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A REVIEW ON MEDICINAL PLANTS WITH POTENTIAL WOUND HEALING ACTIVITY

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Abstract: Healing of wounds, either accidental or surgical interventions, involves complex activities of blood cells, tissues, soluble mediators, cytokines and several growth factors. This increased cellular activity of damaged tissue enhances metabolic demands and active drug therapy. The main objective of treating a wound is to either shorten the time required for healing process or to minimize the undue effects. Plants due to presence of various valuable active phytoconstituents have immense potential for management and treatment of wounds over the years. All the Traditional systems of medicine, Ayurveda, Siddha and Unani describe applications of drugs of plant, mineral and animal origin to treat and heal wounds. Herbal drugs induce healing and regeneration of lost tissue by number of mechanismsThe present review is an attempt to highlight various Indian ethno-medicinal plants which are to be scientifically proved for the treatment of wounds and pharmacological activities and role of plants in wound management and parameters used to assess wound healing.

Key words: Wound healing, potential medicinal plants, Traditional medicine, pharmacological activities

I.INTRODUCTION

Skin covers the external surface of the body. Skin contributes in thermoregulation, serve as water repellent, and synthesize a number of useful compounds like vitamin D and most importantly it act as a protective barrier between the external environment and internal tissue¹. According to medical dictionary; breaching of skin or underlying tissue due to any accident, act of violence or surgery is called as wound ². Following an injury, the skin has a tremendous capacity to heal.

When skin gets injured, the repair process entails removal of the damaged tissue and laying down of a new extracellular matrix (ECM) over which epidermal continuity can be reestablished³. Wound repair must occur in a physiologic environment to promote tissue repair and regeneration. However, several clinically significant factors are known to impede wound healing including hypoxia, infection, tumors, metabolic disorders such as diabetes mellitus, the presence of debris and necrotic tissue, certain medications, and a diet deficiency in protein, vitamin, and minerals etc⁴. Current estimates indicate that approximately 6 million people suffer from chronic wounds worldwide⁵. There are very few Indian studies on the epidemiology of wounds. The prevalence of wounds in the population studied was 15.03 per 1000. The prevalence of chronic wounds in the community was reported as 4.5 per 1000 population whereas that of acute wounds was nearly doubled at 10.5 per 1000 population⁶. Today, the principles of topical wound therapy involve elimination of necrotic tissue, control of bacterial loads, management of wound exudates, maintenance of open proliferative wound edges, and provision of a moist and protected wound surface⁷. Medical treatment of wound includes administration of drugs either locally (topical) or systemically (oral or parenteral) or both in an attempt to aid wound repair⁸. Antimicrobial dressings including disinfectants, antiseptics and antibiotics are applied topically to exert a broad spectrum of non-selective antibacterial action⁹.

The most commonly used antiseptic products in clinical practice include povidone-iodine complex, chlorhexidine, alcohol, triclosan, hydrogen peroxide, boric acid, silver nitrate, silver sulfadiazine and sodium hypochlorite¹⁰. In clinical practices, topical antibiotics are commonly prescribed in wounds, cuts and burns for their potential use in localized cutaneous infections. However frequent and overuse of topical antibiotics can cause problems like development of resistant organisms¹¹. Therefore attention should be directed towards discovering an agent that accelerates wound healing either when it is progressing normally, or when it is suppressed by various agents like corticosteroids, anti-neoplastics, or non-steroidal anti-inflammatory agents¹². Natural product research is often based on ethno-botanical information and many of the drugs used today were developed from medicinal plants employed in indigenous societies¹³. This article provides a general description on normal wound healing process. Plant phytoconstituents that play a role in wound management is also explained in this review. It also provides knowledge regarding the parameters used to assess wound healing and also enlist various traditional Indian medicinal plant used for wound healing.

II.Normal wound healing process

Wound is defined as loss or breaking of cellular and anatomic or functional continuity of living tissue due to physical, chemical, thermal, microbial or immunological exploitation to the tissues^{14, 15}. Wound healing disorders present a serious clinical problem and are likely to increase when they are associated with diseases such as diabetes, hypertension, and obesity. Additionally, increasing life expectancies will cause more people to face such disorders and therefore wounds become an unavoidable event of life¹⁶. Wound healing is a complex multistep physiological process that involves multitude of cells and events. It is a dynamic, interactive process which involves soluble mediators, blood cells, extracellular matrix and parenchymal cells. It is dependent on a number of inter-related factors¹⁷⁻¹⁹.

In normal conditions, the epidermis (outermost layer of the skin) and dermis (inner layer) forms a protective barrier against the external environment. If this protective barrier is broken due to any kind of injury, a set of complex biochemical events of wound healing takes place in a highly sequenced manner to repair the damage²⁰. Normal wound healing is mostly characterized by four continuous, overlapping and precisely planned phases: hemostasis phase (formation of blood clot), inflammation phase, proliferation or granulation phase, and remodeling or maturation phase (formation of scar) shown in **Fig. 1**^{21, 22}.

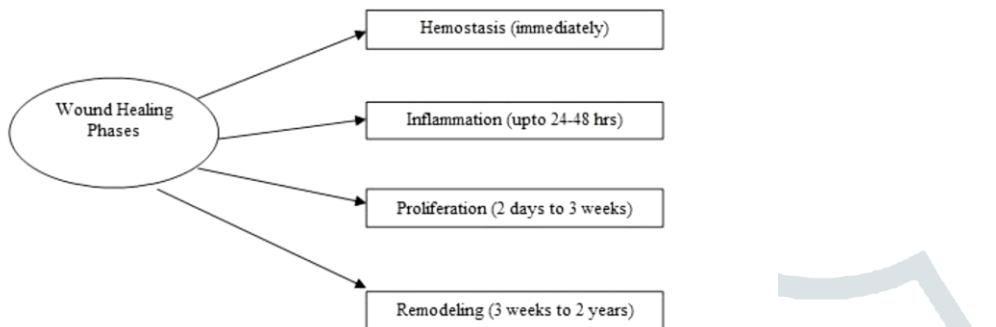


FIG. 1: NORMAL WOUND HEALING PHASES

Optimal wound healing involves the following the events: (1) rapid hemostasis; (2) appropriate inflammation; (3) mesenchymal cell differentiation, proliferation, and migration to the wound site; (4) suitable angiogenesis; (5) prompt re-epithelialization (re-growth of epithelial tissue over the wound surface); and (6) proper synthesis, cross-linking, and alignment of collagen to provide strength to the healing tissue. Various cellular and bio-physiological events occur during wound healing process are shown in **Table 1**²³.

TABLE 1: NORMAL WOUND HEALING PROCESS

Phases	Cellular and Bio-physiological events
Hemostasis	1. Vascular constriction 2. Platelets aggregation, degranulation and fibrin formation (Thrombus)
Inflammation	1. Neutrophil infiltration 2. Monocyte infiltration and differentiation to macrophages 3. Lymphocyte infiltration
Proliferation	1. Re-epithelialization 2. Angiogenesis 3. Collagen synthesis 4. Extracellular matrix formation
Remodeling	1. Collagen remodelling 2. Vascular maturation and regression

III.Role of traditional medicines in wound healing

It has been estimated by WHO that at least 80% of the world population, mainly in the developing countries, still dependent on herbal medicines for their primary health care needs. Use of traditional medicine is based on its accessibility, affordability and its firm embedment within the faith systems of people^{24, 25}. Traditional knowledge is a valuable asset for any country as it plays a vital role in making the nation more progressive and transforming its society²⁶. Traditional medicine is a collection of therapeutic experience of various physicians on indigenous/traditional system of medicine²⁷. According to WHO, “Traditional medicine refers to health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being.”

Traditional medicine is called in various ways such as alternative medicine, complementary medicine, natural medicine, herbal medicine, phyto-medicine, non-conventional medicine, indigenous medicine, folk medicine, ethno medicine etc²⁸. People in the rural places where modern health care services remains inaccessible are still use their knowledge, skill and practices on various plant products for treating various ailments²⁹. It has been estimated that 70% of wound healing Ayurvedic drugs are plant based, 20% of mineral based and remaining 10% consists of animal products as their base material³⁰. Traditional wound management involves disinfection, debridement and providing a moist environment to encourage the establishment of a suitable environment for the natural healing process³¹.

IV.Pharmacological activities of plants supporting wound healing

4.1.Anti- inflammatory activity

Inflammation phase in normal wound healing process is essential, because it generates neutrophils that are responsible for microbial clearance in the region of the wound (phagocytosis) and also playing a role in antigen presentation. In this phase production of inflammatory cytokines and growth factors also occur. Any pathological process that interferes with this self-limited physiological process can result in a non healing wound because of net destruction of soluble growth factors and matrix elements^{32, 33}. Various traditional texts and animal studies indicate the anti-inflammatory effect of plant extract thus can be used as wound healer drugs^{34, 35}.

4.2. Antioxidant activity

Plant produces various anti oxidative compounds to counteract reactive oxygen species (ROS) in order to survive. ROS include free radicals such as superoxide anion radicals, hydroxyl radicals and non free-radical species such as hydrogen peroxide etc are exacerbating factors in cellular injury and aging process³⁶. Various antioxidant natural remedies derived from plant such as polysaccharides from *Angelica sinensis*, *Aloe vera* gel, *Eucommia ulmoides* Oliver leaf extract possess wound healing by scavenging free radical and promoting collagen synthesis³⁷.

4.3.Antimicrobial activity

Microorganisms are believed to play a significant role in impaired healing of chronic wounds and the development of infection-related complications³⁸. Bacterial infection can cause sepsis which impedes the repair process³⁹. A number of polyherbal preparations containing antimicrobial action have been scientifically proved to possess wound healing activity e.g. polyherbal gel formulated from *Terminalia arjuna*, *Centella asiatica* and *Curcuma longa* reported to possess antimicrobial and wound healing activities⁴⁰.

4.4.Analgesic activity

Pain is a common experience for patients with wounds. At a physiological level, wound pain arises from tissue damage (nociceptive pain) or from dysfunction of the nervous system (neuropathic pain)⁴¹. Pain may cause delay in wound healing process by dysregulating neuroendocrine and immune functions which play critical role in wound repair mechanism⁴². Thus, herbal preparations possessing analgesic and anti-inflammatory activities can be employed for pain management of wounds.

4.5.Role of phytoconstituents in wound healing activity

Phytoconstituents present in the plant extracts may interfere with one or more phases of the wound healing process in a positive manner in proper sequence and at the right time frame to show improved efficacy as shown in **Table 2**⁴³. Various substances possessing wound healing activity has been isolated from plants e.g. tannins from *Terminalia arjuna*, polysaccharides from *Opuntia ficus-indica*, asiaticoside, asiatic acid and madecassic acid from *Centella asiatica* and curcumin from *Curcuma longa* etc⁴⁴.

4.6.Parameters used to assess wound healing activity

For the study of wound healing activity many *in-vitro* and *in-vivo* models have been used. *In-vitro* study of wound healing can be done by keratinocytes assay, wound healing migration assay and cell proliferation assay or fibroblasts assay⁴⁵. *In-vivo* models such as incision models, excision models, dead space models and burn models can be performed. Estimation of tensile strength of skin, hydroxyproline content and measurement of wound area, percentage of contraction and period of epithelialization are some more preferable parameters used for evaluation of wound healing activity of any compound⁴⁶⁻⁴⁸.

V. Medicinal plants possessing wound healing activity

India is eighth major centre of origin and diversification of domesticated taxa due to its glorious part of traditional medicinal system and is one of the world's twelve mega diversity countries⁴⁹. Therefore, it has a rich traditional knowledge for management and treatment of wounds since thousands of years. Indian religious book „Ramayana“ described the use of plant based medicine from Himalayas for treating Lord Rama's Brother Lakshman in the battlefield of Lanka.

Herbal products are in huge demand in developed countries too due to undue side effects of synthetic products and comparatively safe parameters of herbal products. Various scientifically evident plants used by local communities of India for management of wound healing are given as:

5.1.*Acalypha indica* Linn. (Euphorbiaceae)

Acalypha indica L. is a weed plant widely distributed throughout the plains of India. It has been reported to be useful in treating pneumonia, asthma, rheumatism and several other skin ailments. *A. indica* leaves and flowers showed antioxidant activity due to presence of flavanoids, kaempferol, glycosides, mauritianin, ciltoria and nictiflorin. The ethanolic extract of dried leaves of *A. indica* has been used for bedsores and wounds treatment^{50, 51}. Raja *et al.* showed the anti-bacterial activity of aqueous and acetone extract of leaves of plant⁵².

5.2.*Aloe vera* (Liliaceae)

Aloe vera is indigenous medicinal plant found throughout India. There are over 100 active constituent are found in *A. vera* plant which possesses astringent, haemostatic, antidiabetic, antiulcer, antiseptic, antibacterial, anti-inflammatory, antioxidant, anticancer, antidiarrhoeal, and wound healing properties⁵³. The mucilage content present in leaves of this plant that is also called as aloe gel is used for various cosmetics and medical applications⁵⁴. *A. vera* leaves pulp was found to have better and faster wound healing effect than standard drug Povidone Iodine ointment (5 % w/w) on excision wound model⁵⁵.

5.3.*Asparagus racemosus* (Liliaceae)

Asparagus racemosus is an indigenous medicinal climber found all over India; especially in Northern India. Plant value is known for its saponin content which is a precursor of many pharmacologically active steroids⁵⁶. Prabhat *et al.* studied the wound healing activity of aqueous root extract of *A. racemosus* on dead space model on albino rat. The extract showed a facilitating effect on wound healing by a significant increase in hydroxyproline, hexosamine and hexuronic acid in granulating tissue⁵⁷.

5.4.*Azadirachta indica* (Meliaceae)

Azadirachta indica commonly known as Neem is a well known versatile plant of India for more than 2000 years possess wide spectrum of medicinal activities. Nimbidine, nimbin, sodium nimbidate and nimbolide main active constituent extracted from oil of its seed kernels showed antibacterial, anti-pyretic and anti-inflammatory properties⁵⁸. Purohit *et al.* evaluated the wound healing activity of ethanolic extract of leaves of *A. indica* in male albino rats⁵⁹.

5.5.*Bryophyllum pinnatum* (Lam.) Kurz. (Crassulaceae)

Bryophyllum pinnatum also known as *Bryophyllum calycinum* is a perennial herb used as folkloric medicine in India and many other countries. The main phytochemical constituents present in plant are phenols,

flavanoids, alkaloids, tannins, glycosides, saponins, coumarins and sitosterols^{60, 61}. Leaves of plant possess disinfectant and anti-bacterial properties used for boils, swelling, insect- bite, burns and wounds⁶².

5.6.*Calotropis gigantea* (L.) R. Br. (Asclepiadaceae)

In ancient Ayurvedic medicine the plant *Calotropis gigantea* is known as “Sweta Arka.” It is a native to India, China, Malaysia and in many other countries. The main active phytoconstituents isolated from plant are flavonoids, triterpenoids, phenolic compounds, tannins, alkaloids, steroids, glycosides, saponins, terpenes, enzymes, alcohol, resin, fatty acids and esters of calotropoels⁶³. Deshmukh *et al.* evaluated the wound healing activity of topical application of *Calotropis gigantea* in excision wound model. Percentage of wound contraction was found to be increased due to elevating hydroxyproline content in incision wound and dead space wound model⁶⁴.

5.7.*Centella asiatica* (Linn.) Urban (Apiaceae)

Centella asiatica or Indain Pennywort is distributed throughout the plains of India. It is known as Brahmi in Unani medicine and Mandookaparni in Ayurvedic medicine system⁶⁵. The main therapeutic active biomarker compounds reported in plant are saponins containing triterpens namely, asiatic acid, madecassic acid, asiaticoside and madecassoside⁶⁶. It has been reported that 1% *C. asiatica* extract cream improves chronic wound healing⁶⁷. Shukla *et al.* studied the wound healing activity of topical application of asiaticoside in normal as well as in diabetic animals. The rate of wound healing in normal animals significantly enhanced due to increase in collagen synthesis and tensile strength of the wound tissues⁶⁸. Liu investigated the effect of madecassoside, on wound healing involved several mechanisms including antioxidative activity, collagen synthesis and angiogenesis affect⁶⁹.

5.8.*Curcuma longa* Linn. (Zingiberaceae)

Curcuma longa is an oldest spice and very useful herb of Ayurvedic medicine. It has been used throughout India since thousands of years. It is also referred to as „Indian saffron” and turmeric⁷⁰. Major components of turmeric are named curcuminoids, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. Curcumin, a potent antioxidant is believed to be the most important bioactive component of the herb turmeric and posses the properties like antioxidant, anti-inflammatory, anti-platelet, cholesterol lowering, antibacterial and anti-fungal effects⁷¹. Purohit *et al.* investigated that ethanolic extract of *C. longa* rhizomes have better and faster wound healing effect than standard drug Povidone Iodine ointment on excision wound model⁷².

5.9.*Elephantopus scaber* Linn. (Asteraceae)

E. scaber is a weed plant that grows under shady places. Main bioactives compounds isolated from ethanolic extract of plant are sesquiterpene lactones suh as elescaberin, isodeoxyelephantopin, deoxyelephantopin, isoscabertopin and scabertopin⁷³. Singh *et al.* evaluated the wound healing potential of aqueous leaf extract

and deoxyelephantopin, a compound isolated from ethanolic extract of leaf. Wound healing found to be more effective in animals treated with deoxyelephantopin⁷⁴.

5.10.*Euphorbia neriifolia* Linn. (Euphorbiaceae)

Euphorbia neriifolia L. grows luxuriously in north, central and south India⁷⁵. Bigonia et al evaluated the wound healing activity of *E. neriifolia* leaf on excision and dead space wound model. *E. neriifolia* augmented wound contraction and epithelisation by increased protein and hydroxyproline content⁷⁶. Gour et al. evaluated the anti-inflammatory and analgesic effect of hydroalcoholic leaf extract plant⁷⁷.

5.11.*Ficus racemosa* Linn. (Moraceae)

Ficus racemosa Linn. large deciduous tree distributed all over India especially in north India⁷⁸. Murti et al. evaluated the wound healing activity of aqueous and ethanolic extract of roots of *F. racemosa* on incision and excision wound model. Aqueous extract of root increased the percentage closure due to enhanced epithelialization and collagen synthesis⁷⁹.

5.12.*Jatropha curcas* Linn. (Euphorbiaceae)

Jatropha curcas Linn. commonly known as physic nut or jungali arandi. Plant extract is used in the treatment of allergies, burns, cuts, wound inflammation, leprosy, leucoderma and smallpox⁸⁰. Nwala et al. formulated an herbal ointment of *J. curcas* leaf extract and evaluated its wound healing activity. Ointment was found to be good wound care product⁸¹. Similarly, Esimone et al. showed the potential wound healing activity of methanolic leaf extract of *J. curcas* on excision wound model⁸².

5.13.*Lantana camara* Linn. (Verbenaceae)

Lantana camara is a flowering ornamental plant found throughout in India. It is also known as lantana, wild sage, Surinam tea plant or Spanish flag. In India tea of leaves is used as remedy against cough and pounded leaves are applied as a paste to cuts, ulcers, swellings and wound healing^{83, 84}. Nayak et al. found the better burn wound healing activity of the leaf extract of *L. camara* in rats as compare to control group⁸⁵.

5.14.*Ocimum sanctum* Linn. (Labiaceae)

Ocimum sanctum Linn. a commonly known as „Tulsi“ is widely distributed plant throughout India and different parts of the world. It possesses anti-inflammatory, analgesic, immunostimulatory, free radical scavenging and antimicrobial activity. The free radical scavenging activity of plant flavonoids help in the healing of wounds. Asha et al. evaluated the topical wound healing activity of aqueous extract of leaves of *O. sanctum*⁸⁶. Goel et al. studied the wound healing activity of cold aqueous extract of *O. sanctum* along with its effect on tumor α production⁸⁷. Some other plants used traditionally and also scientifically validated are tabulated in **Table 3**.

TABLE 3: SCIENTIFICALLY EVIDENT PLANTS USED FOR WOUND HEALING ACTIVITY

Botanical name/Common name (Family)	Part used	Extract used	Wound healing model used
<i>Acorus calamus</i> /Bach plant (Acoraceae)	Green leaves	Ethanolic	Excision and incision ⁸⁸
<i>Allium sativum</i> L./Garlic (Liliaceae)	Bulb	Aqueous and Ethanolic	Excision, incision and dead space ⁸⁹
<i>Adhatoda vasica</i> N./Adalsa (Acanthaceae)	Leaves	Methanolic, chloroform and diethyl ether	Excision ⁹⁰
<i>Alternanthera brasiliiana</i> Kuntz./ Gudaari saag (Amaranthaceae)	Leaves	Methanolic	Excision, incision and chorioallantoic membrane ⁹¹
<i>Andrographis paniculata</i> /Kalmegh (Acanthaceae)	Whole plant	Pet ether and Ethanolic	Excision ⁹²
<i>Areca catechu</i> L./Betel nut (Arecaceae)	Areca nut	Ethanolic	Burn wound ⁹³
<i>Butea monosperma</i> Lam. /Palash (Fabaceae)	Stem bark	Ethanolic	Excision, incision and dead space ⁹⁴
<i>Cassia fistula</i> L./Amaltas (Caesalpinoideae)	Leaves	Ethanolic	Incision ⁹⁵

VI.CONCLUSION

Utilization of plants for medicinal purposes in India has been documented long back in ancient literature because they are essential for human survival. Traditional medicinal system is widely distributed in India. A major proportion of population mostly belonging to rural areas is still dependent on traditional system of medicines for their various health needs. It is evident that any system of healthcare solely will not capable to cope-up with the health care demands of public. Therefore, traditional and cultural medical knowledge has a catalyzing effect in meeting health care demands. There are a number of plants which have been reported for their wound healing activity due to presence of valuable phytoconstituents. Most of these studies involve random screening of plant or extracts for wound healing activity. Since in actual experiments and usage, all the plant products as cited in the table have shown efficacious results, there are a number of plants which have been reported for their wound healing activity due to presence of valuable phytoconstituents. Most of these studies involve random screening of plant or extracts for wound healing activity. Since in actual

experiments and usage, all the plant products as cited in the table have shown efficacious results, there are increased needs to isolate and investigate each active ingredient that has a positive role in the healing process.

The combination of traditional and modern knowledge can produce better drugs for wound healing with fewer side effects. Such type of traditional knowledge on plant can form a basis for clinical, medicinal, pharmacological and novel drug delivery system for wound healing products.

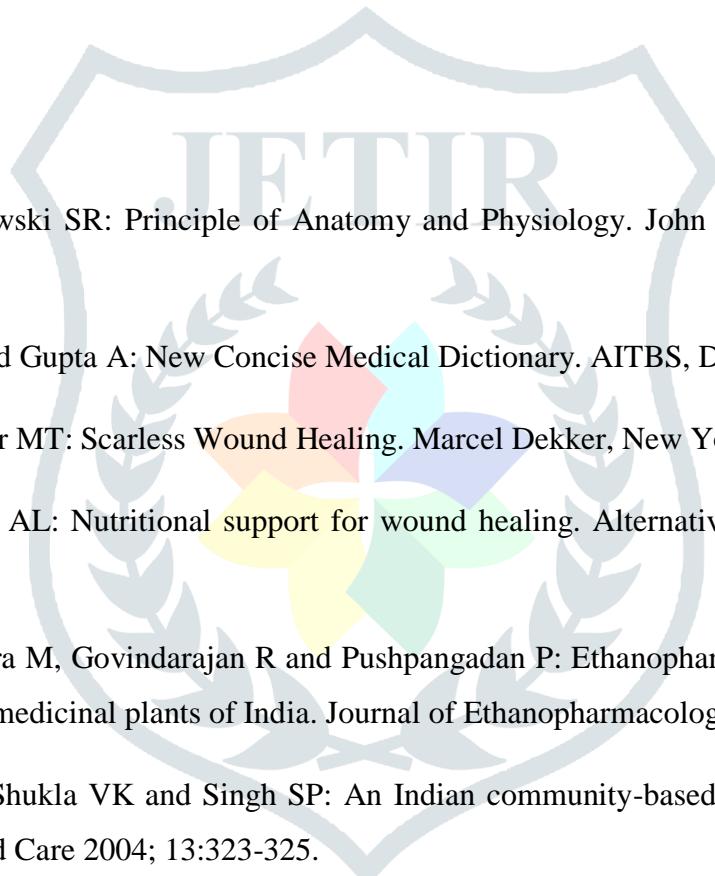
VII. ACKNOLEDGEMENT

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VIII.CONFLICT OF INTEREST

No conflict of Interest

IX. REFERENCES

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