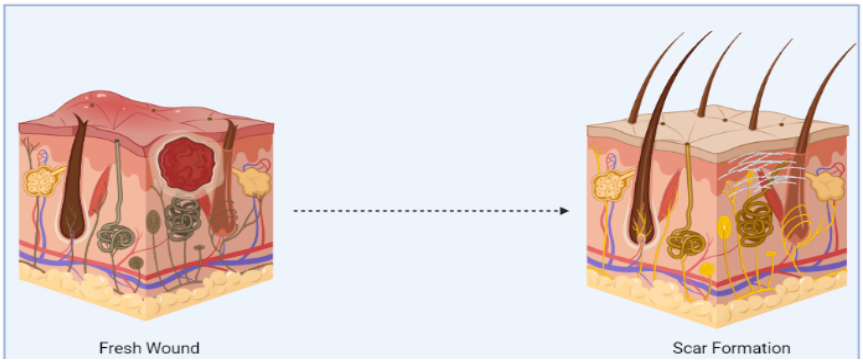

Fig: 2: Classic Wound Healing

Classic Wound Healing: The physiological result of mammalian wound healing is scar formation. Several examples show that inflammation during the healing of a wound is closely related to how much scar tissue forms [81].

Towards tissue regeneration in humans

In humans, the problem with wound healing can be categorised as either excessive healing or delayed wound healing (which happens with diabetes or radiation exposure) (as occurs with hypertrophic and keloid scars). Excessive quantities of extracellular matrix buildup, local changes in vascularization, and cell proliferation are used to define excessive healing. A "bad scar" is how these excessive fibrotic reactions manifest in people. Several such cases of "overheating" result in enormous disfiguring masses that are able to physically alter the surface structures (such as the nose or eyelids). They are frequently brought on by severe wounds like burns, in which case they are known as hypertrophic scars. As is the case with keloid scars, which may have a genetic basis, they can also manifest for unknown reasons following a relatively mild trauma. The finding that increased levels of TGF- are started in wounds that heal through scar formation as opposed to tissue regeneration as seen in poor scars has generated further interest [82, 83]. Using antibodies and small compounds targeted against TGF- and other pro-inflammatory mediators, clinical attempts have been made as a result of this discovery to prevent the formation of scars [84]. The available data also points to the possibility that changes in the physical environment may cause overheating by impacting the mechanical environment of the wound's cells [85]. Although significant progress has been made in identifying the numerous elements involved in both normal and pathological tissue repair, these discoveries have not significantly improved patient care. It has become abundantly clear that single-agent therapies, such as controlling a growth factor, only have a moderate impact on wound healing in a clinical setting. This is most likely because the components of wound healing are highly plastic and plentiful, or because they degrade quickly at the wound site. Administration of cells with the potential to elaborate the complete complexity of biological signalling, along with the environmental signals necessary to regulate the differentiation and proliferation of these cells, is likely to be the final cure to both under healing and overheating.

Medicinal Plants that traditionally used for wound healing

1. **Neem:**

Neem (*Azadirachta indica*), also known as nim or margosa, is a fast-growing tree in the mahogany family (Meliaceae) that is prized for its timber, medical properties, and use as a source of natural insecticides. Neem probably originated in the Indian subcontinent and other dry parts of South Asia.

A study was conducted both in excision and incision wound models to understand the wound healing activity of extracts o A. indica and T. cordifolia leaves in Sprague Dawley rats, and the results obtained for both the extracts in both excision and incision wound models showed significant wound healing activity[86]. Additionally, it was discovered that both plant-treated groups' healing tissue tensile strength was much higher than that of the control group in incision wounds [87]. Other research shown that *Azadirachta indica* leaf extracts stimulate wound healing activities by enhancing the inflammatory response and neovascularization [88].

2. **Aloe vera:**

Aloe barbadensis miller is the name of the plant that produces aloe vera belonging to Liliaceae family. Africa, Asia, Europe and America's dry climates are the prime places it grows.

A three-dimensional porous structure, strong biocompatibility, biodegradability, suitable mechanical properties, ease of access and preservation, non-cytotoxicity, and non-sensitivity are just a few of the wonderful qualities that make up the perfect wound dressing. Additionally, it should keep the area around the wound wet, permit

gas exchange, stop microbial invasion, get rid of extra exudate, and speed up the healing process. Future wound dressings will be multipurpose and individualised, and people will even be able to design their own suitable skin to suit their needs. Reduced scarring after surgery or trauma, antibacterial qualities for chronic wound care, quick hemostasis in the event of a battlefield or accident, thermal stabilisation or anti-freeze dressings in adverse weather conditions, and other attributes are some examples of these tailored traits [89].

3. **Vinca rosea**:

A class of medications called vinca alkaloids is derived from the Madagascar periwinkle plant. They are cytotoxic and hypoglycemic agents that are naturally derived from the pink periwinkle plant Catharanthus roseus G. Don.

In some rural areas, extracts from dried or wet plant blossoms and leaves are applied to wounds as a paste. Ayurvedic doctors in India have utilised the freshly extracted floral juice of C. roseus to make a tea that is used topically to treat skin conditions like dermatitis, eczema, and acne. To the best of our knowledge, there has never been a report on the wound-healing properties of C. roseus in the literature. In this study, we present the first report on the effectiveness of C. roseus flower extract in the treatment of wounds [90].

4. **Bael:**

The fruit of a native Indian tree of the species Aegle marmelos is also referred to as the "wood apple," or "Bael." The moniker "wood apple" comes from the fruit's hard shell and its apple-like form.

The effects of epidermal and intraperitonial organisation of Aegle marmelosbalm methanolic concentrates and infusion on two different types of twisted rodent models, extraction and entrance point, were investigated. Critical responses were received from both the Aegle marmelosmethanolic separate infusion and salve. The concentration aids in the repair cycle, as demonstrated by an increase in elasticity in the entry point model. The results were also compared to those of the controversial medication nitrofurazone [91].

5**. Cinnamon**:

The cinnamon tree, *Cinnamomum zeylanicum*, is native to Sri Lanka, but the majority of the oil presently originates from cultivated regions. It is the source of cinnamon bark and leaf oils. C. zeylanicum is a significant spice and aromatic crop with several uses in flavouring, perfumes, alcoholic beverages, and pharmaceuticals.

Cinnamon extracts support faster, more effective wound contraction in addition to wound healing. In actuality, the primary characteristics of medicines which hasten the healing of wounds are anti-inflammation, antioxidant and antibacterial. Cinnamon promotes wound healing and enhances the environment at the wound site to facilitate faster containment and healing [92].

6. **Carica Papaya**:

The Carica papaya is a member of the Caricaceae family. It was first cultivated in Central America and is now spread throughout the world's tropical and subtropical climates (Morton, 1987). It has a lifespan of five to ten years and often has a single, unbranched trunk (Morton, 1987).

In streptozotocin-induced diabetic rats, a study was conducted with the aqueous extract of C. papaya fruit [100 mg/(kg.d) for 10 d] has been shown to have wound healing properties utilising excision and dead space wound models. In comparison to the controls' 59% contraction to the wound, the aqueous extract demonstrates a 77% reduction in the wound area. The aqueous extract of C. papaya demonstrated a strong ability to heal wounds [93].

7. **Acalpha langiana**

The medicinal plant Acalypha indica thrives in moist, temperate, and tropical climates, mainly near the equator. The majority of people view this plant as a weed, and it is widely distributed in these areas. Although being a weed, Acalypha indica is recognised by the locals as a valuable source of medication for a number of therapeutic therapies.

The healing process in diabetic rats was significantly and dose-dependently affected by topical applications of the aqueous leaves extract of A. langinia. It reduced the area of the wounds by 9% to 88% in excision wounds and by 8% to 82% in incision wounds at concentrations between 0.05% and 0.5% [94].

8. **Turmeric:**

Several Languages' Names for Turmeric/Curcumin. The herbaceous perennial plant Curcuma longa, a member of the ginger family Zingiberaceae and a native of tropical South Asia, produces turmeric. There are 133 different species of Curcuma in the globe. Turmeric, the most active component of rhizome of Curcuma longa L. (common name: turmeric) has been widely studied due to its various bio-functional properties, especially antioxidant, radical scavenger, antimicrobial and anti-inflammatory activities, that play a crucial role in the wound healing process. Also, an ideal dressing incorporated with curcumin extract for wound healing prevents bacterial infection, lessens inflammation, and promotes cell proliferation to help the body repair injured tissue [95].

9. Lotus:
Nelumbo nucifera belongs to the family *Nelumbonaceae*, which has a number of botanical names as well as multiple local tribal names, including Indian lotus, bean of India, Chinese water lily. In a study, the wound healing assay shows that Nelumbo nucifera efficiently inhibits cell migration in a dose-dependent manner [96].
10 **Honey:** A botanical known for its antibacterial and antifungal properties, has gained acceptance as a treatment to accelerate wound healing.
11.**Indian Olive**: Several investigations have been conducted on the effectiveness of olives on wound healing. In general, olives have antioxidant, antibacterial, anti-inflammatory, and antiviral properties and can promote the repair of epithelial tissue, which is productive in the wound healing process.

CONCLUSION:
Mammal skin progenitor cells have been isolated and characterised as a result of recent developments in stem-cell and progenitor-cell biology. Delivering extracellular or intracellular signals exactly in the appropriate temporal and spatial sequence is now possible because to advances in material science. In a biomimetic matrix that mimics the conditions present during prenatal growth and development, when tissue regeneration takes place, adult epidermal progenitor cells (obtained from skin biopsies or standardised cell lines) are established.
The most medicinal plants act through antioxidant and antibacterial properties. The replacement to manufactured medications are being evolved through medicinal plants. The medicinal plants cannot certainly be stated as efficient in improving wound healing, but they play major potential role in improving wound healing. It is obvious that there are still valuable lessons to be gained from conventional procedures given their popularity and proof of ongoing use. Both experiences related to traditional and modern can be combined to create more effective wound healing drugs with lesser side effects. There are several drugs that bear the medical industry which satisfy the medicinal urge and further focus on research and development on utilization of these herbal plants for treating wounds. Unknown reagents, untested combinations and adjunct compounds that might have a place in the current therapeutic inventory can be found mysteriously in the multiplicity of natural goods and derivatives from natural products. Several studies have been conducted on the topic of wound care, with a focus on modern therapeutic approaches and the development of acute and chronic wound therapy methods in Ayurveda (herbal). Researchers are looking into a variety of new formulas, wound dressings, and medicinal plant components to build a cost-effective, logical, stable and sustainable delivery method for the management of wounds.

ACKNOWLEDGEMENT:
The authors are thankful to the Department pf Pharmaceutical Sciences, Adamas University for providing the necessary resources for compilation of this article.

CONFLICT OF INTEREST:
The authors declare that they do not have any Conflicts of Interests

FUNDING SOURCES:
This study received no external funding.

REFERENCES:
1. George Broughton, I. I., Janis, J. E., & Attinger, C. E. (2006). Wound healing: an overview. *Plastic and reconstructive surgery*, *117*(7S), 1e-S.
2. Kirsner, R. S., & Eaglstein, W. H. (1993). The wound healing processes. *Dermatologic clinics*, *11*(4), 629-640.
3. Gonzalez, A. C. D. O., Costa, T. F., Andrade, Z. D. A., & Medrado, A. R. A. P. (2016). Wound healing-A literature review. *Anais brasileiros de dermatologia*, *91*, 614-620.
4. George Broughton, I. I., Janis, J. E., & Attinger, C. E. (2006). The basic science of wound healing. *Plastic and reconstructive surgery*, *117*(7S), 12S-34S.
5. Menke, N. B., Ward, K. R., Witten, T. M., Bonchev, D. G., & Diegelmann, R. F. (2007). Impaired wound healing. *Clinics in dermatology*, *25*(1), 19-25.
6. Witte, M. B., & Barbul, A. (1997). General principles of wound healing. *Surgical Clinics of North America*,*77*(3), 509-528.
7. Eckel, R. H., Barouch, W. W., & Ershow, A. G. (2002). Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the pathophysiology of obesity-associated cardiovascular disease.*Circulation*, *105*(24), 2923-2928.
8. Anderson, R. N., & Smith, B. L. (2003). Deaths: leading causes for 2001.
9. Selman, M., King Jr, T. E., & Pardo, A. (2001). Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Annals of internal medicine*, *134*(2), 136-151.
10. Mescher, A. L., & Neff, A. W. (2005). Regenerative capacity and the developing immune system. *Regenerative medicine I: theories, models and methods*, 39-66.
11. Klein, L., O'Connor, C. M., Gattis, W. A., Zampino, M., De Luca, L., Vitarelli, A., ... & Gheorghiade, M. (2003). Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials

and practical considerations. *The American journal of cardiology*, *91*(9), 18-40.
12. Nichols, S. A., Dirks, W., Pearse, J. S., & King, N. (2006). Early evolution of animal cell signaling and adhesion genes. *Proceedings of the National Academy of Sciences*, *103*(33), 12451-12456.
13. Adamska, M., Matus, D. Q., Adamski, M., Green, K., Rokhsar, D. S., Martindale, M. Q., & Degnan, B. M. (2007). The evolutionary origin of hedgehog proteins. *Current Biology*, *17*(19), R836-R837.
14. Adamska, M., Degnan, S. M., Green, K. M., Adamski, M., Craigie, A., Larroux, C., & Degnan, B. M. (2007). Wnt and TGF-β expression in the sponge Amphimedon queenslandica and the origin of metazoan embryonic patterning. *PloS one*, *2*(10), e1031.
15. Adamska, M., Matus, D. Q., Adamski, M., Green, K., Rokhsar, D. S., Martindale, M. Q., & Degnan, B. M. (2007). The evolutionary origin of hedgehog proteins. *Current Biology*, *17*(19), R836-R837.
16. Woolner, S., Jacinto, A., & Martin, P. (2005). The small GTPase Rac plays multiple roles in epithelial sheet fusion-dynamic studies of Drosophila dorsal closure. *Developmental biology*, *282*(1), 163-173.
17. Samakovlis, C., Manning, G., Steneberg, P., Hacohen, N., Cantera, R., & Krasnow, M. A. (1996). Genetic control of epithelial tube fusion during Drosophila tracheal development. *Development*, *122*(11), 3531-3536.
18. Wood, W., Jacinto, A., Grose, R., Woolner, S., Gale, J., Wilson, C., & Martin, P. (2002). Wound healing recapitulates morphogenesis in Drosophila embryos. *Nature cell biology*, *4*(11), 907-912.
19. Woolley, K., & Martin, P. (2000). Conserved mechanisms of repair: from damaged single cells to wounds in multicellular tissues. *Bioessays*, *22*(10), 911-919.
20. Martin, P., & Parkhurst, S. M. (2004). Parallels between tissue repair and embryo morphogenesis.
21. Suzuki, M., Satoh, A., Ide, H., & Tamura, K. (2005). Nerve-dependent and-independent events in blastema formation during Xenopus froglet limb regeneration. *Developmental biology*, *286*(1), 361-375.
22. Brockes, J. P., & Kumar, A. (2002). Plasticity and reprogramming of differentiated cells in amphibian regeneration. *Nature Reviews Molecular Cell Biology*, *3*(8), 566-574.
23. Endo, T., Bryant, S. V., & Gardiner, D. M. (2004). A stepwise model system for limb regeneration. *Developmental biology*, *270*(1), 135-145.
24. Kumar, A., Godwin, J. W., Gates, P. B., Garza-Garcia, A. A., & Brockes, J. P. (2007). Molecular basis for the nerve dependence of limb regeneration in an adult vertebrate. *science*, *318*(5851), 772-777.
25. Alvarado, A. S. (2006). Planarian regeneration: its end is its beginning. *Cell*, *124*(2), 241-245.
26. Klapka, N., & Müller, H. W. (2006). Collagen matrix in spinal cord injury. *Journal of neurotrauma*, *23*(3-4), 422-436.
27. Stichel, C. C., & Müller, H. W. (1998). The CNS lesion scar: new vistas on an old regeneration barrier. *Cell and tissue research*, *294*, 1-9.
28. Grose, R., & Werner, S. (2004). Wound-healing studies in transgenic and knockout mice. *Molecular biotechnology*, *28*, 147-166.
29. Martin, P., & Leibovich, S. J. (2005). Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends in cell biology*, *15*(11), 599-607.
30. Martin, P., D'Souza, D., Martin, J., Grose, R., Cooper, L., Maki, R., & McKercher, S. R. (2003). Wound healing in the PU. 1 null mouse—tissue repair is not dependent on inflammatory cells. *Current biology*, *13*(13), 1122-1128.
31. Werner, S., & Grose, R. (2003). Regulation of wound healing by growth factors and cytokines. *Physiological reviews*, *83*(3), 835-870.
32. Galiano, R. D., Tepper, O. M., Pelo, C. R., Bhatt, K. A., Callaghan, M., Bastidas, N., ... & Gurtner, G. C. (2004). Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. *The American journal of pathology*, *164*(6), 1935-1947.
33. Bluff, J. E., Ferguson, M. W., O'Kane, S., & Ireland, G. (2007). Bone marrow–derived endothelial progenitor cells do not contribute significantly to new vessels during incisional wound healing. *Experimental hematology*, *35*(3), 500-506.
34. Opalenik, S. R., & Davidson, J. M. (2005). Fibroblast differentiation of bone marrow-derived cells during wound repair. *The FASEB Journal*, *19*(11), 1561-1563.
35. Werner, S., Krieg, T., & Smola, H. (2007). Keratinocyte–fibroblast interactions in wound healing. *Journal of investigative dermatology*, *127*(5), 998-1008.
36. Szabowski, A., Maas-Szabowski, N., Andrecht, S., Kolbus, A., Schorpp-Kistner, M., Fusenig, N. E., & Angel, P. (2000). c-Jun and JunB antagonistically control cytokine-regulated mesenchymal–epidermal interaction in skin. *Cell*, *103*(5), 745-755.
37. Lovvorn Iii, H. N., Cheung, D. T., Nimni, M. E., Perelman, N., Estes, J. M., & Adzick, N. S. (1999). Relative distribution and crosslinking of collagen distinguish fetal from adult sheep wound repair. *Journal of pediatric surgery*, *34*(1), 218-223.
38. Levenson, S. M., Geever, E. F., Crowley, L. V., Oates III, J. F., Berard, C. W., & Rosen, H. (1965). Healing of rat skin wounds. *Annals of surgery*, *161*(2), 293.
39. Rubin, G. M., Yandell, M. D., Wortman, J. R., Gabor, G. L., Miklos, Nelson, C. R., ... & Lewis, S. (2000). Comparative genomics of the eukaryotes. *Science*, *287*(5461), 2204-2215.
40. Cole, J., Tsou, R., Wallace, K., Gibran, N., & Isik, F. (2001). Early gene expression profile of human skin to injury using high-density cDNA microarrays. *Wound repair and regeneration*, *9*(5), 360-370.
41. Cooper, L., Johnson, C., Burslem, F., & Martin, P. (2005). Wound healing and inflammation genes revealed by array analysis of'macrophageless' PU. 1 null mice. *Genome biology*, *6*(1), 1-17.
42. Chang, H. Y., Sneddon, J. B., Alizadeh, A. A., Sood, R., West, R. B., Montgomery, K., ... & Brown, P. O. (2004). Gene expression signature of fibroblast serum response predicts human cancer progression:

similarities between tumors and wounds. *PLoS biology*, *2*(2), e7.
43. Raja, K. S., Garcia, M. S., & Isseroff, R. R. (2007). Wound re-epithelialization: modulating keratinocyte migration in wound healing. *Frontiers in Bioscience-Landmark*, *12*(8), 2849-2868.
44. Chmielowiec, J., Borowiak, M., Morkel, M., Stradal, T., Munz, B., Werner, S., ... & Birchmeier, W. (2007). c-Met is essential for wound healing in the skin. *The Journal of cell biology*, *177*(1), 151-162.
45. Werner, S., Smola, H., Liao, X., Longaker, M. T., Krieg, T., Hofschneider, P. H., & Williams, L. T. (1994). The function of KGF in morphogenesis of epithelium and reepithelialization of wounds. *Science*, *266*(5186), 819-822.
46. Braun, S., auf dem Keller, U., Steiling, H., & Werner, S. (2004). Fibroblast growth factors in epithelial repair and cytoprotection. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *359*(1445), 753-757.
47. Jameson, J., Ugarte, K., Chen, N., Yachi, P., Fuchs, E., Boismenu, R., & Havran, W. L. (2002). A role for skin γδ T cells in wound repair. *Science*, *296*(5568), 747-749.
48. Shirakata, Y., Kimura, R., Nanba, D., Iwamoto, R., Tokumaru, S., Morimoto, C., ... & Hashimoto, K. (2005). Heparin-binding EGF-like growth factor accelerates keratinocyte migration and skin wound healing. *Journal of cell science*, *118*(11), 2363-2370.
49. Schäfer, M., & Werner, S. (2007). Transcriptional control of wound repair. *Annu. Rev. Cell Dev. Biol.*, *23*, 69-92.
50. Li, G., Gustafson-Brown, C., Hanks, S. K., Nason, K., Arbeit, J. M., Pogliano, K., ... & Johnson, R. S. (2003). c-Jun is essential for organization of the epidermal leading edge. *Developmental cell*, *4*(6), 865-877.
51. Sano, S., Itami, S., Takeda, K., Tarutani, M., Yamaguchi, Y., Miura, H., ... & Takeda, J. (1999). Keratinocyte-specific ablation of Stat3 exhibits impaired skin remodeling, but does not affect skin morphogenesis. *The EMBO journal*, *18*(17), 4657-4668.
52. Amendt, C., Mann, A., Schirmacher, P., & Blessing, M. (2002). Resistance of keratinocytes to TGFβ-mediated growth restriction and apoptosis induction accelerates re-epithelialization in skin wounds. *Journal of Cell Science*, *115*(10), 2189-2198.
53. Ashcroft, G. S., Yang, X., Glick, A. B., Weinstein, M., Letterio, J. J., Mizel, D. E., ... & Roberts, A. B. (1999). Mice lacking Smad3 show accelerated wound healing and an impaired local inflammatory response. *Nature cell biology*, *1*(5), 260-266.
54. Werner, S., & Alzheimer, C. (2006). Roles of activin in tissue repair, fibrosis and inflammatory disease. *Cytokine & growth factor reviews*, *17*(3), 157-171.
55. Chernyavsky, A. I., Arredondo, J., Wess, J., Karlsson, E., & Grando, S. A. (2004). Novel signaling pathways mediating reciprocal control of keratinocyte migration and wound epithelialization through M3 and M4 muscarinic receptors. *The Journal of cell biology*, *166*(2), 261-272.
56. Pullar, C. E., Rizzo, A., & Isseroff, R. R. (2006). β-Adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. *Journal of Biological Chemistry*, *281*(30), 21225-21235.
57. Michalik, L., Desvergne, B., Tan, N. S., Basu-Modak, S., Escher, P., Rieusset, J., ... & Wahli, W. (2001). Impaired skin wound healing in peroxisome proliferator–activated receptor (PPAR) α and PPAR β mutant mice. *The Journal of cell biology*, *154*(4), 799-814.
58. Icre, G., Wahli, W., & Michalik, L. (2006, September). Functions of the peroxisome proliferator-activated receptor (PPAR) α and β in skin homeostasis, epithelial repair, and morphogenesis. In *Journal of Investigative Dermatology Symposium Proceedings* (Vol. 11, No. 1, pp. 30-35). Elsevier.
59. Di-Poï, N., Tan, N. S., Michalik, L., Wahli, W., & Desvergne, B. (2002). Antiapoptotic role of PPARβ in keratinocytes via transcriptional control of the Akt1 signaling pathway. *Molecular cell*, *10*(4), 721-733.
60. Zhao, M., Song, B., Pu, J., Wada, T., Reid, B., Tai, G., ... & Penninger, J. M. (2006). Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-γ and PTEN. *Nature*, *442*(7101), 457-460.
61. Claudinot, S., Nicolas, M., Oshima, H., Rochat, A., & Barrandon, Y. (2005). Long-term renewal of hair follicles from clonogenic multipotent stem cells. *Proceedings of the National Academy of Sciences*, *102*(41), 14677-14682.
62. Taylor, G., Lehrer, M. S., Jensen, P. J., Sun, T. T., & Lavker, R. M. (2000). Involvement of follicular stem cells in forming not only the follicle but also the epidermis. *Cell*, *102*(4), 451-461.
63. Oshima, H., Rochat, A., Kedzia, C., Kobayashi, K., & Barrandon, Y. (2001). Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell*, *104*(2), 233-245.
64. Rochat, A., Kobayashi, K., & Barrandon, Y. (1994). Location of stem cells of human hair follicles by clonal analysis. *Cell*, *76*(6), 1063-1073.
65. Ito, M., Liu, Y., Yang, Z., Nguyen, J., Liang, F., Morris, R. J., & Cotsarelis, G. (2005). Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. *Nature medicine*, *11*(12), 1351-1354.
66. Levy, V., Lindon, C., Harfe, B. D., & Morgan, B. A. (2005). Distinct stem cell populations regenerate the follicle and interfollicular epidermis. *Developmental cell*, *9*(6), 855-861.
67. Clayton, E., Doupé, D. P., Klein, A. M., Winton, D. J., Simons, B. D., & Jones, P. H. (2007). A single type of progenitor cell maintains normal epidermis. *Nature*, *446*(7132), 185-189.
68. Potten, C. S., & Booth, C. (2002). Keratinocyte stem cells: a commentary. *Journal of investigative dermatology*, *119*(4), 888-899.
69. Barker, N., Van Es, J. H., Kuipers, J., Kujala, P., Van Den Born, M., Cozijnsen, M., ... & Clevers, H. (2007). Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature*, *449*(7165), 1003-1007.
70. Kiel, M. J., He, S., Ashkenazi, R., Gentry, S. N., Teta, M., Kushner, J. A., ... & Morrison, S. J. (2007). Haematopoietic stem cells do not asymmetrically segregate chromosomes or retain BrdU. *Nature*, *449*(7159), 238-242.

71. Vauclair, S., Majo, F., Durham, A. D., Ghyselinck, N. B., Barrandon, Y., & Radtke, F. (2007). Corneal epithelial cell fate is maintained during repair by Notch1 signaling via the regulation of vitamin A metabolism. *Developmental cell*, *13*(2), 242-253.
72. Pearton, D. J., Yang, Y., & Dhouailly, D. (2005). Transdifferentiation of corneal epithelium into epidermis occurs by means of a multistep process triggered by dermal developmental signals. *Proceedings of the National Academy of Sciences*, *102*(10), 3714-3719.
73. Nishida, K., Yamato, M., Hayashida, Y., Watanabe, K., Yamamoto, K., Adachi, E., ... & Tano, Y. (2004). Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *New England Journal of Medicine*, *351*(12), 1187-1196.
74. Nishida, K., Yamato, M., Hayashida, Y., Watanabe, K., Yamamoto, K., Adachi, E., ... & Tano, Y. (2004). Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *New England Journal of Medicine*, *351*(12), 1187-1196.
75. Nishida, K., Yamato, M., Hayashida, Y., Watanabe, K., Yamamoto, K., Adachi, E., ... & Tano, Y. (2004). Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *New England Journal of Medicine*, *351*(12), 1187-1196.
76. Metcalfe, A. D., & Ferguson, M. W. (2007). Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *Journal of the Royal Society Interface*, *4*(14), 413-437.
77. Ito, M., Yang, Z., Andl, T., Cui, C., Kim, N., Millar, S. E., & Cotsarelis, G. (2007). Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. *Nature*, *447*(7142), 316-320.
78. Reynolds, A. J., Lawrence, C., Cserhalmi-Friedman, P. B., Christiano, A. M., & Jahoda, C. A. (1999). Trans-gender induction of hair follicles. *Nature*, *402*(6757), 33-34.
79. Fernandes, K. J., McKenzie, I. A., Mill, P., Smith, K. M., Akhavan, M., Barnabé-Heider, F., ... & Miller, F. D. (2004). A dermal niche for multipotent adult skin-derived precursor cells. *Nature cell biology*, *6*(11), 1082-1093.
80. Wong, C. E., Paratore, C., Dours-Zimmermann, M. T., Rochat, A., Pietri, T., Suter, U., ... & Sommer, L. (2006). Neural crest–derived cells with stem cell features can be traced back to multiple lineages in the adult skin. *The Journal of cell biology*, *175*(6), 1005-1015.
81. Blanpain, C., Lowry, W. E., Geoghegan, A., Polak, L., & Fuchs, E. (2004). Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell*, *118*(5), 635-648.
82. Lin, R. Y., Sullivan, K. M., Argenta, P. A., Meuli, M., Lorenz, H. P., & Adzick, N. S. (1995). Exogenous transforming growth factor-beta amplifies its own expression and induces scar formation in a model of human fetal skin repair. *Annals of surgery*, *222*(2), 146.
83. Ghahary, A., Shen, Y. J., Scott, P. G., Gong, Y., & Tredget, E. E. (1993). Enhanced expression of mRNA for transforming growth factor-β, type I and type III procollagen in human post-burn hypertrophic scar tissues. *The Journal of laboratory and clinical medicine*, *122*(4), 465-473.
84. Ferguson, M. W., & O'Kane, S. (2004). Scar–free healing: from embryonic mechanisms to adult therapeutic intervention. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *359*(1445), 839-850.
85. Aarabi, S., Bhatt, K. A., Shi, Y., Paterno, J., Chang, E. I., Loh, S. A., ... & Gurtner, G. C. (2007). Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *The FASEB Journal*, *21*(12), 3250-3261.
86. Lutolf, M. P., & Hubbell, J. A. (2005). Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. *Nature biotechnology*, *23*(1), 47-55.
87. Ofusori, D. A., Falana, B. A., Ofusori, A. E., Abayomi, T. A., Ajayi, S. A., & Ojo, G. B. (2010). Gastroprotective effect of aqueous extract of neem Azadirachta indica on induced gastric lesion in rats. *Int J Biol Med Res*, *1*(4), 219-222.
88. Osunwoke Emeka, A., Olotu Emamoke, J., Allison Theodore, A., & Onyekwere Julius, C. (2013). The wound healing effects of aqueous leave extracts of Azadirachta indica on Wistar rats. *J Nat Sci Res*, *3*(6), 181-186.
89. Liang, J., Cui, L., Li, J., Guan, S., Zhang, K., & Li, J. (2021). Aloe vera: a medicinal plant used in skin wound healing. *Tissue Engineering Part B: Reviews*, *27*(5), 455-474.
90. El-Sayed, A., & Cordell, G. A. (1981). Catharanthus alkaloids. XXXIV. Catharanthamine, a new antitumor bisindole alkaloid from Catharanthus roseus. *Journal of natural products*, *44*(3), 289-293.
91. Lambole, V. B., Murti, K., Kumar, U., Bhatt, S. P., & Gajera, V. (2010). Phytopharmacological properties of Aegle marmelos as a potential medicinal tree: an overview. *Int J Pharm Sci Rev Res*, *5*(2), 67-72.
92. Farahpour, M. R., & Habibi, M. (2012). Evaluation of the wound healing activity of an ethanolic extract of Ceylon cinnamon in mice. *Vet Med*, *57*(1), 53-57.
93. Vij, T., & Prashar, Y. (2015). A review on medicinal properties of Carica papaya Linn. *Asian Pacific Journal of Tropical Disease*, *5*(1), 1-6.
94. Gutierrez, R. P. (2006). Evaluation of the wound healing properties of Acalypha langiana in diabetic rats. *Fitoterapia*, *77*(4), 286-289.
95. Zahidin, N. S., Saidin, S., Zulkifli, R. M., Muhamad, I. I., Ya'akob, H., & Nur, H. (2017). A review of Acalypha indica L. (Euphorbiaceae) as traditional medicinal plant and its therapeutic potential. *Journal of ethnopharmacology*, *207*, 146-173.
96. Rafiq, S., Majeed, R., Qazi, A. K., Ganai, B. A., Wani, I., Rakhshanda, S., ... & Hamid, R. (2013). Isolation and antiproliferative activity of Lotus corniculatus lectin towards human tumour cell lines. *Phytomedicine*, *21*(1), 30-38.