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SUMMARY OF WOUND HEALING ACTIVITY

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ABSTRACT

Wounds are the day-to-day problem which range from simple to complex wounds. This article is mainly reviewed to understand anatomical aspects of skin, healing mechanism of the body role of oxidative stress in the processes of wound healing.

Key words:
Wound Healing activity

INTRODUCTION:

A wound is defined as damage in the epithelial integrity of skin. The wound healing process begins with the restoration of a damaged tissue as closely as possible to its natural state and wound contraction is the course of shrinkage in wounded area. The healing primarily depends on the repairing ability of the tissue in addition to the type and degree of damage and general health status of the tissue.[1]

ANATOMY AND PHYSIOLOGY OF SKIN:

Structurally skin consists of two principal parts. The outer, thinner portion composed of epithelium, is called the epidermis. The epidermis is attached to the inner, thicker, connective tissue part called the dermis. Beneath this is a subcutaneous layer, also called hypodermis or superficial fascia, consists of areolar and adipose tissues. Fibers from the dermis extend down into the subcutaneous layer and anchor the skin to it. The hypodermis attaches to underlying tissues and organs.[1]

SKIN RECEPTORS[2]:

Skin receptors, also called cutaneous receptors, are part of the somatosensory system. They detect pressure, temperature, and vibrations on or around the skin. Cutaneous mechanoreceptors respond to pressure sensations on the skin and include Merkel's corpuscles, Meissner's corpuscles, and Bulboid corpuscles. Receptors that detect temperature are made up of free nerve endings on the skin and are called Thermoreceptors. Pain receptors on the skin are also free nerve endings called Nociceptors. Cutaneous mechanoreceptors are probably the first type of skin receptors that respond to different kinds of touch stimulation. Merkel's corpuscles are the most densely populated in the fingertips and respond to pressure. They are particularly sensitive to points and edges, and the response is directly related to the amount of pressure applied. Meissner's corpuscles are a type of touch receptor in the skin. The tips of the dermal papillae are covered in Meissner's corpuscles. When pressure is applied to the corpuscles, the nerve endings are stimulated, which registers in the brain as a touch sensation. Bulboid/Pacinian corpuscles are the skin receptors that respond to vibrations. They are found all over the body, including the lips and tongue as well as the penis and clitoris. They are also found in the joints of the fingers. Skin receptors that detect temperature are called Thermoreceptors. They respond to temperatures such as a burn or an ice cube, as well as overall environmental changes in temperature. The skins receptors that sense pain is called Nociceptors, which are made of free nerve endings in the skin, respond very quickly and send information directly to the brain and spinal cord.

WOUNDS:

A wound is a type of injury in which skin is torn, cut or punctured (an *open* wound), or where blunt force trauma causes a contusion (a *closed* wound). In pathology, it specifically refers to a sharp injury which damages the dermis of the skin.[3]

ETIOLOGY[4]:

- Blunt or penetrating trauma
- Surgery
- Chemical injury
- Thermal injury
- Temperature extremes (e.g., burns, frostbite)
- Ionizing radiation
- Tissue breakdown due to malnutrition or diabetes

SIGNS AND SYMPTOMS[4]:

- Erythema, Edema
- Pain and tenderness
- Heat
- Possible fever with infection
- Purulent exudate
- Loss of function (or mobility)
- Foul smell (in infected wounds only)

CLASSIFICATION OF WOUNDS:

Wounds are classified as open and closed.[5]

1) **OPEN WOUNDS**: Open wounds can be classified according to the object that caused the wound. The types of open wound are:

- **INCISION WOUNDS**: They are caused by a clean, sharp-edged object such as a knife, a razor or a glass splinter. Incisions tend to bleed freely because the blood vessels are cut cleanly and without ragged edges. Of all classes of wounds, incisions are the least likely to become infected, since the free flow of blood washes out many of the microorganisms (germs) that cause infection.
- **LACERATIONS**: They are irregular tear-like wounds caused by some blunt trauma. They have ragged, irregular edges and masses of torn tissue underneath are frequently contaminated with dirt, grease, or other material that is ground into the tissue. They are therefore very likely to become infected.
- **ABRASIONS:** Superficial wounds in which the topmost layer of the skin (the epidermis) are scraped off. Abrasions are often caused by a sliding fall onto a rough surface. This kind of wound can become infected quite easily because dirt and germs are usually embedded in the tissues
- **PUNCTURE WOUNDS**:
  Punctures are caused by objects that penetrate into the tissues while leaving a small surface opening. Wounds made by nails, needles, wire, and bullets are usually punctures. The possibility of infection is great in all puncture wounds, especially if the penetrating object has tetanus bacteria on it.
- **PENETRATION WOUNDS:** They are caused by an object such as a knife entering and coming out from the skin.
- **AVULSIONS**: An avulsion is tearing away tissue from a body part. Bleeding is usually heavy. In certain situations, the torn tissue may be surgically reattached.

2) **CLOSED WOUNDS**: Closed wounds are few but are just as dangerous as open wounds. The types of closed wounds are:

CONTUSIONS:

- They result from a forceful blow to the skin and soft tissues but leave the outer layer of skin intact.
- HEMATOMAS: They are also called a blood tumor, caused by damage to a blood vessel that in turn causes blood to collect under the skin.
- CRUSH INJURY: They occur when heavy objects fall onto a person, splitting the skin and tearing underlying edges.[3]

Table 1. Classification Of Surgical Wounds

TYPE OF WOUND	FEATURES
Clean	1. No hollow viscous entered 2. Primary wound closure 3. No inflammation 4. No breaks in septic technique
Clean contaminated	1. Hollow viscous entered 2. No inflammation 3. Primary wound closure 4. Minor break in aseptic technique
Contaminated	1. Uncontrolled spillage from viscous 2. Inflammation apparent

	3. Major break in aseptic technique
Dirty	1. Untreated, uncontrolled spillage from viscous 2. Pus in operative wound 3. Open and severe inflammation[6]

PATHOPHYSIOLOGY OF WOUNDS:

Wound pathophysiology refers to the processes that impair the normal healing of a wound, such as infection or certain types of scarring, and lead to complications such as a chronic wound.[7]

WOUND HEALING (Cicatrisation):

Healing is the body response to injury in an attempt to restore normal structure and function. Wound healing is a systemic process, which occurs stepwise and involves the stages of hemostasis, inflammation, and repair. Hemostasis with fibrin formation creates a protective wound scab. Repair begins immediately after wounding and proceeds rapidly through the processes of epithelialization, fibroplasia, and capillary proliferation into the healing area. In normal skin, the epidermis (outermost layer) and dermis (inner or deeper layer) exists in steady-state equilibrium, forming a protective barrier against the external environment. Once the protective barrier is broken, the normal (physiological) process of wound healing is immediately set in motion. There are four phases of normal wound healing. [8]

(a) Hemostasis
(b)Inflammation
(c) Proliferation
(d) Maturation and Remodeling[8]

I.HEMOSTASIS:

Just before the inflammatory phase is initiated, the clotting cascade takes place in order to obtain hemostasis or stop blood loss by forming a fibrin clot. After injury, blood comes in contact with collagen, triggering blood platelets to begin secreting inflammatory factors. Platelets also express glycoproteins on their cell membranes that allow them to stick to one another and to aggregate, forming a mass. Fibrin and fibronectin cross-link together form a plug that traps proteins and particles and prevents further blood loss. This plug is also the main structural support for the wound until collagen is deposited. The clot is eventually lysed and replaced with granulation tissue and then later with collagen. Platelets release a number of things into the blood, including ECM proteins and cytokines, including growth factors. Growth factors stimulate cells to speed their rate of division. Platelets also release other proinflammatory factors like serotonin, bradykinin, prostaglandins, prostacyclins, thromboxane, and histamine.[9]

II.INFLAMMATORY PHASE:

In the inflammatory phase, bacteria and debris are phagocytosed and removed, and factors are released that cause the migration and division of cells involved in the proliferative phase.[10]

Vasoconstriction and vasodilation: Immediately after a blood vessel is breached, ruptured cell membranes release inflammatory factors like thromboxanes and prostaglandins that cause the vessel to spasm to prevent blood loss and to collect inflammatory cells and factors in the area. This vasoconstriction lasts 5-10 mins and is followed by vasodilation, a widening of blood vessels, which peaks at about 20 minutes post-wounding. The main factor involved in causing vasodilation is histamine.[11]

Polymorphonuclear neutrophils: Within an hour of wounding, PMNs arrive at the wound site and become the predominant cells in the wound for the first two days after the injury. They are attracted to the site by fibronectin, growth factors, and substances such as kinins. Neutrophils phagocytise debris and bacteria and also kill bacteria by releasing free radicals in what is called a 'respiratory burst'. They also cleanse the wound by secreting proteases that break down damaged tissue, undergo apoptosis once they have completed their tasks, engulfed and degraded by macrophages.[11]

Macrophages: Macrophages replace PMNs as the predominant cells in the wound by two days after injury. Attracted to the wound site by growth factors released by platelets and other cells, monocytes from the bloodstream enter the area through blood vessel walls. Once they are in the wound site, monocytes mature into macrophages. The macrophages main role is to phagocytize bacteria and damaged tissue, and they also debride damaged tissue by releasing proteases. Macrophages also secrete a number of factors such as growth factors and other cytokines, especially during the 3rd and 4th post-wounding days. As inflammation dies, fewer inflammatory factors are secreted, existing ones are broken down, and numbers of neutrophils and macrophages are reduced at the wound site. These changes indicate that the inflammatory phase is ending, and the proliferative phase is underway. However, inflammation can lead to tissue damage if it lasts too long.[12]

III.PROLIFERATIVE PHASE:

About two or three days after the wound occurs, fibroblasts begin to enter the wound site, marking the onset of the proliferative phase even before the inflammatory phase has ended.[13]

Angiogenesis or neovascularization:

The process of angiogenesis occurs concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound. Because the activity of fibroblasts and epithelial cells requires oxygen and nutrients, angiogenesis is imperative for other stages in wound healing, like epidermal and fibroblast migration. The tissue in which angiogenesis has occurred typically looks red due to the presence of capillaries. Stem cells of endothelial cells, originating from parts of uninjured blood vessels, develop pseudopodia and push through the ECM into the wound site to establish new blood vessels. Endothelial cells are attracted to the wound area by fibronectin found on the fibrin scab and chemotactically by angiogenic factors released by other cells.[13]

Fibroplasia and granulation tissue formation:

Simultaneously with angiogenesis, fibroblasts begin accumulating in the wound site 2-5days after wounding. In the first 2-3days after injury, fibroblasts mainly migrate and proliferate, while later, they are the main cells that lay down the collagen matrix in the wound site. Granulation tissue begins to appear in the wound already during the inflammatory phase; 2-5days post wounding and continues growing until the wound bed is covered. Granulation tissue consists of new blood vessels, fibroblasts, inflammatory cells, endothelial cells, myofibroblasts, and the components of a new, provisional extracellular matrix (ECM). The provisional ECM is different in composition from the ECM in normal tissue and its components originate from fibroblasts. Such components include fibronectin, collagen, glycosaminoglycans, elastin, glycoproteins and proteoglycans. Growth factors (PDGF, TGF-β) and fibronectin encourage proliferation, migration to the wound bed, and production of ECM molecules by fibroblasts. Fibroblasts also secrete growth factors that attract epithelial cells to the wound site.[14]

Collagen deposition*:*

One of fibroblasts most important duties is the production of collagen. Collagen deposition is important because it increases the strength of the wound; before it is laid down, the only thing holding the wound closed is the fibrin-fibronectin clot, which does not provide much resistance to traumatic injury. Also, cells involved in inflammation, angiogenesis, and connective tissue construction attach to, grow and differentiate on the collagen matrix laid down by fibroblasts. Type III collagen and fibronectin are generally beginning to be produced in appreciable amounts at somewhere between approximately 10 hours and 3 days, depending mainly on wound size. In the later phase of maturation, they are replaced by the stronger type I collagen. At the end of the granulation phase, fibroblasts begin to commit apoptosis, converting granulation tissue from an environment rich in cells to one that consists mainly of collagen.[15]

Epithelialization: The formation of granulation tissue in an open wound allows the reepithelialization phase to take place, as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment. Basal keratinocytes from the wound edges and dermal appendages such as hair follicles, sweat glands and sebacious (oil) glands are the main cells responsible for the epithelialization phase of wound healing. They advance in a sheet across the wound site and proliferate at its edges, ceasing movement when they meet in the middle. Though in healing that results in a scar, sweat glands and hair follicles do not form. Migration of keratinocytes over the wound site is stimulated by lack of contact inhibition and by chemicals such as nitric oxide. Cells can only migrate over living tissue, so they must excrete collagenases and proteases like matrix metalloproteinases (MMPs) to dissolve damaged parts of the ECM in their way. Keratinocytes themselves also secrete growth factors and basement membrane proteins, which aid both in epithelialization and in other phases of healing.[16]

Contraction:

Contraction is a key phase of wound healing. If contraction continues for too long, it can lead to disfigurement and loss of function. Contraction can last for several weeks and continues even after the wound is completely reepithelialized. A large wound can become 40 to 80% smaller after contraction. At first, contraction occurs without myofibroblast involvement. Later, fibroblasts, stimulated by growth factors, differentiate into myofibroblasts. Myofibroblasts are responsible for contraction. Myofibroblasts contain the same kind of actin as that found in smooth muscle cells. As the actin contracts, the wound edges are pulled together. Fibroblasts lay down collagen to reinforce the wound as myofibroblasts contract. [16]

MATURATION AND REMODELING:

When the levels of collagen production and degradation equalize, the maturation phase of tissue repair is said to have begun. During maturation, type III collagen, which is prevalent during proliferation, is replaced by type I collagen. Originally disorganized collagen fibers are

rearranged, cross-linked, and aligned along tension lines. The maturation phase can last for a year or longer, similarly depending on wound type. As the phase progresses, the tensile strength of the wound increases, with the strength approaching 50% that of normal tissue by three months after injury and ultimately becoming as much as 80% as strong as normal tissue.[17]

Table 2. Types Of Healing

Types of Healing	Description
Primary	In primary closure, such as with a surgical incision, wound edges are pulled together and approximated with sutures, staples, or adhesive tapes, and healing occurs mainly by connective tissue deposition. Epithelial migration is short-lived and may be completed within 72 hours. Within 24 -48hours, epithelial cells migrate from the wound edges in a linear movement along the cut margins of the dermis. Most surgical wounds heal by primary intention healing. **Ex**: well-repaired lacerations, well reduced bone fractures, healing after flap surgery
Secondary	In wounds that heal by secondary intention, wound edges are not approximated, and healing occurs by granulation tissue formation and contraction of the wound edges. Healing process can be slow due to the presence of drainage from infection. **Ex**: tooth extraction sockets, poorly reduced fractures.
Tertiary	Wounds heal by tertiary intention (delayed primary intention). The wound is kept open for several days and the superficial wound edges are then approximated, and the center of the wound heals by granulation tissue formation. **Ex:** healing of wounds by using tissue grafts.[18]

FACTORS INFLUENCING HEALING:

Various factors may delay or impede healing. Local factors occur directly within the wound, whereas systemic factors occur throughout the body. [6]

A. LOCAL FACTORS: Infection and poor blood supply are the most important factors acting locally which delays the process of healing. Ex: Injuries to face heal quickly due to rich blood supply while injury to leg with varicose ulcers having poor blood supply heals slowly. Foreign bodies cause intense inflammatory reaction and infection. Exposure to UV light facilitates healing. Type, size and location of injury determine whether healing takes place by resolution or organization.

B. SYSTEMIC FACTORS: Wound healing is rapid in young and somewhat slow in aged and debilitated people due to poor blood supply to the injured tissue in the latter. Nutritional deficiency, systemic infection and uncontrolled diabetics delay the wound healing. Also, the administration of glucocorticoids has anti-inflammatory effect. Haematologic abnormalities like defects of neutrophil functions, neutropenia and bleeding disorders slow the process of wound healing.

COMPLICATIONS OF WOUND HEALING:

Infection of wound due to entry of bacteria delays the healing. Implantation cyst formation may occur due to persistence of epithelial cells in the wound after healing. Pigmentation, deficient scar formation, hypertrophied scars and keloid formation, incisional hernia, excessive contraction and neoplasia are other complications.[6]

Table 3. Drugs Used In Wound Healing

S.NO	CLASSIFICATION	EXAMPLES
1.	**ANTI-SEPTIC AGENTS**	Povidone iodine, Chlorhexidine (0.05%), Silver nitrate, Hydrogen peroxide
2.	**TOPICAL ANTIBIOTICS**	Silver sulphadiazine, Nitrofurazone, Gentamycin sulfate, Polymyxin-B, Bacitracin, Neomycin, Cefazolin (1st generation)
3.	**ANALGESICS**	Paracetamol, Ibuprofen
4.	**ANTI OXIDANTS**	Glyceryl trinitrate (1970s- cutaneous application), Retinoids (derived from vitamin A), Zinc[19]

HERBS:

- Turmeric (*Curcuma longa*) is an anti-inflammatory that potentiates bromelain. Use the dried extract 250 to 500 mg tid.
- Gotu kola (*Centella asiatica*) promotes connective tissue repair, supports normal wound healing, and prevents scar hypertrophy and keloid formation. For best results, use a standardized extract 60 mg one to two times daily. For tincture, take 60 drops tid to qid. Gotu kola may also be used topically as a wash for burns to minimize skin shrinking.
- Coneflower (*Echinacea purpurea*) increases macrophage activity. Goldenseal (*Hydrastis canadensis*) is an antimicrobial that enhances healing. Use them together to protect against secondary infection. Equal parts of tincture may be taken 30 to 60 drops tid to qid.
- Powders of goldenseal, comfrey (*Symphytum officinale*), and marshmallow root (*Althea officinalis*) may be applied topically to enhance healing and minimize infection.
- St. John's wort (*Hypericum perforatum*) oil applied topically helps prevent postsurgical adhesions and may relieve nerve pain.
- Aloe vera gel applied to burns and wounds provides excellent pain relief and speeds healing.
- Marigold (*Calendula officinalis*) and plantain (*Plantago major*) aid in healing and can be used topically as salves or creams. These should only be used in incisional or "clean" wounds. Due to their fast action, they could encapsulate an infection.[20]

OTHER TOPICAL AGENTS:

Live yeast, Phenytoin,Lanolin, Gallium nitrate, Recombinant vasoactive protein, Vitamin E.[21]

Table 4. Role Of Nutrients in Healing

NUTRIENTS	FUNCTION	DEFICIENCY EFFECT
Proteins	Required for cellular synthesis & proliferation, Maintains tissue integrity & Co-factor for healing	Delayed healing ↓Fibroblasts, collagen synthesis & elasticity
Carbohydrate	Energy source for tissues, essential-WBC functioning	↓ Energy, Altered WBC function
Fat	Membrane synthesis & proliferation	↓ Tissue repair
Vitamin-A	↑fibroplasia & collagen synthesis	↓Ability to prevent infection
Vitamin-C	Co-factor-hydroxylation of proline	Delayed healing
Vitamin-K	Synthesis of clotting factors	Bleeding, wound disruption
Zinc	Co-factor for enzyme-cell proliferation	Impaired overall wound strength, and delayed epithelialization.
Copper, manganese	Enzyme cofactors in collagen metabolism	Altered collagen formation [22]

Wound assessment:

Assessment of the wound is a prerequisite to the selection of appropriate dressing. Cause, Local wound characteristics: Location, Size (length x width x depth), Wound bed (black, yellow, red, pink, undermined), Exudate (copious, moderate, mild, none)Wound edge (callus and scale, maceration, erythema, edema), Odor (absent, present), Patient concerns: pain (persistent, temporary), Condition of surrounding skin (normal, edema, warmth, erythema), Clinical signs of critical colonization/local infection and infection.[23]

Table 5. Growth Factors Involved in Wound Healing:

GROWTH FACTORS	SOURCE	FUNCTIONS
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, keratinocytes	Chemotactic for PMNs, macrophages, fibroblasts, activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction; remodelling

Transforming growth factor-β (including isoforms β1, β2, and β3) (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, and fibroblasts; stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; induces TGF-β production
Epidermal growth factor (EGF)	Platelets, macrophages	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration
Transforming growth factor-α (TGF-α)	Macrophages, T lymphocytes, keratinocytes	Similar to EGF
Fibroblast growth factor-1 and -2 family (FGF)	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Keratinocyte growth factor (also called FGF-7) (KGF)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Insulin-like growth factor (IGF-I)	Macrophages, fibroblasts	Stimulates synthesis of sulfated proteoglycans, collagen, keratinocyte migration, and fibroblast proliferation; endocrine effects similar to those of growth hormone
Vascular endothelial cell growth factor (VEGF)	Keratinocytes	Increases Vaso permeability; mitogenic for endothelial cells[3]

PRECLINICAL STUDY

Animal wound healing models are important biological tools to understand basic processes of tissue repair and to develop and validate strategies for clinical treatment. In general, animal models (with the exception of some transgenic and targeted gene deletions) attempt to reflect human wound healing problems: dehiscence, ischemia, ulceration, infection, and scarring. Yet many investigators continue to investigate problems of impaired healing in young, rapidly growing animals where manipulating the course of a robust healing process is a much more difficult process.[24]

CLINICAL STUDY:

Clinical approach to wounds:

Clinical experience and existing research strongly support debridement as a necessary component of wound bed preparation when slough or eschar is present. The current techniques in wound bed preparation are found to be effective in assisting the wound-healing process. The process begins with the identification of a correct diagnosis of the wound's etiology and continues with optimizing the patient's medical condition, including blood flow to the wound site. Debridement as the basis of most wound-healing strategies is then emphasized. Various debridement techniques, includes surgery, topical agents, and biosurgery. To properly determine the timing of advance therapeutic intervention, the wound-healing progress needs to be monitored carefully with weekly measurements.[25]

Enzymatic debriding agents are an effective alternative for removing necrotic material from pressure ulcers, leg ulcers, and partial-thickness wounds. They may be used to debride both adherent slough and eschar. Enzymatic agents may be used as the primary technique for debridement in certain cases, especially when alternative methods such as surgical or conservative sharp wound debridement (CSWD) are not feasible owing to bleeding disorders or other considerations. Many clinicians will select enzymes when CSWD is not an option. Clinical experience strongly suggests that combined therapy, such as initial surgical debridement followed by serial debridement using an enzymatic agent or enzymatic debridement along with serial CSWD, is effective for many patients with chronic, indolent, or nonhealing wounds.[25]

Hyperbaric oxygen therapy (HBOT) has been suggested to improve oxygen supply to wounds and therefore improve their healing.[26]

POST OPERATIVE CARE:

Principles of postoperative wound care include providing a moist wound healing environment through the use of proper dressings, protecting the surgical site from further injury, and providing nutritional substrates are essential to the healing process.[27]

STEM CELL THERAPY IN WOUND HEALING:

Stem cells can also be used to stimulate the growth of human tissues. In an adult, wounded tissue is most often replaced by scar tissue, which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells. A possible method for tissue regeneration in adults is to place adult stem cell "seeds" inside a tissue bed "soil" in a wound bed and allow the stem cells to stimulate differentiation in the tissue bed cells. This method elicits a regenerative response more similar to fetal wound-healing than adult scar tissue formation. Researchers are still investigating different aspects of the "soil" tissue that are conducive to regeneration.[28]

NEUTRACEUTICALS IN WOUND HEALING:

"Herbal remedies are considered the oldest forms of health care known to mankind on this earth. The parts of the plant used for medicinal purposes are leaves, root, stem, fruits, the complete aerial parts, the whole plant, barks (root and stem) and flowers. However, leaves were found most frequently used part".[29]

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