WOUND HEALING

The skin serves its primary function as a protective barrier against environmental insult. A wound is a break in the epithelial integrity of the skin and may be accompanied by disruption of the structure and function of underlying normal tissue. A wound may result from precise disruption of tissue by the surgeon's knife (incision) to widespread damage of tissue (e.g. major trauma, burns). A wound may also result from a contusion, haematoma, laceration or an abrasion due to injury. The continuity of the skin must be restored expeditiously because it plays a crucial role in maintaining homeostasis. When the structural integrity of the skin is compromised its primary responsibility to the immune system is impacted leading to serious morbidity and mortality, therefore, care of the wound is atmost necessary. Wound healing involves a complex series of events including chemotaxis, cell division, neovascularization, synthesis of new extracellular matrix, and the formation and remodeling of the scar tissue. These events are regulated by several mediators including platelets, inflammatory cells, cytokines and growth factors, and matrix metalloproteinases and their inhibitors. In acute wounds, these processes (which are triggered by tissue injury) involve the four overlapping (but well-defined) phases of haemostasis, inflammation, proliferation and remodeling (Dreifke et al., 2015; Enoch and Leaper, 2005)

In contrast to acute healing, chronic wounds either require a prolonged time to heal, do not heal, or recur frequently. These wounds tend to occur when the normal wound healing process has been compromised for example, by infection, metabolic disturbances, or an underlying disease. The most common examples are pressure ulcers,

venous leg ulcers and diabetic ulcers, all of which are characterized by a relative inability to generate new tissue. Such impaired healing inflicts a huge cost upon society, diminishing the quality of life for millions worldwide and, thus recent attention has turned to the investigation of cost effective, accessible alternative therapeutic strategies (Krishnan, 2006).

In everyday pathology, wounds remain a challenging clinical problem, with early and late complications presenting a frequent cause of morbidity and mortality (Natarajan et al., 2000; Alonso et al., 1996). In an attempt to reduce the wound burden, much effort has focused on understanding the physiology of healing and wound care with an emphasis on new therapeutic approaches and the continuing development of technologies for acute and long-term wound management (Robson et al., 2001; Szycher and Lee, 1992). The immense social and economic impact of wounds worldwide is a consequence of their high rate of occurrence in general and their increasing frequency in the ageing population. In addition to a high number of acute wounds, there are also a large number of chronic, hard-to-heal wounds associated with diseases and abnormalities that directly or indirectly culminate in damage of the cutaneous coverage, including arterial, venous, diabetic and pressure ulcers. The prevalence of these chronic wounds increases with age. For example, it has been estimated that chronic wounds affect 120 per 100 000 people aged between 45 and 65 years and rises to 800 per 100 000 people > 75 years of age. Furthermore, due to the complications that accompany acute wounds, when their healing does not progress in a timely and orderly manner, they can convert into chronic wounds, which are more difficult to manage (Velnar et al., 2009).

Classification of wounds

Wounds can be classified according to various criteria. Time is an important factor in injury management and wound repair. Thus, wounds can be clinically categorized as acute and chronic (Figure 1) according to their time frame of healing (Velnar et al., 2009).

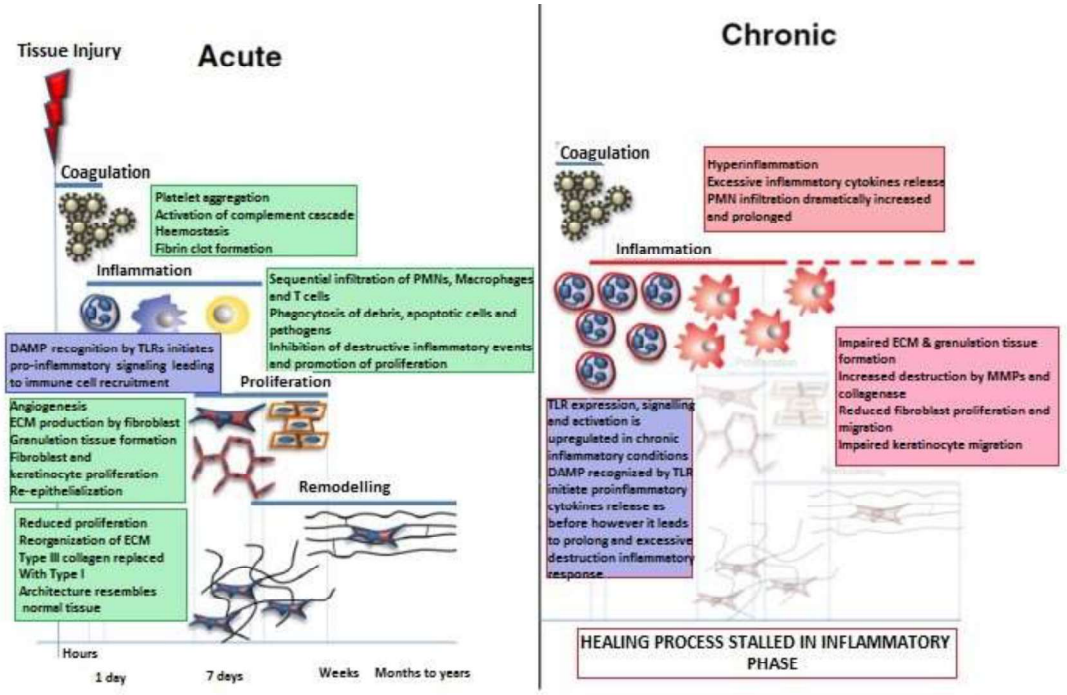


Figure 1: A comparison between stages of normal wound healing following acute wound and chronic wounds

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, are classified as acute wounds. 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 surgical procedure.

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. The healing process is incomplete and disturbed by various factors, which prolong one or more stages in the phases of haemostasis, inflammation, proliferation or remodelling. These factors include infection, tissue hypoxia, necrosis, exudate and excess levels of inflammatory cytokines. A continuous state of inflammation in the wound creates a cascade of tissue responses that together perpetuate a non-healing state. Because the healing then proceeds in non-coordinated manner, functional and anatomical outcomes are poor and these wounds frequently relapse. Chronic wounds may result from various causes, including pressure, arterial and venous insufficiency, burns and vasculitis.

Healing abnormalities

There are many local and systemic factors that contribute to impaired wound healing. In addition, there are situations where healing occurs but in a disorganized way. Local factors pertain mainly to persistence of debris within the wound; for example, devitalized tissue, clot, foreign material, including sutures and bacterial contamination. These can act as a physical barrier to the ordered development of granulation tissues and collagen deposition, or may exaggerate the evoked inflammatory response.

Systemic factors that impair healing include nutritional status, diabetes, glucocorticoid treatment, irradiation, hypoxia, jaundice and renal failure. Old age is a contentious issue: certainly wounds in older patients take longer to heal. Several dietary deficiencies have been implicated in wound healing. As mentioned vitamin C (ascorbic acid) is essential for collagen synthesis. Apart from hydroxylation of proline, vitamin C

is also required for production of n-acetyl galactosamine, a component of matrix and granulation tissue. Zinc deficiency impairs function of MMPs, which are essential for collagen and matrix remodeling. Any dietary state that limits the availability of amino acids will have a profound effect on healing and the quality of collagen made. Amino acids containing sulphydryl groups (e.g. methionine) are especially important. Diabetic patients suffer from a variety of problems affecting healing. In diabetics initially, high plasma sugar decreases both neutrophil chemotaxis and phagocytic ability. Additionally, a sugar-rich environment will favour microbial growth, further interfering in the healing process (Winter and Scales, 1963).

Wounds in patients who have received high-dose glucocorticoids are known to heal poorly. This effect is probably due to the anti-inflammatory action of glucocorticoids as well as their direct depression of fibroblast collagen deposition. Any condition that reduces blood flow and induces tissue hypoxia at the injured site, ultimately reduces healing (e.g. cardiorespiratory disease and sepsis). Conditions that reduce the number of lymphocytes or macrophages, or their ability to migrate, also have a similar effect.

Neoplastic cachexia, uraemia or jaundice all produces hypercatabolic state and similarly interfere in the healing process. There are occasions when abnormal healing occurs in an otherwise normal setting. Over-granulation (proud flesh) occurs when the margin of the granulation tissue protrudes above the margin of the wound. Other abnormalities can occur which result in ugly raised scars. Hypertrophic scars are limited to the wounded area and do not increase in size beyond 6 months. Keloid scars extend beyond the wound area and increase in size even after 6 months (Halloran and

Slavin, 2002). Factors affecting wound healing (Guo and DiPietro, 2010) are summarized in table 1.

Table 1: Factors influencing tissue healing

Local Factors	Systemic Factors
Inadequate blood supply	Age and gender
Increased skin tension	Sex hormones
Poor venous drainage	Stress
Presence of foreign body and foreign body reactions	Disease: Diabetes, Keloids, Fibrosis, Hereditary healing disorders, Jaundice, Uremia
Presence of slough and/or non-viable tissue	Obesity
Presence of micro-organisms	Ischemia
Infection	Medications: glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapy
Hypoxia	Alcohol and smoking
	Immunocompromised conditions: cancer, radiation therapy, AIDS
	Nutrition

PATHOPHYSIOLOGY OF WOUND HEALING

Wound healing is a dynamic, complex mechanism aimed towards re-attainment of tissue integrity and homeostasis (Eming et al., 2007) involving four overlapping (but well-defined) phases of haemostasis, inflammation, proliferation and remodelling and scar maturation (Figure 2). It is coordinated by a complicated signaling system involving various growth factors, cytokines and chemokines. Cell proliferation is an imperative step in tissue repair and regeneration in wound healing process (Xing et al., 2015).

PHASES OF WOUND HEALING (Enoch and Leaper, 2005)

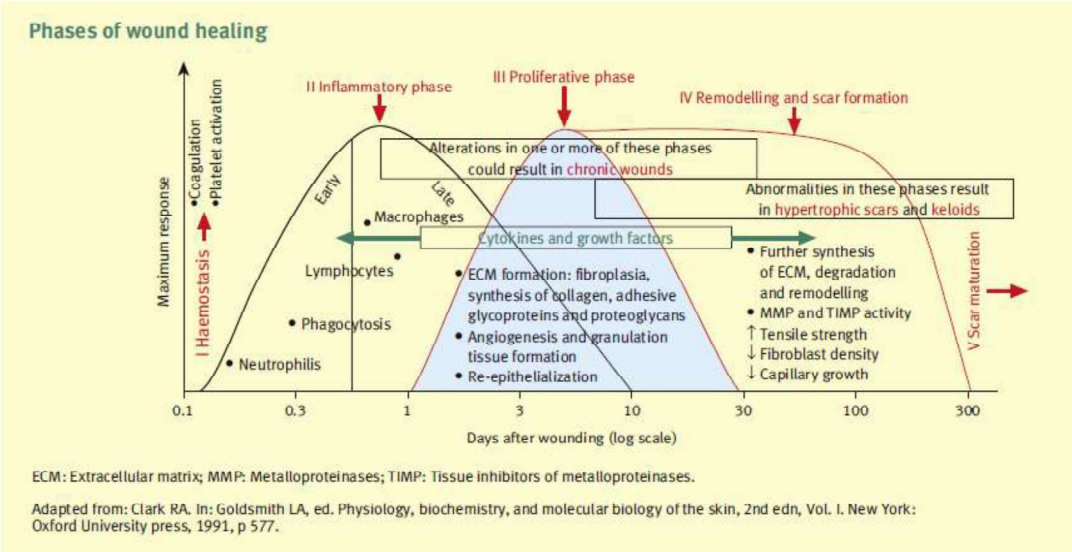


Figure 2: Phases of wound healing

Haemostasis (immediate)

Tissue injury is characterized by microvascular injury and extravasation of blood into the wound area. Loss of structural integrity, initiates the coagulation cascade and constriction of vessel walls; the resulting clot formation and platelet aggregation limits further blood loss. The platelets trapped in the clot are essential for haemostasis and a normal inflammatory response. The platelets degranulate and release their alpha granules, which secrete several growth factors, including platelet-derived growth factor, insulin-like growth factor-1, epidermal growth factor, transforming growth factor-β and platelet factor-IV.

These proteins initiate the wound healing cascade by attracting and activating fibroblasts, endothelial cells and macrophages, which activates four major amplification systems (complement cascade, clotting mechanism, kinin cascade and plasmin generation). This contributes to haemostasis and the subsequent stages of the

healing process. However, healing can occur in wounds where there is no haemorrhage (and therefore no platelets). The clot (comprising fibrin, fibronectin, vitronectin, von Willibrand factor, thrombospondin) provides the provisional matrix for cellular migration. The platelets also contain dense bodies that store vasoactive amines (e.g. serotonin), that increase microvascular permeability, leading to exudation of fluid into the extravascular space.

Inflammation

Inflammation can be divided into early and late phases depending on the time and duration of response and the type of inflammatory cell involved.

Early inflammatory phase (days 1–2): Inflammation begins with the activation of the classical and alternative pathways of the complement cascade. This leads to infiltration of the wound with neutrophil granulocytes (polymorphonuclear leukocytes) that are attracted to the wound site within 24–48 hours of injury by a number of chemoattractants such as fragments of extracellular matrix protein, transforming growth factor-β, complement components (e.g. C3a, C5a) and formyl-methionyl peptide products from bacteria.

Within a short time, the polymorphonuclear leukocytes begin to adhere to the endothelial cells in the adjacent blood vessels (margination) and start to actively move through the vessel wall (diapedesis). Once in the wound environment, they phagocytose bacteria and other foreign particles, and kill them by releasing degrading enzymes and free radicals derived from oxygen.

During this period, basal cells at the cut edge of the epidermis begin to exhibit increased mitotic activity. Within 24–48 hours, epithelial cells from both edges begin to

migrate and proliferate along the dermis, depositing components of basement membrane as they progress. The activity of polymorphonuclear leukocytes usually stops within a few days of wounding (after the contaminating bacteria have been cleared). Redundant cells are cleared from the wound by extrusion to the wound surface as slough or by phagocytosis by macrophages. The main function of polymorphonuclear leukocytes is to minimize bacterial contamination of the wound, thus preventing infection, and they add little to the normal process of wound healing beyond this stage.

Late inflammatory phase (days 2–3): On arriving at the wound site, blood monocytes undergo a phenotypic change to become tissue macrophages. Monocytes are attracted to the wound by a variety of chemoattractants, including complement, clotting components, fragments of immunoglobulin G, breakdown products of collagen and elastin and cytokines.

Macrophages are the most important cells present in the later (48–72 hours) stages of the inflammatory process and appear to act as the key regulatory cells for repair. They function as phagocytic cells as well as being the primary producer of growth factors responsible for the proliferation and production of the extracellular matrix by fibroblasts, of smooth muscle cells and of endothelial cells resulting in angiogenesis.

Also, macrophages release proteolytic enzymes (e.g. collagenase) that help to debride the wound. If depleted, circulating monocytes and tissue macrophages cause severe alterations in wound healing, leading to poor debridement of the wound, delayed proliferation of fibroblasts, inadequate angiogenesis, and poor fibrosis. Additional growth factors (e.g. transforming growth factor-α, heparin-binding epidermal growth factor, basic fibroblast growth factor) are secreted by polymorphonuclear leukocytes

and macrophages, which further stimulate the inflammatory response. During the late inflammatory phase, collagen fibres are evident at the incision margins of the wound, but these are vertically oriented and do not bridge the incision. Further, epithelial cell proliferation continues, yielding a thickened epidermal covering layer.

Proliferation (day 3 to week 2)

The proliferative phase starts at about day 3 and lasts for 2–4 weeks after wounding and is characterized by fibroblast migration, deposition of the extracellular matrix and formation of the granulation tissue. With progression of the proliferative phase, the provisional fibrin/fibronectin matrix is replaced by the newly formed granulation tissue. Epithelialization of the wound represents the final stage of the proliferative phase.

Fibroblast migration: Fibroblasts appear in the wound 2–4 days after wounding and endothelial cells follow about one day later. Following injury, fibroblasts are attracted to the wound by a number of factors, including platelet-derived growth factor and transforming growth factor-β. Once within the wound, fibroblasts proliferate and produce the matrix proteins fibronectin, hyaluronan and, later collagen and proteoglycans. These components help to construct the new extracellular matrix, which supports further ingrowth of cells and is essential for the repair process. Crucial interaction exists between the fibroblasts and the extracellular matrix which helps to regulate further synthesis of the extracellular matrix and subsequent remodelling.

Formation of the extracellular matrix: Besides providing turgor to soft tissues and rigidity to bone, extracellular matrix supplies a substratum for cell adhesion and critically regulates the growth, movement and differentiation of the cells within it. The extracellular matrix consists of fibrous structural proteins (collagens, elastin) and an

interstitial matrix composed of adhesive glycoproteins embedded in a proteoglycan and glycosaminoglycan gel. The seemingly random array of interstitial matrix in connective tissues soon becomes highly organized around epithelial cells, endothelial cells and smooth muscle cells, forming the specialized basement membrane (which directs cell polarity and is required for the orderly renewal of the epithelial tissue).

Collagens are synthesized by fibroblasts and are the most abundant family of proteins in the body. They provide strength and integrity to all tissues and so play a vital role in wound repair. Platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-β, interleukin-1, tumour necrosis factor induce collagen synthesis during the proliferative and remodelling phases.

Collagens are composed of three protein α-chains braided into a rope-like triple helix; the individual chains are able to intertwine tightly because each α polypeptide has one glycine molecule at every third position. More than 30 distinct α-chains form about 18 different collagen types (some of which may be unique to specific cells and tissues). Some collagen types (e.g. I, III, V) form fibrils due to lateral crosslinking of the triple helices, and form most of the connective tissue in healing wounds; other collagens (e.g. type IV) are non-fibrillar and become components of the basement membrane.

Adhesive glycoproteins are structurally diverse proteins that link the components of the extracellular matrix to one another and to cells, which includes fibronectin, laminin, and thrombospodin.

• Fibronectin, a large (400-kD) disulphide-linked heterodimer, is associated with cell surfaces, basement membranes and the pericellular matrix. It has specific domains that bind to a wide spectrum of components of the extracellular matrix (e.g. collagen, fibrin,

proteoglycans) and can also attach to cell integrins. Adhesive matrix proteins such as; fibronectin can directly mediate the attachment, spreading and migration of cells. Fibronectin also enhances the sensitivity of certain cells (e.g. endothelial) to the proliferative effect of growth factors by activating intracellular signalling pathways.

• Integrins are a family of α/β heterodimeric glycoproteins that mediate cell–cell and cell–matrix adhesion. They are important in the integration of function between the extracellular matrix and the cytoskeleton.

Proteoglycans consist of glycosaminoglycans (e.g. dermatan sulphate, heparan sulphate) linked to a protein backbone; they help to regulate the structure and permeability of the extracellular matrix. Proteoglycans can modulate the growth and differentiation of cells (e.g. syndecan binds extracellular matrix collagen, fibronectin, thrombospondin and basic fibroblast growth factor, and associates with the intracellular actin cytoskeleton to maintain the normal morphology of epithelial sheets). Glycosaminoglycans without a protein core (e.g. hyaluronan) are important constituents of the extracellular matrix.

Formation of granulation tissue: By 3–5 days, granulation tissue (indicative of optimal healing) is well established. Granulation tissue has a pink, soft, granular gross appearance (such as that seen beneath the scab of a skin wound). Histologically, it is denoted by proliferating fibroblasts and loops of capillaries in a loose extracellular matrix. This phase is characterized by angiogenesis or formation of new blood vessels from pre-existing vessels at the site of injury (neovascularization). Four steps are recognized during this process:

1. Proteolytic degradation of the basement membrane of the parent vessel, allowing formation of a 'capillary sprout'
2. Migration of endothelial cells towards the angiogenic stimulus
3. Proliferation of endothelial cells behind the leading front of migrating cells
4. Maturation of endothelial cells with organization into capillary tubes.

These new vessels are oedematous due to incompletely formed inter endothelial junctions and increased transcytosis. Several factors (including vascular endothelial growth factor, platelet derived growth factor, basic fibroblast growth factor and transforming growth factor-β) induce angiogenesis. Angiogenic capillary sprouts invade the fibrin/fibronectin-rich wound clot and within a few days organize into a microvascular network throughout the granulation tissue. The density of blood vessels diminishes because collagen accumulates in the granulation tissue to produce scar; disturbance of this dynamic process may influence the development of chronic wounds. Granulation tissue bleeds easily if traumatized. The appearance of the granulation tissue may indicate wound status:

Healing wounds have a moist and shiny, hyperaemic, and reddish appearance Excessive, soft, friable wounds with a beefy-red colour indicate poor healing.

Epithelialization: Within a few hours of wounding, a single layer of epidermal cells migrates from the wound edges to form a delicate covering over the exposed raw area, a process known as 'epiboly'. From about 12 hours, there is a marked increase in mitotic activity within the basal epithelial cells of the wound edges. These cells migrate as a sheet, extending lamellipodia along the advancement edge. Later, they loosen their normally firm attachments to the underlying dermis, allowing them to migrate in a

'leapfrog' fashion across the provisional matrix. When advancing epithelial cells meet, further movement is halted by 'contact inhibition' and a new basement membrane regenerates; further growth and differentiation of epithelial cell re-establishes the stratified epithelium. Epithelialization requires a moist environment, adequate nutrition, bacteriological control, which is modulated by several growth factors, including keratinocyte growth factor, epidermal growth factor and basic fibroblast growth factor.

Remodelling and scar maturation (week 1 to several weeks)

The synthesis and remodelling of the extracellular matrix is initiated concurrently with the development of granulation tissue and continues over prolonged periods. There is continuous synthesis and breakdown of collagen as the extracellular matrix is constantly remodelled, equilibrating to a steady state about 21 days after wounding. Wound contraction occurs through the interactions between fibroblasts and the surrounding extracellular matrix and is influenced by a number of cytokines including transforming growth factor-β, platelet-derived growth factor and basic fibroblast growth factor.

Collagen degradation is achieved by specific metalloproteinases that are produced by fibroblasts, neutrophils and macrophages at the wound site.

Metalloproteinases – the synthesis and secretion of metalloproteinases is regulated by growth factors, cytokines, and phagocytic stimuli. Metalloproteinases include interstitial collagenases (which cleave the fibrillar collagen types I, II, and III), Gelatinases (or type-IV collagenases; which degrade amorphous collagen and fibronectin) and Stromelysins (which catabolize a variety of constituents of the

extracellular matrix, including proteoglycans, laminin, fibronectin and amorphous collagen).

Metalloproteinases are dependent on zinc ions for their activity and should be distinguished from neutrophil elastase, cathepsin G, plasmin, and other serine proteases that can also degrade the extracellular matrix, but are not metalloenzymes. The activity of metalloproteinases is tightly regulated because they have the potential to degrade essential collagen and thereby cause impaired healing. They are typically elaborated as inactive (zymogen) precursors that must be first activated; this is accomplished by certain proteases (e.g. plasmin) likely to be present only at injury sites. Also, activated collagenases can be rapidly inhibited by specific tissue inhibitors of metalloproteinases, produced by most mesenchymal cells.

Further remodelling of the wound causes:

• Decrease in the activity of metalloproteinases and an increase in activity of tissue inhibitors of metalloproteinase

• Reduction in the density of macrophages and fibroblasts

• Halt in the outgrowth of capillaries

• Reduction in the blood flow and metabolic activity

• Decrease in size of the underlying contractile connective tissue (which brings the wound margins closer together).

Ultimately, the granulation tissue scaffolding evolves into an avascular scar which is composed of largely inactive fibroblasts, dense collagen, fragments of elastic tissue and other components of the extracellular matrix.

Scar maturation: As the scar matures, fibronectin and hyaluronan are broken down and collagen bundles increase in diameter, corresponding with increasing tensile strength of the wound. However, these collagen fibres never regain the original strength of unwounded skin, and a maximum of 80% strength of unwounded skin can be achieved (Enoch and Leaper, 2005).

GROWTH FACTORS AND CYTOKINES: EMPHASIS ON THEIR ROLE IN WOUND HEALING

Growth factors and cytokines are the signaling peptides involved in the regulation of various physiological responses. The role of these signaling molecules is not limited to the normal physiological regulation; they are vital mediators of various pathological abnormalities as well. Numerous cell types including macrophages (Rappolee et al., 1988), neutrophils (Cassatella, 1995), lymphocytes (Barbul, 1988) and fibroblasts (Clark, 2013) produce a plethora of growth factors and cytokines. In return, these molecules control in part, their survival, proliferation and migration. Important growth factor and proinflammatory cytokines involved in the process of wound healing are listed in Table 2.

Table 2: Important growth factor and proinflammatory cytokines involved in the process of wound healing (Nicholas et al., 2013; Safferling et al., 2013; Janis and Harrison, 2014)

Molecule	Source	Function	Clinical Application
VEGF	Macrophage, platelet, endothelial cell, keratinocyte, fibroblast, myofibroblast, fibrocyte, mast cell	Angiogenesis	
IL-1	Neutrophil, monocyte, macrophage, keratinocyte	Neutrophil chemotaxis Early activator of growth factor Fibroblast proliferation Extracellular matrix degradation	Increased in chronic wound
IL-6	Keratinocyte, fibroblast, macrophage	Keratinocyte mitogen, mitogen	
TNF α	Neutrophil, monocyte, macrophage, keratinocyte, mast cell	Leukocyte chemoattractant Fibroblast proliferation	Elevated levels linked to deficient healing

VEGF: vascular endothelial growth factor; IL: interleukin; TNF: tumour necrosis factor

The majority of wound healing investigations take the form of *in vitro* assays based on cell culture models of the various phases of healing. Although insightful in terms of possible modes of drug action, it is conceded that *in vitro* assessments are insufficient to demonstrate efficacy and both animal testing and human trials are required for global scientific acceptance (Krishnan, 2006).

Table 3 summarizes most frequently utilized wound healing models. It should be kept in mind that the etiology of human chronic wounds often includes a combination of multiple factors and underlying comorbidities, and that various models typically address a single factor (e.g., diabetes, infection, and ischemia). In spite of research efforts focused on improving existing models and developing new ones, a

model that fully replicates human nonhealing chronic wounds remains missing (Pastar et al., 2014).

Table 3: Summary of frequently used models to study wound healing (Pastar et al., 2014)

Model	Advantage
In vitro	
Wound Scratch Assay	Utilizes human epidermal keratinocytes By inhibiting proliferation, one can assess keratinocyte migration and its underlying biology
Ex vivo	
Human ex vivo acute wound model	Presence of full-thickness epidermis and dermis; langerhans cell, pigment cells and nerve ending present
Human ex vivo linear excisional wound model	Standardized wound depth Presence of full-thickness epidermis and dermis; langerhans cell, pigment cells and nerve ending present
Partial Thickness human skin culture model (incision)	Presence of full-thickness epidermis and dermis; langerhans cell, pigment cells and nerve ending present
Murine and human skin equivalents	Ability for studying the interaction between keratinocytes and fibroblasts
In vivo	
Tape stripping	Partial removal of epidermis Several levels of barrier disruption can be induced
Murine incision/excision wound model	Ability for studying the interaction and influence of different cell types on epithelialization Use of wound splinting in full-thickness wounds to minimize contraction Uncomplicated standardization and multiple replicates
Porcine partial/full-thickness wound model	Greatest structural similarity and the wound healing process to the humans Multiple replicates within single animal
Rabbit ear wound model	Decreased blood flow Absent wound contraction Multiple replicates within single animal

Plants have the immense potential for the management and treatment of wounds. A large number of plants are used by tribal and folklore in many countries for the treatment of wounds and burns. These natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. These phytomedicine are not only cheap and affordable but are also safe. The presence of various life-sustaining constituents in plants has urged scientist to examine these plants with a view to determine potential wound healing properties (Nayak and Pereira, 2006). Many phytopharmaceutical laboratories are now concentrating their efforts to identify the active constituents and modes of action of various medicinal plants (Hwang et al., 2000). The medicinal value of these plants lies in bioactive phytochemical constituents that produce definite physiological action on the human body (Akinmoladun et al., 2007). These constituents include various chemical constituents like alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, and phenolic compounds (Edeoga et al., 2005). India has a rich tradition of plant-based knowledge on healthcare. A large number of plants/plant extracts/decoctions or pastes are equally used by tribals and folklore traditions in India for treatment of cuts, wounds, and burns.

The screening of herbal extracts has been of great interest to the scientists for the discovery of new effective drugs (Kosger et al., 2009). A number of reports concerning the wound healing activity of various plants have appeared in the literature, but the vast majority has yet to be explored. Various pharmacological reports are available on plants employing different wound healing models and its underlying molecular mechanism for the validation of their traditional claims and development of safe and effective and globally accepted herbal drugs for wounds. Table 4 enlists medicinal plants with wound healing potential.

MEDICINAL PLANTS WITH WOUND HEALING ACTIVITY

Table 4: Medicinal plants with wound healing activity

Plant name	Part used	Model studied	References
Abutilon indicum Linn.	Whole Plant	Excision and incision	Suresh et al., 2011
Acacia caesia Linn.	Bark	Excision and incision	Suriyamoorthy, et al., 2014
Acalypha fruticosa Forssk.	Aerial Part	Excision and dead space	Gopalakrishnan et al., 2010
Acalypha indica Linn.	Whole plant	Excision and incision	Reddy et al., 2002
Acanthus ebracteatus Vahl.	Stem	Incision	Somchaichana et al., 2012
Achillea biebersteinii Afan.	Root	Excision and incision	Akkol et al., 2011
Achillea kellalensis Boiss. & Hausskn.	Flowers	Excision	Pirbalouti et al., 2010
Achillea millefolium Linn.	Leaves	Excision, incision and dead space	Nirmala et al., 2010
Achyranthes aspera Linn.	Leaves	Excision and incision	Ghosh et al., 2011, Fikru et al., 2012
Acorus calamus Linn.	Leaves	Excision and incision	Jain et al., 2010
Adhatoda vasica Nees.	Leaves	Excision	Vinothapooshan et al., 2010
Aegle marmelos (Linn.) Correa	Root Seed Leaves	Excision and incision Excision and incision Excision	Jaswanth et al., 2001 Sharma et al., 2011 Solanki et al., 2012
Ageratum conyzoides Linn.	Leaves Root	Excision and incision	Oladejo et al., 2003 Mustafa et al., 2005 Jain et al., 2009
Albizzia lebbeck Benth.	Root	Excision, incision and dead space	Joshi et al., 2013
Alchemilla vulgaris Linn.	Whole Plant	Excision and cell lines	Shrivastava et al.,

			2007
Allmanda cathartica Linn.	Leaves	Excision and incision	Nayak et al., 2006
Aleurites moluccana Linn.	Leaves	Excision and incision	Cesca et al., 2012
Allium cepa Linn.	Tuber	Excision, incision and dead space	Shenoy et al., 2009
Alocasia denudate Schott.	Stem	Excision	Latif et al., 2015
Aloe arborescens Mill.	Leaves	Incision	Jia et al.,2008
Aloe barbadensis Mill.	Leaves	Excision	Oryan et al., 2010
Aloe ferox Mill.	Leaves	Incision	Jia et al.,2008
Aloe littoralis Baker	Leaves	Incision	Hajhashemi et al., 2012
Aloe vera (L.) Burm.f.	Leaves	Excision	Subramanian et al., 2006
Alternanthera brasiliana Kuntz.	Leaves	Excision and incision	Barua et al., 2009
Alternanthera sessilis Linn.	Leaves	Excision, incision and dead space	Jalapure et al., 2008
Ammannia baccifera Linn.	Leaves	Excision and incision	Rajasekaran et al., 2012
Anadenanthera colubrina var. cebil (Griseb.) Altschul	Bark	Excision and incision	Pessoa et al., 2012
Andrographis peniculata (Burm.f.) Nees	Whole Plant	Excision	Mohanty et al., 2010
Angelica sinensis (Oliv.) Diels	Whole Plant	Human fibroblast cell proliferation assay	Zhao et al.,2006
Annona muricata Linn.	Stem bark	Excision	Paarakh et al., 2009
Annona squamosal Linn.	Leaves	Excision	Ponrasu et al., 2012
Anogeissus latifolia Roxb.	Bark	Excision and incision	Govindarajan et al., 2004
Anogeissus leiocarpus (DC.) Guill. & Perr.	Leaves	Excision	Barku et al., 2013
Anthocephalus cadamba Roxb.	Whole Plant	Excision and incision	Umachigi et al., 2007

Argyreia nervosa Burm.	Leaves	Excision	Singhal et al., 2011
Arisaema leschenaultii Blume.	Tuber	Excision, incision and dead space	Suruse et al., 2011
Aristolochia bracteolata Lam.	Leaves	Excision, incision and dead space	Shirwaikar et al., 2003 Jayasutha et al., 2011
Artemisia absinthium Linn.	Aerial Part	Cell line assay	Craciunescu et al., 2012
Arnebia densiflora (Nordm.) Ledeb.	Roots	Incision	Akkol et al., 2009
Arrabidaea chica Verl.	Leaves	Incision	Jorge et al., 2008
Artocarpus heterophyllus Lam.	Leaves	Excision	Gupta et al., 2009
Asparagus racemosus Willd.	Root	Excision and incision	Kodancha et al., 2011
Aspilia africana (Pers.) C.D.Adams	Leaves	Excision	Attama et al., 2011
Astragalus membranaceus (Fisch.) Bunge	Root	Incision	Ren et al., 2012
Atropa belladonna Linn.	Leaves	Incision	Gal et al., 2012
Avena sativa Linn.	Whole Plant	Excision and incision	Kupeli et al., 2011
Azadirachta indica A.Juss.	Leaves	Excision and incision	Barua et al., 2010
Bacopa monnieri (L.)Wettest.	Whole Plant	Excision, incision and dead space	Sharath et al., 2010
Baliospermum montanum (Willd.) Müll.Arg.	Root	Excision	Kumar et al., 2011
Barleria cuspidate F.Heyne ex Nees	Leaves	Excision and incision	Mazumder et al., 2009
Bauhinia purpurea	Leaves	Excision, incision and dead space	Ananth et al., 2010
Bauhinia variegate Linn.	Seeds	Incision	Neto et al., 2011
Bidens pilosa Linn.	Leaves	Excision	Hassan et al., 2011
Blechnum orientale Linn	Leaves	Excision	Lai et al., 2011

Blepharis maderaspatensis (L.) B.Heyne ex Roth	Leaves	Excision and incision	Rajasekaran et al., 2012
Blumea Balsamifera (L.) DC.	Leaves	Excision	Pang et al., 2014
Boesenbergia rotunda (L.) Mansf.	Rhizome	Excision	Mahmood et al., 2010
Bombax malabaricum DC.	Bark	Excision and incision	Chandrika et al., 2010
Brassica juncea Linn.	Leaves	Excision	Malan et al., 2011
Bridelia ferruginea Benth.	Stem bark	Excision	Udegbunam et al., 2011
Bryophyllum pinnatum (Lam.) Oken	Leaves	Excision, incision and dead space	Khan et al., 2004
Buchanania lanzan Spreng.	Fruit	Excision, incision and dead space	Chitra et al., 2009
Buddleja globosa Hope.	Leaves	Fibroblast Assay	Mensah et al., 2001
Bulbine frutescens (L.) Willd.	Leaves	Excision and incision	Pather et al., 2001
Bulbine natalensis Baker.	Leaves	Excision and incision	Pather et al., 2001
Butea monosperma (Lam.) Taub.	Bark Stem Bark Flower	Excision Excision, incision and dead space Excision	Sumitra et al., 2005 Muralidharet al., 2011 Sharma et al., 2012 Gavimath et al., 2009
Calendula officinalis Linn.	Flower	Excision	Preethi et al., 2009 Parente et al., 2012
Calotropis gigantean (L.) Dryand.	Flower Root Bark Leaves Latex	Excision and incision Excision, incision and dead space Excision and incision Excision and incision	Patil et al., 2012 Deshmukh et al., 2009 Suresh babu et al., 2012 Nalwaya et al., 2009

Calotropis procera (Aiton) Dryand.	Stem bark	Excision	Samy et al., 2012
Camellia sinensis (L.) Kuntze	Leaves	Incision	Asadi et al., 2013
Canthium parviflorum Lam.	Leaves	Excision	Mohideen et al., 2003
Capparis zeylanica Linn.	Roots Whole Plant	Excision and incision Excision	Das et al., 2011 Padhan et al., 2011
Carapa guianensis Linn.	Leaves	Excision, incision and dead space	Nayak et al., 2011
Carica papaya Linn.	Root Leaves Fruit	Excision Excision Excision and dead space	Tiwari et al., 2011, Anuar et al., 2008, Mahmood et al., 2005, Nayak et al., 2007
Caryocar coriaceum Wittm.	Fixed oil	Excision	De Oliveira et al., 2010
Cassia fistula Linn.	Leaves	Excision	Senthil et al., 2006
Cassia tora Linn.	Leaves	Excision	Jayasutha et al., 2011
Catharanthus roseus (L.) G.Don	Flower	Excision, incision and dead space	Nayak et al., 2007
Cecropia peltata Linn.	Leaves	Excision	Nayak et al., 2006
Celastrus paniculatus Willd.	Leaves	Excision, incision and dead space	Harish et al., 2008
Cenostigma macrophyllum Tul.	Seeds	Excision	Coelho et al., 2013
Centaurea iberica Trev. Ex Spreng.	Aerial Parts	Excision and incision	Koca et al., 2009
Centella asiatica (L.) Urb.	Whole plant Aerial Parts	Excision Incision, excision, and dead space	Maquart et al., 1999 Hong et al., 2005 Chatterjee et al., 2011
Centrosema pubescens Benth.	Leaves	Excision and incision	Epko et al., 2011
Chamomilla recutita (L.)	Flower and	Incision	Duarte et al., 2011

Rauschert	aerial parts		
Chromolaena odorata (L.) R.M. King & H.Rob.	Leaves	Excision	Mahmood e al., 2005
Cichorium intybus Linn.	Aerial parts, leaves and roots	Excision and incision	Suntar et al., 2012
Cinnamomum zeylanicum Blume.	Bark	Excision, incision and dead space	Kamath et al., 2003
Coronopus didymus (L.) Sm.	Whole plant	Incision	Prabhakar et al., 2002
Crinum zeylanicum Linn.	Bulbs	Excision	Yahaya et al., 2012
Crossandra infundibuliformis (L.) Nees	Leaves	Excision	Sumalatha et al., 2012
Crotalaria verrucosa Linn.	Whole Plant	Excision, incision and dead space	Kumari et al., 2010
Croton zehntneri Pax & K.Hoffm.	Leaves	Excision	Cavalcanti et al., 2012
Cucumis sativus Linn.	Fruit	Excision	Patil et al., 2011
Cuminum cyminum Linn.	Seed	Excision, incision and dead space	Patil et al., 2009
Curculigo orchioides Gaertn	Root tuber	Excision	Agrahari et al., 2010 Singh et al., 2014
Curcuma aromatic Salisb.	Rhizome	Excision	Kumar et al., 2009
Curcuma longa Linn.	Rhizome	Excision, incision and dead space	Thakare et al., 2011
Curculigo orchioides Gaertn.	Root tubers	Excision	Singh et al., 2014
Cynodon dactylon (L.) Pers.	Leaves Whole Plant	Excision Excision, incision and dead space	Thakare et al., 2011 Saroja et al., 2012
Cydonia oblonga Mill.	Seed	Excision	Tamri et al., 2014
Cyperus rotundus Linn.	Tuber	Excision, incision and dead space	Puratchikody et al., 2006
Daphne oleoides chreb.	Aerial parts of	Excision and incision	Suntar et al., 2012

	the plant		
Dendrophthoe falcata (L.f) Ettingsh.	Aerial parts	Excision and incision	Pattanayak et al., 2008
Desmodium gangeticum (L.) DC.	Aerial parts	Excision, incision and dead space	Jain et al., 2006
Desmodium gyrans (L.f.) DC.	Leaves	Excision	Kalirajan et al., 2012
Desmodium triquetrum (L.) DC.	Leaves	Excision, incision and dead space	Shirwaikar et al., 2004
Dissotis theifolia (G. Don) Hook. f.	Stem Leaves	Excision Excision, incision and dead space	Odimegwu et al., 2008
Dodonea viscosa Jacq.	Whole Plant	Excision and incision	Ramya et al., 2011
Drypetes klainei Pierre ex Pax	Stem Bark	*In vitro* scratch wound-healing assay	Brusotti et al., 2015
Echinacea pallida (Nutt.) Nutt.	Roots	Excision	Zhai et al., 2009
Eichornia crassipes (Mart.) Solms	Leaves	Excision	Ali et al., 2010
Elaeagnus angustifolia Linn.	Fruit	Excision	Natanzi et al., 2012
Elaeis guineensis Jacq.	Leaves	Excision	Sasidharan et al., 2010
Elephantopus scaber Linn.	Leaves	Excision, incision and dead space	Singh et al., 2005
Eleusine coracana (L.) Gaertn.	Seeds	Excision	Hedge et al., 2005
Embelia ribes Burm.	Leaves	Excision, incision and dead space	Kumara Swamy et al., 2007
Emblica officinalis Gaertn.	Fruit	Excision	Sumitra et al., 2009
Equisetum arvense Linn.	Leaves	Excision	Ozay et al., 2010
Eucalyptus globulus Labill.	Leaves	Excision, incision and dead space	Hukkeri et al. , 2002
Eugenia malaccensis Blanco.	Seeds	Incision	Brustein et al., 2012
Euphorbia caducifolia	Latex	Incision and excision	Goyal et al., 2012

Haines.			
Euphorbia heterophylla Linn.	Leaves	Excision	James et al., 2010
Euphorbia neriifolia Linn.	Latex	Excision	Rasik et al., 1996
Fagonia schweinfurthii Had.	Whole plant	Excision	Alqasoumi et al., 2011
Ficus amplissima Sm.	Leaves	Excision and incision	Arunachalam et al., 2013
Ficus benghalensis Linn.	Bark Roots	Excision and incision Excision, incision and dead space	Garg et al., 2011 Murti et al., 2011 Murti et al., 2011
Ficus racemosa Linn.	Roots Fruit	Excision and incision Excision	Murti et al., 2012 Rao et al., 2011
Ficus religiosa Linn.	Leaves	Excision and incision	Roy et al., 2008 Nayeem et al., 2009
Flabellaria paniculata Cav.	Leaves	Excision	Olugbuyrio et al., 2010
Flaveria trinervata (Willd.) Baill.	Leaves	Excision and incision	Umadevi et al., 2006
Gentiana lutea Linn.	Rhizomes	Excision, incision and dead space models	Mathew et al., 2004
Ginkgo biloba Linn.	Leaves	Excision and dead space	Bairy et al., 2001
Glycine max (L.) Merr.	Seed	Incision	Xu et al., 2013
Glycosmis arborea (Roxb.) DC.	Leaves	Excision and incision	Silambujanaki et al., 2011
Glycyrrhiza glabra Linn.	Roots	Excision	Kishore et al., 2001
Gmelina arborea Roxb.	Leaves	Excision, incision and dead space	Shirwaikar et al., 2002
Gossypium herbaceum Linn.	Leaves	Excision, incision and dead space	Velmurugun et al., 2012
Grewia tiliifolia Vahl.	Stem bark	Excision, incision and dead space	Khadeer et al., 2009

Gymnema sylvestre (Retz.) R.Br. ex Sm.	Whole plant Leaves	Excision Excision, incision and dead space	Kiranmai et al., 2011 Malik et al., 2009
Gynura procumbens (Lour.) Merr.	Leaves	Excision	Zahra et al., 2011
Hamelia patens Jacq.	Whole plant	Incision	Gomez-Beloz et al., 2003
Helichrysum graveolens (M.Bieb.) Sweet	Flowers	Excision and incision	Suntar et al., 2013
Heliotropium indicum Linn.	Whole plant Leaves	Excision and incision Excision, incision and dead space	Reddy et al. , 2002 Dodehe et al., 2011 Dash et al., 2011
Hemidesmus indicus (L.) R. Br. ex Schult.	Roots	Excision	Ganesan et al., 2012
Hemigraphis colorata W.Bull	Leaves	Excision	Subramoniam et al., 2001
Hibiscus rosa sinensis Linn.	Flowers	Excision, incision and dead space	Nayak et al., 2007
Hippophae rhamnoides Linn.	Leaves	Excision	Upadhyay et al., 2009 Upadhyay et al., 2011
Hiptage benghalensis Linn.	Roots	Excision	Gandhimathi et al., 2012
Holoptelea integrifolia Planch.	Leaves and stem bark	Excision and incision	Reddy et al., 2008
Hylocereus undatus (Haw.) Britton & Rose	Leaves, Rind, Fruit pulp, Flowers	Excision and incision	Perez et al., 2005
Hypericum hookerianum Wight & Arn.	Leaves	Incision and excision	Mukherjee et al., 2000a
Hypericum mysorense F. Heyne	Leaves	Excision and incision	Mukherjee et al., 2000b
Hypericum perforatum Linn.	Aerial Part	Excision and incision	Suntar et al., 2010
Hyptis suaveolens (L.) Poit.	Leaves	Excision, incision and dead space	Shenoy et al., 2009

Ichnocarpus frutescens (L.) W.T.Aiton	Roots	Excision and incision	Pandurangan et al., 2010
Indigofera aspalathoides DC.	Whole Plant	Excision	Saritha et al., 2012
Indigofera enneaphylla Linn.	Aerial parts	Excision and incision	Hemalatha et al., 2001
Inula viscosa (L.) Aiton	Whole plant	Excision	Khalil et al., 2007
Ipomoea batatas (L.) Lam.	Tubers	Excision and incision	Panda et al., 2011
Ipomoea carnea Jacq.	Flower	Excision and incision	Ambiga et al., 2007
Ixora coccinea Comm. ex Lam.	Flowers Roots	Dead space Excision and incision	Nayak et al., 1999 Selvaraj et al., 2011
Jasminum grandiflorum Linn.	Flowers	Excision and dead space	Mishra et al., 2010
Jasminum sambac Linn.	Leaves	Excision	Sabharwal et al., 2012
Jatropha curcas Linn.	Bark Leaves Stem bark	Excision, Incision and Dead Space Excision Excision and incision	Shetty et al., 2006 Esimone et al., 2009 Sachdeva et al., 2011
Jatropha gossypiifolia Linn.	Leaves and flowers	Incision	Servin et al., 2006
Juniperus occidentalis Hook.	Wood	Excision and incision	Tumen et al., 2013
Juniperus oxycedrus Linn.	Berries/Fruit	Excision	Tumen et al., 2012
Juniperus. phoenicea Linn.	Berries/Fruit	Excision	Tumen et al., 2012
Kaempferia galanga Linn.	Rhizomes	Excision, incision and dead space	Shanbhag et al., 2006
Kalanchoe petitiana A. Rich	Leaves	Excision, incision and dead space	Mekonnen et al., 2013
Kalanchoe pinnata Lam.	Leaves	Excision	Nayak et al., 2010
Kigelia africana (Lam.) Benth.	Leaves and Stem Bark	Excision	Agyare et al., 2013

Kigelia pinnata (Jacq.) DC.	Bark	Excision, incision and dead space	Sharma et al., 2010
Lantana camara Linn.	Leaves	Excision	Abdulla et al., 2009
Lantana wightiana Wall.	Leaves	Excision	Reddy et al., 2011
Lawsonia alba Lam.	Leaves	Excision and incision	Nithya et al., 2011
Lawsonia inermis Linn.	Leaves	Excision, incision and dead space	Nayak et al., 2007
Leucas hirta (B.Heyne ex Roth) Spreng.	Leaves	Excision, incision and dead space	Manjunatha et al., 2006
Leucas lavandulaefolia Rees.	Whole Plant	Excision and incision	Saha et al. , 1997
Limonia acidissima Linn.	Fruit	Excision, incision and dead space	Ilango et al., 2010
Litsea glutinosa (Lour.) C.B.Rob.	Leaves	Excision and incision	Devi et al., 2010
Liquidambar orientalis Mill.	Latex	Excision	Oesel et al., 2012
Lonicera japonica Thunb.	Flowering aerial parts	Excision	Chen et al., 2012
Lygodium flexuosum (L.) Sw.	Leaves	Excision, incision and dead space	Chandra et al., 2013
Lycopodium serratum Thunb.	Leaves	Excision, incision and dead space	Manjunatha et al., 2007
Macrotyloma uniflorum (Lam.) Verdc.	Whole plant	Excision and incision	Muthukumar et al., 2014
Malva sylvestris Linn.	Flowers	Excision	Pirbalouti et al., 2010 Pirbalouti et al., 2011
Martynia annua Linn.	Leaves	Excision and incision	Lodhi et al., 2011
Matricaria chamomilla Linn.	Whole plant	Incision	Jarrahi et al., 2008
Matricaria recutita Linn.	Flowers	Excision, incision and dead space	Nayak et al., 2007
Melastoma malabathricum Linn.	Leaves	Excision and incision	Sunilson et al., 2008

Melia azedarach Linn.	Leaves	Excision	Vidya et al., 2012
Michauxia nuda A. D.C.	Root	Excision	Guvenc et al., 2012
Michauxia tchihatchewii Fisch. & C.A. Mey.	Whole Plant	Excision and incision	Guvenc et al., 2012
Michelia champaca Linn.	Whole plant	Excision, incision and dead space	Dwajani et al., 2009
Mimosa pudica Linn.	Roots Leaves	Excision, incision and dead space Excision and incision	Paul et al., 2010 Venkateshwarlu et al., 2011 Kokane et al., 2009
Mimusops elengi Linn.	Bark	Excision, incision and dead space	Gupta et al., 2011
Momordica charantia Linn.	Fruit	Excision, incision and dead space	Prasad et al., 2006 Teoh et al., 2009
Morinda citrifolia Linn.	Leaves	Excision, incision and dead space	Rasal et al., 2008 Nayak et al., 2009
Moringa oleifera Lam.	Bark Leaves	Excision, incision and dead space	Vijay et al., 2012 Hukkeri et al., 2006
Murraya koenigii (L.) Spreng.	Leaves	Excision	Patidar et al., 2010
Musa sapientum Linn.	Fruit peel Fruit pulp	Incision Excision, incision and dead space	Atzingen et al., 2011 Agarwal et al. , 2009
Mussaenda frondosa Linn.	Leaves	Excision, incision and dead space	Patil et al., 2011
Myristica andamanica Hook.f.	Aerial Part	Excision	Arunachalam et al., 2011
Napoleona imperialis P.Beauv.	Leaves	Excision	Esimone et al., 2005
Napoleona vogelii Hook. & Planch.	Leaves	Incision	Adiele et al., 2014

Naravelia zeylanica (L.) DC.	Leaves	Excision, incision and dead space	Shenoy et al., 2009
Nauclea latifolia Sm.	Stem bark	Excision	Udobre et al., 2012
Nelumbo nucifera Gaertn.	Rhizomes	Excision, incision and dead space	Mukherjee et al., 2000b
Nyctanthes arbor-trisitis Linn.	Leaves	Excision and incision	Bharti et al., 2011
Ocimum basilicum Linn.	Leaves	Excision	Solanki et al., 2012
Ocimum gratissimum Linn.	Leaves	Excision	Osuagwu et al., 2004
Ocimum kilimandscharicum Gurke.	Leaves	Excision, incision and dead space	Paschapur et al., 2009
Ocimum sanctum Linn.	Leaves	Excision, incision and dead space	Shetty et al., 2008
Ocimum suave Wild.	Leaves	Excision	Hassan et al., 2011
Olea europaea Linn.	Leaves and Fruits	Excision and incision	Koca et al., 2011
Oncidium flexuosum Lodd.	Leaves	Incision	De G de Gaspi et al., 2011
Orbignya phalerata Mart.	Mesocarp from ripecoconut	Incision	Parada et al., 2006 Brito et al., 2006
Oxalis corniculata Linn.	Whole plant	Excision, incision and dead space	Taranalli et al., 2004
Panax ginseng C.A.Mey.	Leaves	Excision	Kim et al., 2013
Parietaria diffusa Merlet & W.D.J.Koch	Whole plant	Incision	Khalil et al., 2007
Passiflora edulis Sims.	Leaves	Excision and incision	Gomes et al., 2006 Garros et al., 2006
Pedilanthus tithymaloides (L.) Poit.	Leaves	Excision	Sriwiroch et al., 2010
Pentas lanceolata (Forssk.) Deflers	Flowers	Excision	Nayak et al., 2005
Persea americana Mill.	Fruit	Excision and dead space	Nayak et al., 2008

Phyllanthus emblica Linn.	Plant extract	Excision	Suguna et al., 2000
Phyllanthus niruri Linn.	Aerial parts	Excision and dead space	Okoli et al., 2009
Pinus halepensis Mill.	Essential oils from cones and needles	Excision and incision	Suntar et al., 2012
Pinus pinea Linn.	Essential oils from cones and needles	Excision and incision	Suntar et al., 2012
Piper hayneanum C. DC.	Leaves, Stem and roots	Excision	Bastos et al., 2011
Pisonia grandis R. Br.	Leaves	Excision and incision	Prabhu et al., 2008
Pistacia atlantica Desf.	Leaves and fruits	Excision	Tohidi et al., 2011
Pistacia khinjuk Stocks.	Leaves and fruits	Excision	Tohidi et al., 2011
Plagiochasma appendiculatum Lehm. & Lindenb.	Whole Plant	Excision and incision	Singh et al., 2006
Plagiochila beddomei Steph.	Thallus	Excision and incision	Manoj et al., 2012
Plantago major Linn.	Leaves	Excision	Mahmood et al., 2006
Plectranthus tenuiflorus (Vatke) Angew.	Leaves	Excision	Khorshid et al., 2010
Plumbago zeylanicum Linn.	Whole plant	Excision and incision	Reddy et al., 2002
Polygonum barbatum Linn.	Whole plant	Excision and incision	Kinger et al., 2012
Polygonum cuspidatum Willd. ex Spreng.	Whole plant	Excision	Wu et al., 2012
Polyscias scuttellaria (Burm.f.) Fosberg	Leaves	Excision, incision and dead space	Divakar et al., 2001
Portulaca oleracea Linn.	Aerial parts	Excision	Rashed et al., 2003
Prosthechea michuacana (Lex.) W.E.Higgins	Bulbs	Excision and incision	Gutierrez et al., 2009

Pseudarthria viscida (L.) Wight & Arn.	Whole plant	Excision	Vijayabaskaran et al., 2011
Pterocarpus marsupium Roxb.	Heart Wood	Excision	Singhal et al., 2012
Pterospermum acerifolium (L.) Willd.	Flower	Excision	Senapati et al., 2011
Pueraria tuberosa (Willd.) DC.	Tubers	Excision and incision	Kambhoja et al., 2007
Punica granatum Linn.	Peel	Excision	Murthy et al., 2004
Pyrostegia venusta (Ker Gawl) Miers.	Flower	Excision and incision	Roy et al., 2012
Quercus infectoria G.Olivier	Leaves	Excision, incision and dead space	Umachigi et al., 2008
Ranunculus pedatus Waldst. & Kit.	Whole plant	Excision and incision	Akkol et al., 2012
Rhodiola imbricate Edgew.	Rhizome	Excision	Gupta et al., 2007
Rosmarinus officinalis Linn.	Aerial parts	Excision	Abu-Al-Basal et al., 2010
Rubia cordifolia Linn.	Roots	Excision	Karodi et al., 2009
Rubus ellipticus Sm.	Leaves	Excision and incision	George et al., 2015
Rubus fairholmianus Gard.	Roots	Excision and incision	George et al., 2014
Rubus sanctus Schreb.	Aerial parts	Excision and incision	Suntar et al., 2011
Salvia cryptantha Montbret & Aucher ex Benth.	Whole plant	Excision and incision	Suntar et al., 2011
Salvia cyanescens Boiss. & Balansa	Whole plant	Excision and incision	Suntar et al., 2011
Salvia splendens Sellow ex Roem. & Schult.	Leaves	Excision and incision	Narayan et al., 2011
Sambucus ebulus Linn.	Leaves	Excision and incision	Suntar et al., 2010
Schinus terebinthifolius Raddi.	Bark	Incision	Dos Santos et al., 2012 Coutinho et al., 2006
Schrebera swietenioides Roxb.	Bark	Excision, incision and dead space	Rasal et al., 2009

Scorzonera cana (C.A.Mey.) Grossh.	Areial parts	Excision and incision	Suntar et al., 2012
Scorzonera eriophora D.C.	Areial parts	Excision and incision	Suntar et al., 2012
Semecarpus anacardium L.f.	Stem bark	Incision and dead space	Lingaraju et al., 2012
Senna alata Linn.	Leaves	Excision	Midawa et al., 2010
Sesamum indicum Linn.	Seeds	Excision, incision and dead space	Kiran et al., 2008
Sesbania grandiflora (L.) Pers.	Bark Flower	Excision Excision and Incision	Karthikeyan et al., 2011 Sheikh et al., 2011
Shorea robusta Gaertn.	Resin	Excision and Incision	Wani et al., 2012
Sida acuta Burm.f.	Whole plant	Excision and Incision	Akilandeswari et al., 2010
Sida spinosa Linn.	Leaves	Excision and Incision	Krishnan et al., 2011
Siegesbeckia pubescens Mak.	Fruits Leaves	Excision and Incision Excision and Incision	Kumar et al., 2010 Wang et al., 2011 Dewangan et al., 2012
Spathodea campanulata P.Beauv.	Stem bark	Excision	Ofori-Kwakye et al., 2011
Sphaeranthus amaranthoides Burm.f.	Whole plant	Excision	Geethalakshmi et al., 2013
Sphaeranthus indicus Linn.	Aerial Parts Flower	Excision Excision and Incision	Sadaf et al., 2006 Jha et al., 2011
Stachys lavandulifolia Vahl.	Flowers	Excision	Pirbalouti et al., 2011
Stevia rebaudiana (Bertoni) Bertoni.	Leaves	Excision and Incision	Das et al., 2012
Strobilanthes crispus Blum.	Leaves	Excision	Al-Henhena et al., 2011
Strophanthus hispidus DC	Roots and leaves	Excision	Agyare et al., 2013

Symphytum officinale Linn.	Leaves	Incision model	Araujo et al., 2012
Tagetes erecta Linn.	Leaves Whole Plant	Excision, incision and dead space Excision	Chatterjee et al., 2011 Ghosh et al., 2004 Kiranmai et al., 2011
Tamarindus indica Linn.	Seeds	Excision	Mohamad et al., 2012
Tamarix aphylla (L.) H.Karst	Leaves	Excision	Yusufoglu et al., 2011
Tecomaria capensis (Thunb.) Spach	Leaves	Excision, incision, burn and dead space	Saini et al., 2012
Tectona grandis L.f.	Leaves	Excision, incision, burn and dead space	Majumdar et al., 2007
Tephrosia purpurea (L.) Pers.	Aerial Part	Excision, incision and dead space	Lodhi et al., 2006
Terminalia arjuna (Roxb. ex DC.) Wight & Arn.	Bark	Excision and incision	Chaudhari et al., 2006
Terminalia avicennioides Guill. & Perr.	Root bark	Excision and incision	Mann et al., 2011
Terminalia bellirica Roxb.	Fruit	Excision and incision	Choudhary et al., 2008
Terminalia chebula Retz.	Leaves Bark	Incision Excision and incision	Suguna et al., 2002 Choudhary et al., 2011
Terminalia coriacea (Roxb.)Wight & Arn	Stem Bark	Excision	Khan et al., 2012
Thespesia populnea (L.) Sol. ex Correa	Fruits	Incision and excision	Nagappa et al., 2001
Tinospora cordifolia Willd.	Roots	Excision and incision	Nema et al., 2012
Toddalia asiatica (L.) Lam.	Stem bark	Excision and incision	Kar et al., 2005
Tragia involucrate Linn.	Roots	Excision	Perumal Samy et al., 2006
Tribulus terrestris Linn.	Leaves	Excision and incision	Weshley et al., 2009
Trichosanthes dioica Roxb.	Fruit	Excision and incision	Shivhare et al.,

			2010
Tridax procumbens Linn.	Whole plant Leaves	Dead space Excision	Diwan et al., 1982 Udupa et al., 1995 Yaduvanshi et al., 2011
Trifolium canescens Wild.	Aerial parts	Excision and incision	Renda et al., 2013
Typha domingensis Pers.	Female flower inflorescence	Excision and incision	Akkol et al., 2011
Trigonella foenum graecum Linn.	Seeds	Excision, incision and dead space	Taranalli et al., 1996
Vaccinium macrocarpon Aiton.	Seeds	Excision wound	Shivananda et al., 2011
Vanda roxburghii R.Br.	Whole plant	Excision	Nayak et al., 2005 a,b
Verbascum mucronatum Lam.	Flowers	Excision and incision	Akdemir et al., 2011
Verbascum thapsus Linn.	Flower	Excision	Mehdinezhad et al., 2012
Verbena officinalis Linn.	Bark	Excision	Sanjay et al., 2007
Vernonia arborea Buch.-Ham.	Leaves	Excision, incision and dead space	Manjunatha et al., 2005
Vernonia scorpioides (Lam.) Cass.	Leaves	Incision	Leite et al., 2005
Vinca rosea Linn.	Leaves	Excision	Nayak et al., 2006
Viscum articulum Brm.	Whole Plant	Excision, incision and dead space	Garg et al., 2012
Vitex altissima Linn.	Leaves	Excision, incision and dead space	Manjunatha et al., 2007
Vitex leucoxylon Span. ex Miq.	Stem Bark	Incision	Sarma et al., 1990
Vitex negundo Linn.	Leaves	Excision and incision	Talekar et al., 2012
Vitex trifolia Linn.	Leaves	Excision, incision and dead space	Manjunatha et al., 2007
Vitis vinifera Linn.	Seed	Excision	Shivananda et al., 2011

			Khanna et al., 2002
Vitis vitigenia (L.) W.Theob.	Leaves	Excision and Incision	Murti et al., 2011
Warburgia ugandensis Spr.	Leaves	Excision	Ogwang et al., 2011
Wattakaka volubilis (L.f.) Stapf	Leaves	Excision, incision and dead space	Ashoka Babu et al., 2012
Wedelia biflora Linn.	Leaves	Excision and incision	Biswas et al., 2013
Withania coagulans (Stocks) Dunal	Fruit	Excision	Prasad et al., 2010
Wrightia arborea (Dennst.) Mabb.	Leaves	Excision and incision	Lakshmi Devi et al., 2012
Wrightia tinctoria (Roxb) R. Br.	Leaves	Excision and incision	Divakar et al., 2012
Zanthoxylum chalybeum Engl.	Roots and Leaves	Excision	Ogwang et al., 2011
Ziziphus nummularia Linn.	Leaves	Excision	Yusufoglu et al., 2011
Zizyphus oenoplia (L.) Mill.	Fruits	Excision, incision and dead space	Kuppast et al., 2012

PLANT PROFILE

***Leea macrophylla* Roxb. ex Hornem.**

Leea macrophylla Roxb. ex Hornem. (Figure 3) belonging to the family Leeaceae, is commonly known as Hastikarna, owing to its very big size and fanlike leaves (like the ear of an elephant).

Figure 3: Plant of *Leea macrophylla* Roxb. ex Hornem.

Geographical Distribution

Leea macrophylla is distributed throughout the hotter parts of India, extending from Ganges eastwards Bihar, Bengal, Assam to Western India like Konkan. It is also found in Nepal, Bhutan, Myanmar, Bangladesh, Thailand, Cambodia, Siam and Laos (Singh and Singh, 1981).

Taxonomical description

Kingdom	:	Plantae, Plants
Class	:	Magnoliopsida
Sub class	:	Rosidae
Order	:	Vitales
Superorder	:	Vitanae
Family	:	Leeaceae (Vitaceae)
Genus	:	Leea
Species	:	*Leea macrophylla*

Vernacular Names

Hindi	:	Hathikana; hatkana;
Marathi	:	Gajakarni, Dinda;
Bengali	:	Dholsamudra;
Sanskrit	:	Hastikarna
Orissa	:	Hatikena, Hathikana;

Botanical description

It is an erect herb about 30-90 cm high with perennial red tuberous roots. Leaves are simple, broadly ovate, cordate, acute or acuminate, coarsely serrate or sublobed, nearly as broad as long, the lower leaves are up to 60 cm, the upper 15-23 cm. long, dark green glabrous above and cano-pubescent below , main nerves opposite, 8-10 pairs very prominent .They are simple broadly ovate, cordate, acute or acuminate, coarsely senate

or subloaded. Petioles are long glabrous and deeply striate. White branched puberulous corymbose cymes flowers are present with oblong buds, short pedicels and deeply grooved peduncle with oblong petals. Calyx are divided about 1/3rd of the way down with triangular ovate lobes tipped with small hard points. Staminal tube is deeply divided with oblong lobes, entire or emarginated along laterally united anthers in bud. Black, 3-6 celled depressed globose 3-6 lobed berries are also present (Kirtikar and Basu, 1975).

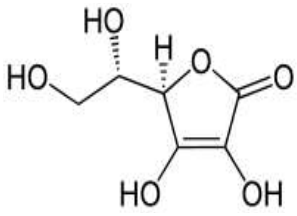
Traditional Uses

Leea macrophylla Roxb. ex Hornem. (Leeaceae), commonly known as Hastikarnapalasa is a wild edible plant with high nutritive value in terms of minerals and vitamins content (B1, B2, C and B12) (Jadhao et al., 2009). The dried powdered root of *Leea macrophylla* is taken along with clarified butter in the morning as age sustainer (Jadhao and Wadekar, 2010). Traditionally, the plant has been reported to be effective against guinea worm, ringworm and is applied on sores and wounds (Kirtikar and Basu, 1975; Misra, 2010). Roots are applied externally to allay pain and are alexipharmic (Kirtikar and Basu, 1975). In Uttar Pradesh (India) its local name is Bado hanshia where the local tribes use the root tubers orally and locally for treating wound (Anonymous, 1999). In literature it has been used in bone fracture, body pain, sprains, haemostatic, vermic and wounds (Jain, 1991).

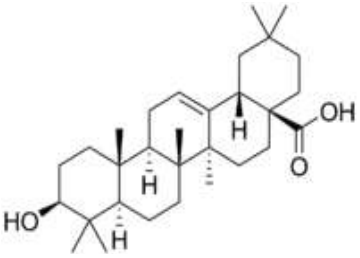
Phytochemical Review

The whole plant of *Leea macrophylla* have been evaluated for estimation of minerals like sodium, potassium, calcium, sulphur, boron and iron where plant showed maximum content of potassium and sulphur while boron was present in least quantity

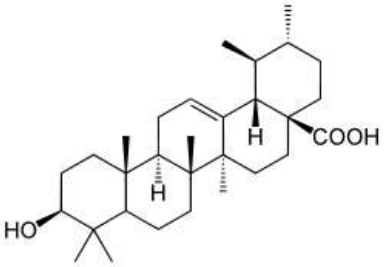
(Jadhao and Wadekar, 2010). Methanolic extract of *Leea macrophylla* leaves revealed presence of sterols, triterpenoids and ascorbic acid (Figure 4) in phytochemical investigation which was further analyzed using HPLC confirmed the presence of ascorbic acid, two triterpenic acids (Oleanolic acid and ursolic acid), lupeol, β -amyrin, stigmasterol and β-sitosterol (Dewanjee et al., 2013).



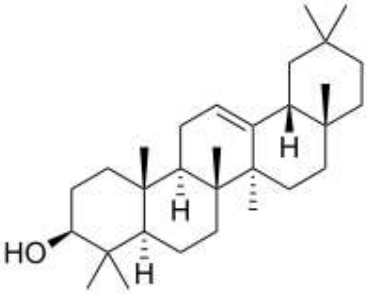
Ascorbic Acid



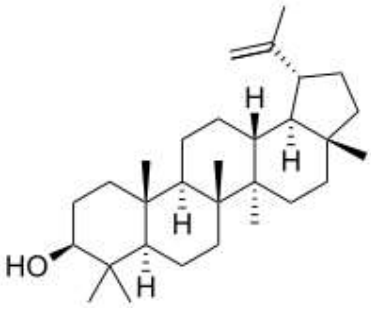
Oleanolic acid



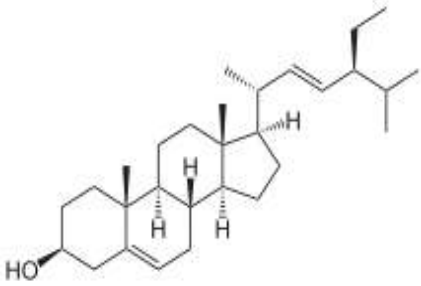
Ursolic Acid



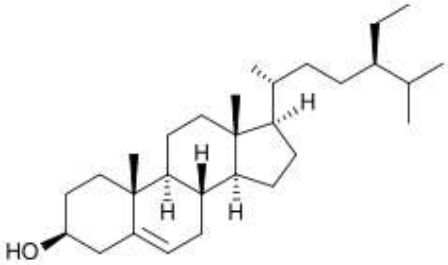
β –amyrin



Lupeol



Stigmasterol



β-sitosterol

Figure 4: Phytoconstituents present in *Leea macrophylla* leaves

The ethanolic extract of leaves of *Leea macrophylla* mainly demonstrated the presence of alkaloids, steroids, tannins and reducing sugars while seed showed the presence of phenolic, saponin, glycosides, carbohydrate and protein (Faruq et al., 2014; Islam et al., 2013).

Pharmacological Review

The roots of *Leea macrophylla* (Leeaceae) has shown to exhibit analgesic and preliminary cytotoxic activities (Mahmud et al., 2011). Whereas whole plant have been reported with promising antiurolithiatic effect (Nizami et al., 2012). Methanolic extract of leaves of *Leea macrophylla* have shown potent anti-inflammatory, analgesic and antipyretic activity by inhibiting lipopolysaccharide stimulated production of inflammatory mediators viz. prostaglandin E2, tumor necrotic factor-α, interleukin-6 and interleukin-1β (Dewanjee et al., 2013). Leaves have also shown to demonstrate significant hepatoprotective activity where CCl_4 induced damages were reversed towards normalization. The plant not only increased the regenerative and reparative capacity of the liver but, at the same time, prevented from oxidative damage. Reports have also shown that the leaves possess antimicrobial, anti-inflammatory, membrane stabilizing and anti-atherothrombosis activities (Akhter et al., 2015).