MIRACLE OF HERBS IN ANTIBIOTIC RESISTANT WOUNDS AND SKIN INFECTIONS: TREASURE OF NATURE – A REVIEW/ PERSPECTIVE

Ruchi Tiwari¹, Sandip Chakraborty²* and Kuldeep Dhama³

¹Department of Veterinary Microbiology and Immunology, Uttar Pradesh Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishvavidhyalaya Ewam Go-Anusandhan Sansthan (DUVASU), Mathura (U.P.)–281001;
²Veterinary Officer, Animal Resources Development Department, Pt. Nehru Complex, Agartala, Pin – 799006;
³Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.) – 243122, India

ABSTRACT

Wound is unavoidable in life and is caused by tearing of skin or external surface. As mentioned in Ayurveda different types of wound may be endogenous or exogenous in origin. Now-a-days skin affections due to microbial agents and various types of topical wounds and ailments are requiring special attention as they make animals prone to various microbes thereby leading to secondary contamination. Development of antimicrobial resistance among the bacteria and fungi is an important issue for treatment of infectious diseases in man and animals. Evolution of Methicillin Resistant Staphylococcus aureus (MRSA); Community Acquired Methicillin Resistant Staphylococcus aureus (CA-MRSA) and Vancomycin Resistant Enterococcus faecalis (VREF) have made the condition grave. Due to rapid development of resistance against chemotherapeutic agents (particularly antibiotics) it has become essential presently to think over some alternative and effective therapeutics like herbs, panchgavya and bacteriophages. Traditional system of medicines that incorporates plants for therapeutic purpose came into existence long back (around 60,000 years ago). In modern era uses of herbal plants in health industry are gaining increasing attention in both consumer and scientific circle. The wide availability as well as less toxicity and absence of unwanted side effects after use along with being more potent in their crude form have made the use of herbs in wound and skin infection invaluable. They contain a wide variety of active components viz. flavonoids; saponins; alkaloids and tannins; aminoglycosides and fatty acids; amino acids which facilitate the healing process by hastening the formation of blood and cellular components along with granulation tissue and extracellular matrix. Along with a wide variety of plants certain conventional therapies involving the use of honey or cow urine are also gaining popularity. The present review elaborates the potential role of herbs in treating skin infections and various types of wounds for safeguarding animal and human health.

Keywords: Alternative medicine, antibiotic resistance, herbal therapy, skin infections, traditional medicine, wound management.

INTRODUCTION

Wound is such a kind of injury wherein either skin or any other external surface gets torn and are considered as unavoidable events of life. Physical as well as chemical and thermal or even microbial and immunological factors may be responsible for causing
wound resulting in the loss of epithelial continuity with or without the underlying connective tissue loss \[1\]. Patients (either animal or human) and professionals involved in their health care suffer from the burden of wound and currently approximately 6 million people prove to be the sufferers especially from chronic wounds \[2\]. Inflammatory mediators are constantly produced by wounds that show no sign of healing and the risk of death is involved when multiple organ failure occurs due to chronic wound making it alarming to mankind and animals \[3,4\]. As mentioned in Ayurveda different types of wound may be endogenous in origin as a result of functional unit defects such as: Vata (nerve impulse); Pitta (enzymes and hormones); and Kapha (body fluids). They may even be exogenous in origin as a result of trauma such as: Chinna (cut wound); Bhinna (wounds that are perforated); Viddha (punctured wound); Kshata (lacerated wound); Picchita (contusion); and Ghrista (abrasions) \[5\].

Now-a-days skin affections due to microbial agents and various types of topical wounds and ailments are requiring special attention as they make the animals prone to bacterial, fungal and viral contamination, thereby make them further susceptible to other types of secondary complications. Skin ailments or wounds are probably the single most common cause of enhanced susceptibility of animals to infections \[6\]. Skin has maximum exposure to pathogens and hence is very prone to injuries, wound and lesions formation. Skin, 12-24% of an animal’s body weight, being the outermost and first line of defense, easily get exposed to physical agents and different pathogens leading to various infections and wounds \[7\]. These may progress gradually because of secondary infections or as a result of the production of inflammatory mediators into dermatitis with the symptoms of pruritus, scaling, erythema, patches of hair loss, redness, thickening or lichenification of the skin, hyper pigmentation, odor and oily seborrhea. These conditions are further aggravated by the exposure of nosocomial pathogens and environmental contaminants. Moreover, traditional animal husbandry practices with low literacy rate and unawareness regarding hygienic measures in animal owners are of major concern.

Initially these were left ignored in conventional animal rearing practices as to be self-cured until affecting the general condition and productivity of the animal including meat, leather quality, or economy of the owner. If treated, then it was without confirmatory diagnosis of the condition, which led to untargeted therapy and injudicious
use of allopathic drugs, giving way to the emergence of antimicrobial drug resistant pathogens which is reflected in many failure cases of the use of antibiotics and antifungal medicines. In this scenario alternative novel therapies are being always attempted including of homeopathic, ayurvedic / herbal etc. Such ancient period magical chemotherapeutic drugs (herbs) are very interesting due to being safer and cost-effective \cite{8,9,10}. In this context, studies are being performed at various centers and places to know the exact therapeutic mechanisms of herbal products against specific causative bacterial/fungal agent in various types of wound and skin infections/ailments (chronic, deep suppurative, open, gun-shot, lacerated, incised, ulcerated wounds etc.) in different species of animals (cattle, buffalo, goat, horse, camel, dog) of various age groups, and their sensitivity pattern is also being assessed \cite{11,12}. Antibiotic sensitivity testing of the bacterial and fungal agents, isolated from different cases of skin/wound infections, revealed resistant strains even against multiple drugs \cite{13}. Rising frequency of fungal infection especially resistant fungal infections of candida and yeasts \cite{14,15} as well as increased reports of resistance to antibacterial and antifungal agents indicates the importance of in vitro antibiotic and antifungal susceptibility testing \cite{16,17,18}.

The development of antimicrobial resistance among the bacteria and fungi is an important issue for treatment of infectious diseases in man as well as animals \cite{19}. Although, there is progress in research and development of new and improved salts of antimicrobial agent but the bacteria are developing resistances to these antibiotics at a higher speed from it \cite{20}. Hence, due to rapid development of resistance against these chemotherapeutic agents particularly the antibiotics, it is the need of present time to think over some alternative and effective therapeutics like herbs, panchgavya and bacteriophages \cite{21,22}. Such alternatives should be explored, tested, standardized and validated to use them in practice not only in clinical cases but also under field conditions.

Around 60,000 years ago there was development of traditional system of medicines that incorporates plants for therapeutic purpose \cite{23}. Lack of proper documentation has restricted the use of herbal healers in the urban society even though there is no lack of data on the usages of plants in each general ethno botanical prospection and ethnopharmacological aspect \cite{24,25}. In rural areas people in developing countries people still rely on traditional practitioners and their herb based formulations as
primary medicine \cite{26}. The modern developments in therapeutic field have revived the use of traditional medicines, the plant-based remedies as potential source of therapeutic aids in health systems all over the world for both humans and animals \cite{27}. Many developed as well as developing nations including India are rich source of plants used for medicinal purposes (approx. 2500 species of plants found) for which exponential growth has been observed in the field of herbal medicine while treating wound infection. This is due to the natural origin of the plants and less side effects of their active ingredients \cite{28,29} leading to the expansion of the use of herbal drugs in recent years \cite{23,30}. Apart from various beneficial actions like treating diseases, appetizing effect, immune-modulation, effective against diabetes and even cancer vast number of innumerable advantages of medicinal herbs have been reported \cite{31}. In the treasures of herbal medicines a long list of medicinal plants such as Ashwagandha, Amla, Tulsi, Arjuna, Aloevera, Garlic, Turmeric, Ginger, Shatavari, Neem, Guduchi, Kiwifruit, Tut, Kamala, Palashlata, Kokilaksha etc. is there which are being used for human and animal health benefits since long back \cite{10}. The uses of herbal plants in health industry are gaining increasing attention day by day in both consumer and scientific circle. Apart from treating infectious and systemic diseases, topical botanical/herbal application is equally effective against specific conditions of ear infections, wounds, burns and skin irritations by topical applications, pultis/bandages of herbs, spray methods which are easy to apply. Topical application gives soothing effects and immediate relief from superficial infections, burns, skin irritations and wounds. In the context of hypersensitivity reactions for the purpose of wound healing the phyto-medicines are not only cheap and cost-effective but also safe to use when compared with allopathic drugs \cite{4}.

There has been a dramatic increase in our knowledge of the process of wound healing along with which the development of new and exciting technologies have accelerated wound healing normally that has helped to counteract the pathophysiological processes that lead to formation of chronic wound \cite{23}. Interestingly 65 per cent of the population of the world has incorporated methodology of medicinal agents involving plants into primary health care modality as per the World Health Organization (WHO) \cite{8}. Today plants constitute 25 per cent of all the drugs prescribed \cite{32}. 
In the present scenario of increasing emergence of drug resistance on behalf of evolving resistant microbial pathogens, injudicious use of antimicrobials especially the antibiotics, residual toxic effects of drugs in food, and in lieu of emerging and re-emerging pathogenic strains, many novel and safer therapeutic modalities are being explored viz., bacteriophages, virophages, mycophage, apoptins, cytokines, monoclonal antibodies, avian egg yolk antibodies, stem cell therapy, nanomedicines, nutritional immunomodulation, panchgavya, application of honey and herbal remedies [10,29,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47].

Research involving traditional remedies to wound healing fall into different categories viz. herbal remedies; animal or insect products and their uses as agents of wound healing; and effective use of organisms in wound healing. In developing countries in the rural areas seeking medical attention by people for their owns as well as for their livestock due to complications arising from wounds as well as dermatological (skin) conditions is common [48]. The use of traditional medicines in order to treat many of the conditions resulting from wounds and skin infections has received minimum research as well as policy attention [49]. The present review elaborates the potential role of herbs in treating skin infections and various types of wounds for safeguarding health of animals as well as humans. The use of herbal medicine in wound care has proved positive upshot and outcome on acute and chronic wounds, being very encouraging and has a strong potential to be widely used in traditional wound care around the globe [11,50].

The present paper highlights the beneficial applications of traditional herbs and novel phytomedicines, from ancient periods to modern usages, scientific approaches being followed and future perspectives with a vision to counter the emerging antimicrobial resistance against various types of skin and wound affections of animals. The ultimate aim is to promote and popularize herbs as alternatives to conventional chemotherapy/antimicrobials particularly in the event of emerging multiple drug resistant bacterial and other microbial infections which are unresponsive to currently used antibiotics/antifungal agents. As India has a rich biodiversity of herbs and medicinal plants, much effort should be made in their identification and testing/validation for their significant and practical multi-beneficial uses. Global use of herbs as alternative and complementary medicines to antimicrobials would help in safeguarding animal health.
and production in a better way while also keeping away the public health issues like that of antibiotic residual effects in animal meat and meat products.

**SKIN AND WOUND INFECTIONS IN ANIMALS**

Wounds break the continuity of the skin and allow organisms to gain access to tissues and cause infection. Wound infection is the most frequent complication, and may be due to several reasons like lacerations, injuries, penetrating trauma, external irritants, burns, allergens, animal fights and bites etc. Various objects and plant remnants can also puncture the skin and result in a wound infection. In veterinary practice, skin affections and inflammation or dermatitis is a common scenario especially in case of small animals and pets.

**Etiology of wounds:** Most common cause for the skin ailments have been found as bacterial and fungal infections apart from viral and other mechanical causes. Severity and form of the affections vary from a transient involvement of the skin surface only to deep discharging infections which are non-responsive to therapy and are often relapse. In many of the cases, dense hair coat has a protective effect in preventing the pathogenic bacteria from having access to the skin, thereby restricting the infections to glabrous areas. Also inherently normal animal skin is highly resistant to colonization by bacteria. Inflammation of the skin results in temperature changes and increased skin permeability. Colonization is thus favored which in turn results in the production of toxins and irritants and a cycle of further inflammation, infection, etc.\(^{[51]}\).

**Common microbial agents of wounds:** Microbial agents mainly include bacterial, viral and mycotic pathogens. Among them bacterial agents are very prevalent and mainly includes *Staphylococcus* species (*S. aureus, S. albus, S. citras, S. intermedius*), *Streptococcus* species, *Bacillus coli* and *B. pyocyaneus*. Other than these *E. coli, Pseudomonas, Klebsiella* and *Proteus* species etc. have also been observed. Viral agents/diseases affecting skin lesions are mainly Canine distemper virus (CDV), Contagious viral pustular dermatitis (orf), Pox virus, Pseudorabies (mad itch), Papilloma virus, Feline leukemia virus (FeLV), Giant cell dermatosis, Sarcoma virus and Herpes virus. In chronic cases various mycotic disease conditions of superficial layers of skin, hairs and claws (Dermatophytosis, Candidiasis and Mallaseziasis), subcutaneous mycoses (Pseudomycetoma, Eumycotic mycetoma, Phaeohyphomycosis, Pythiosis, Zygomycosis,
Sporotrichosis, Lagenidiosis etc.) and even systemic mycosis (Blastomycosis, Coccidiodomycosis, Cryptococcosis, Histoplasmosis, Aspergillosis, Protothecosis) may also develop depending upon type, stage of skin lesions and level of fungal invasion [52,53].

Once entered, the spread of microbes on the surface of moist and warm mucosa is always faster than on cool and dry skin. Pathogenic microbes have invasive property with the ability to invade interstitium due to the secretion of lytic enzymes and mechanically through their movement. Superficial skin infections are primarily caused by aerobic micro-organism such as Staphylococcus, Streptococcus (Flesh eating bacteria), Vibrio or Aeromonas species, Corynebacteria spp., Pseudomonas aeruginosa, Pasteurella multocida, Erysipelothrix species but deeper wounds may also be infected with anaerobic pathogens such as Bacteroides and Clostridium species. Bacterial infections are typically caused by colonizing normal flora under certain circumstances and may also by antibiotic resistant bacteria such as MRSA (Methicillin Resistant Staphylococcus aureus, CA-MRSA (Community Acquired Methicillin Resistant Staphylococcus aureus), Vancomycin Resistant Enterococcus faecalis (VREF). Bacterial skin infections which are common in small animal veterinary practice, is most frequently by the causal organism Staphylococcus intermedius apart from other common causative agents like Escherichia coli and Proteus species. S. intermedius, which is a normal resident in the nasal cavity, oropharynx, and the perianal region of animals, can be a transient resident in other sites especially if there is trauma to the area and the organism is probably transferred to these sites from the oral and anal mucosae during grooming. Pasteurella multocida is another principle microbial agent especially in subcutaneous abscesses in cats. Gram negative bacteria are generally secondary invaders which are controlled by therapy effective against Staphylococcus. Pseudomonas, however, is a Gram negative bacterium which is difficult to eliminate and requires specific therapy [54,55].

Fungal infections may arise later on as they are not inhibited by antibacterial treatment [14]. Fungi can lead to deep wound infections as well as skin infections viz., Ring worm, athlete’s foot, thrush etc. Ringworm (Dermatophytosis) is caused by fungi and in dogs 70% of them have been reported to be infected by Microsporum canis, 20% by Microsporum gypseum and 10% by Trichophyton mentagrophytes. Main species
involved in fungal infections of skin are *Malassezia furfur, Exophida werneckii, Sporothrix sckenckii, Microsporun spp., Trichophyton spp., Candida spp., Fusarium and Aspergillus* spp. [56,57]. Among the superficial infections sometimes viral infections, caused by Herpes simplex virus and variety of warts such as common and plantar warts due to Papilloma virus may also occur.

Parasitic agents especially the bloodsucking ectoparasites like ticks and mites can also cause skin disease. The common causes include sarcoptic and chorioptic mange, Aujeszky's disease, nervous acetonemia, lice infestation in cattle; lice, mange, ked, blowfly and itch-mite infestations and scrapie in sheep; lice infestation in pig; chorioptic mange on the legs of queensland (sweet) itch along the dorsum of the body, lice infestation, perianal pruritus due to *Oxyuris equi* infestation in horses. In addition to infectious and allergic conditions of skin various types of wounds such as incised wound, gunshot, contusive, abrasive, lacerative, bed sores etc. may also occur to the skin. These wounds generally act as potential sources of skin infections if left untreated for a long time and pathogens found as secondary causative agents.

Among the skin affections due to infection, pyoderma is most prevalent, which can be non-responsive to therapy and relapse repeatedly. Pursuing the underlying predisposing factors and using general principles of therapy, including antibacterials is necessary to successfully manage pyodermas. Pyoderma can be classified as localised or generalised, primary or secondary, and also according to the depth of the affected tissue. Superficial pyoderma involves the epidermis and often the hair follicles and it is important to treat these cases adequately to prevent recurrence and progression to deep pyoderma. Deep pyoderma may be an extension of a surface or superficial pyoderma, or may occur after a primary insult. Acute moist dermatitis is another commonly encountered problem in veterinary practice. It is usually characterized by a single erythematous lesion, starting in the haired areas, which may rapidly enlarge. In dogs, muzzle folliculitis and furunculosis is more prevalent in puppies approaching maturity but in cats, this condition known as 'feline acne', may occur at any age. In dogs, mild cases will self-cure, but furunculosis and cellulitis require both topical and systemic therapy.
Diagnosis: Most of the time contaminants/infectious agents infect the wounds. In this scenario to restore the health and well-timed recovery definitive diagnosis of a range of skin diseases demands a detailed history, physical examination, and appropriate diagnostic tests; various procedures include collection and observation of skin scrapings, examination of hairs, cytology, bacterial and fungal cultures, biopsy etc. However, routine blood and urine tests, intra dermal skin testing and in vitro diagnostic tests also help in determining the cause and ruling out the systemic infections. Initial diagnostic tests for the diagnosis of skin diseases include –

- Wet paper test,
- Coat brushing,
- Diascopy,
- Acetate tape impression smears of coat and skin,
- Skin scrapings- superficial and deep,
- Hair plucking/ trichography,
- Cutaneous cytology- impression smears,
- Fine needle aspirate,
- Microbial culture viz. isolation of bacterial and fungal pathogens,
- Wood lamp test for dermatophytes.

Accurate diagnosis of the etiology helps in the selection of any topical or systemic treatment.

HERBAL REMEDIES IN SKIN AFFECTIONS AND WOUNDS

Plant/Herbal products are considered to be potential agents for healing of wounds and are in great demand due to their wide availability, less toxicity, absence of unwanted side effects after use and being more potent in their crude form. The study and therapeutic implications of ethnomedical as well as ethnoveterinary systems and herbal medicines as potent agents of treating skin and wound infections are of paramount importance in addressing health problems of animals as well as humans. Recent research worldwide in this direction had identified new plants with enormous wound healing potential.

Wound healing is a complex process involving inflammatory proliferative and maturation phase. Healing of any wound is the end result of interactions among
cytokines, growth factors, blood and cellular elements, formation of granulation tissue and the extracellular matrix \[7,64\]. Hence, the goal of every therapy treating wounds should be to promote and maintain asepsis at the site because open wounds offer microorganisms which delay the wound healing. The significance and efficacy of traditional and complementary medicine have risen due to the mount in antibiotic resistance, and hence alternative/traditional medicines are becoming progressively more popular and worth to overcome such multi-resistant organisms.

Any component of plant or an active ingredient alone or in combinations as a part of herbal preparations comprise herbal medicines which are being used since pre-historic times. Literatures are available depicting the use of opium, turmeric, garlic, mint, castor oil, coriander, vetch, indigo, wheat, barley, caraway and rye even from the time of 2700 BC. The Chinese herbal book, the Shennong Bencao Jing has described 365 medicinal plants and their uses in form of herbal therapy \[65\].

The process of wound healing is stimulated by numerous factors some of which are present in medicinal plants containing different effective active principles like flavonoids and triterpenes; alkaloids and saponins etc. that promote the process of wound healing \[66,67,68,69\].

Flavonoids form active constituents of several plants that serve the function of wound healing. By means of either prevention or slowing of the onset of cell necrosis along with improved vascularity they reduce peroxidation of lipid. In addition the astringent and antimicrobial properties of flavonoids held them responsible for contraction and epithelialization of the wound at an increased rate \[70\].

Astringent and antimicrobial properties of triterpenes help them to promote wound healing \[70,71\].

Due to their anti-oxidant as well as antimicrobial activity saponins are effective in wound contraction and epithelialization at an elevated rate \[70,72\].

The activities of scavenging free radicals along with anti-oxidant properties have made sterols and poly-phenols useful in order to reduce lipid peroxidation thereby causing reduction in necrosis of cells along with improvement in vascularity \[73\].

Tannins of herbs have got the properties of chelating free radicals and reactive oxygen species (ROS) as well as promoting wound contraction and increasing capillary
vessel and fibroblast formation in addition to various cellular mechanisms facilitating the process of wound healing.\textsuperscript{74,75}

It has been found that 70% of the Ayurvedic drugs effective in wound healing are of different types based on their origin as plant origin (70%), mineral origin (20%), and animal products (10%) \textsuperscript{5}. Different conditions are described from ancient times in which these drugs are being effective viz., Vrana for wounds and ulcers, Nadivrana for sinuses affections, Vidradhi for abscess, Visarpa for erysipelas, Vranajakrimi for maggots infection in wounds, Dustavarna for septic wounds, Vranashotha for inflammatory changes of wounds etc. \textsuperscript{5}. Various literatures reported in Indian systems of medicine about 163 species of plants were used as Ayurveda, Siddha, Unani and folk medicine for wound healing \textsuperscript{2,5}. Various ethnoveterinary and traditional medicinal practices prevailed throughout the world followed the practice of treating wounds topically with different medicinal herbs or using their extracts solely or in combination with some other plant parts. Considering the wound healing properties of plants, highest number of species belongs to the family \textit{Rubiaceae}, then by \textit{Euphorbiaceae}, followed by \textit{Moraceae} and \textit{Acanthaceae}. List of such medicinal plant species is very long involving a vast variety, few examples being \textit{Typha domingensis} Pers., Scorzonera species, \textit{Ficus amplissima Smith}, \textit{Lonicera japonica}, \textit{heliotropium indicum linn.}, \textit{Achyranthes aspera L.}, \textit{Acalypha indica}, \textit{Carica papaya}, \textit{Andredera diffusa}, \textit{Vernonia arborea}, \textit{lycopodium serratum}, \textit{carapa guianensis}, \textit{Dendrophthoe falcate}, \textit{hippophae rhamnoides} etc. \textsuperscript{76,77,78,79,80,81,82,83,84,85,86,87,88}

There are certain other plants that because of several active components like saponin and alkaloids; fatty acids and sterols; amino acids and amino glycosides are essentially effective in case of both skin affections as well as healing of wounds. Examples include: \textit{Aegle marmelos}, \textit{Allamanda catharica}, \textit{Allium sativum}, \textit{Datura alba}, \textit{Dendrophthoe falcata}, \textit{Desmodium triquetrum}, \textit{Flabellaria paniculata}, \textit{Flaveria trinervia}, \textit{Mimosa pudica}, \textit{Morinda citrofolia} and \textit{Moringa oleifera} \textsuperscript{79,89,90,91,92,93,94,95,96,97,98,99}.  

\textsuperscript{www.pharmasm.com}  IC Value – 4.01
### TABLE 1: LIST OF SOME OF THE IMPORTANT PLANTS AND THEIR DERIVATIVES WHICH WERE FOUND EFFECTIVE FOR SKIN AFFECTIONS AND WOUND HEALING IN ANIMAL MODELS

<table>
<thead>
<tr>
<th>Plant</th>
<th>Active component</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aloe vera</em></td>
<td>B-sitosterol, acemannan and glycoprotein</td>
<td>[89,100]</td>
</tr>
<tr>
<td><em>Alternanthera sessilis</em></td>
<td>A- and β-spinasterols, β- sitosterol, stigmasterol</td>
<td>[101]</td>
</tr>
<tr>
<td><em>Andredera diffusa</em></td>
<td>Oleanolic acid</td>
<td>[77]</td>
</tr>
<tr>
<td><em>Angelica acutiloba</em></td>
<td>Arabinogalactans</td>
<td>[102,103]</td>
</tr>
<tr>
<td><em>Areca catechu L.</em></td>
<td>Arecoline, catechin, tannins, gallic acid, fat, gum, and alkaloids like arecoline and arecaine</td>
<td>[104]</td>
</tr>
<tr>
<td><em>Arnebia densiflora</em></td>
<td>Naphthoquinones, Shikonin and alkannin</td>
<td>[105]</td>
</tr>
<tr>
<td><em>Acalypha indica</em></td>
<td>Flavonoids, acalyphamide, alkaloids and glycosides</td>
<td>[87]</td>
</tr>
<tr>
<td><em>Berberis lyceum</em></td>
<td>Flavonoids, alkaloids including berberine, tannins, saponins and triterpenoids</td>
<td>[106]</td>
</tr>
<tr>
<td><em>Carallia brachiata</em></td>
<td>Tannins, flavonoids and glyceroglycolipids</td>
<td>[107]</td>
</tr>
<tr>
<td><em>Centella asiatica</em></td>
<td>Saponins, Asiaticoside, triterpenoids</td>
<td>[108,109,110]</td>
</tr>
<tr>
<td><em>Chromolaena odorata</em></td>
<td>Phenolic acids</td>
<td>[111]</td>
</tr>
<tr>
<td><em>Cimicifuga sps</em></td>
<td>Fukinolic acid and cimicifugic acids</td>
<td>[112]</td>
</tr>
<tr>
<td><em>Curcuma longa</em></td>
<td>Curcumin</td>
<td>[113,114]</td>
</tr>
<tr>
<td><em>Carica papaya</em></td>
<td>Papain, chymopapain</td>
<td>[80,115]</td>
</tr>
<tr>
<td><em>Elephantopus scaber</em></td>
<td>Sesqueripene lactones deoxyelephantopin, isodeoxyelephantopin, scabertopin and epifriedelinol, lupeol and stigmasterol</td>
<td>[116]</td>
</tr>
<tr>
<td><em>Embelia ribes</em></td>
<td>Quinone derivative embelin, an alkaloid christembine and a volatile oil vilangin</td>
<td>[117]</td>
</tr>
<tr>
<td><em>Gentiana lutea</em></td>
<td>Gentiopicroside, sweroside and swertiamarine</td>
<td>[118]</td>
</tr>
<tr>
<td><em>Hippophae rhamnoides</em></td>
<td>Quercetin, isorhamnetin and Kaempferol</td>
<td>[119,120]</td>
</tr>
<tr>
<td><em>Ixora coccinea L.</em></td>
<td>Lupeol</td>
<td>[121]</td>
</tr>
<tr>
<td><em>Jasminum auriculatum</em></td>
<td>Lupeol and jasminol</td>
<td>[122]</td>
</tr>
<tr>
<td><em>Jasminum grandiflorum</em></td>
<td>Not identified</td>
<td>[123]</td>
</tr>
<tr>
<td><em>Lycopodium serratum</em></td>
<td>Alkaloids like serrtezomines A-C, lycoposerramine- A, Lycoposerramine F-O, quinolizine</td>
<td>[78]</td>
</tr>
<tr>
<td><em>Onosma argentatum</em></td>
<td>3-hydroxy-isovaleryl shikonin and 5, 8- O-dimethyl acetyl shikonin</td>
<td>[124]</td>
</tr>
<tr>
<td><em>Opuntia ficus-indica</em></td>
<td>Polysaachhardies</td>
<td>[125]</td>
</tr>
</tbody>
</table>
Pyrostegia venusta | Gallo-tannic acid and glycoside bellericanin [126]
Peperomia galioides | A-bisabolol [127]
Panax ginseng | Acidic heteroglycans [102]
Plantago major | Polysaccharides [105]
Scrophularia nodosa | Acylated iridoid glycosides [128]
Tamarindus indicus | Xyloglucan [129]
Terminalia arjuna | Tannins [130]
Vitis vinifera | Reseveratrol [131]

Worldwide several studies have been conducted suggesting that *Aloe vera*, or one or more of its constituents is prominent in promoting wound healing in various animal models. Interestingly the plant extract can be used in case of both acute as well as chronic wound [132,133]. *Aloe vera* gel, obtained from the mucilaginous part of the centre of the leaf has been used for many centuries orally and/or topically to treat a wide array of health-related disorders [134,135]. The aloe vera gel contains sugars, amino acids, vitamins A, B, C, E, enzymes, polysaccharides and minerals [136]. Several reports are on hand showing the encouraging role of aloe vera in the management of acute, chronic or burn wounds both [100,137,138,139].

In a study *Acalypha indica* extract was shown to effect the process of dermal wound healing by its capacity to augment collagen synthesis through up-regulation of key players in different phases of wound healing and by its antioxidative potential [87]. Earlier it was thought that *Acalypha indica* contains four glycosides namely mauritianin, clitorin, nicotiflorin and biorobin. Later many other phytochemical constituents like flavonoids, acalyphamide, alkaloids and glycosides have been isolated from this plant [140,141]. The wound healing property of water and acetone extract of *Acalypha indica* was determined by assessing its antimicrobial efficacy against two common and potent wound pathogens namely *Staphylococcus aureus* and *Pseudomonas aeruginosa* [142].

Besides these, many traditional remedies are based on systematic observations and methodologies and have been time-tested but for many of them, scientific evidence is lacking and there are only few prospective randomized controlled trials that have proved the clinical efficacy of these traditional wound healing agents [143]. Major problem with pharmacological validation of the wound healing plants is that the exact mechanism of the healing process of wound is not clearly understood; hence most of the researchers
restricted the screening of plants to simple healing of wounds and did not go into details. The validation by scientific method of the usefulness of various plant species could form the basis for their use as alternative treatments or when conventional therapy by Western medicine is unavailable\[2,144\].

An array of herbal remedies has been in constant use in our folk medicine by the various tribal communities of our country both orally and topically for healing of wounds, burns and against multi-drug resistant bacteria also in animals\[145\]. Some of the good examples of such plants are *Calotropis procera, Cassia fistula, Tridax procumbens, Hypericum japonicun*, *Trigonella foenum-graecum, Heliotropium indicum, Plumbago zeylanicia* and *Acalypha indica, Hypericum papuanum, Hypericum perforatum Cissus quadrangularis, Ocimum gratissimum and Ageratum conyzoides*\[146,147,148,149,150,151\].

*Echinacea* (both *E. angustifolia* and *E. pallida*) have got antiseptic properties which has made this particular plant an herb that is most widely used. *E. pallida* as well as *Eleutherococcus senticosus* (otherwise known as Siberian Ginseng) increase the activity of the white blood cells for which they are used during an infection so that the body can get rid of a skin infection\[152\]. Due to its immunostimulatory property it is found to be extensively used for the treatment of chronic wounds and ulcers apart from the prevention and treatment of viral, bacterial and fungal infections and the treatment of chronic arthritis, thereby decreasing the adverse effects of chemotherapeutic agents\[11,153\]. Essential oils derived from plants have a long history of use for treating wounds; especially in treating skin abrasions, small to medium wounds, excoriations, skin infections and other topical health problems provided, it should be used in an appropriate concentration\[154,155,156,157\]. They consist of complex mixtures of secondary plant metabolites like phenylpropenes and terpenes and are particularly associated with characteristic plant fragrances and essences.

*Elaeis guineensis* of the Arecaceae family is widely used in conventional medicine in African countries. Antioxidant, antibacterial and antifungal properties of *E. guineensis* leaf help to make a potent natural product-based ointment\[158\]. Leaves of *E. guineensis* are squeezed and obtained juice is applied on wounds to promote healing. *E. guineensis* leaf extract has potent wound healing capacity as evident from the better wound closure, improved tissue regeneration at the wound site, hydroxyproline content in
the granulation tissue, biochemical changes and supporting histopathological parameters pertaining to wound healing \[^{159,160,161}\].

\textit{Allium sativum} (popularly known as garlic) has been investigated recently for its efficacy against ringworm and it has been found that an aqueous extract of garlic is effective against 90 per cent of the dermatophytes \[^{162}\]. In another study it has been proved that ajoene (a purified garlic constituent) can lead to inhibition of a wide range of fungi \[^{163}\].

A variety of herbs viz. \textit{Salvia officinalis} (Sage); \textit{Rosmarinus officinalis} (Rosemary) and \textit{Thymus vulgaris} (Thyme) have been used as antifungal agents after confirmation in laboratory based studies \[^{164}\].

\textit{Centella asiatica} (CA), a very important medicinal herb belonging to the family \textit{Umbellifere} (Apiceae) is commonly known as \textit{mandukparni} or Indian pennywort or \textit{jalbrahmi}, has been used as a Ayurvedic medicine of India for several years being listed in the historic ‘\textit{Sushruta Samhita}’. The herb is also known as “miracle elixirs of life” and its extracts is recommended in the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis along with its wound healing properties \[^{110,165}\].

\textit{Lonicera japonica} Thunb. (Caprifoliaceae), a widely used traditional Chinese medicinal plant, exhibited significant antimicrobial activity against \textit{Staphylococcus aureus}, \textit{Staphylococcus epidermidis}, \textit{Escherichia coli}, \textit{Candida albicans}, and \textit{Candida tropicalis} and showed potent wound healing capacity as evidenced by the greater tissue regeneration, more fibroblasts, and angiogenesis, wound contraction to accelerate wound repair by antimicrobial and anti-inflammatory properties of the medicinal plant \[^{85}\].

\textit{Alternanthera sessilis} (L.) R.Br. ex DC. Member of \textit{Amaranthaceae} plant leaves are effectivelu used in treatment of cuts, wounds and skin diseases \[^{101}\]. \textit{Arnebia densiflora} (Nordm.) Ledeb. is another plant with wound healing properties \[^{105}\]. \textit{Berberis lyceum} Royle member of \textit{Berberidaceae} has roots as medicinally useful part which has triterpenoids and saponins as active principles. Due to their antioxidant, antimicrobial andstringent and antimicrobial properties they promote the wound contraction, increase the rate of epithelialization and hence contribute in the wound healing process \[^{106}\]. The bark of plant \textit{Carallia brachiata} Merrill belong to \textit{Rhizophoracea} family have been found effective in the treatment of itching, cuts and wounds, oral ulcers \[^{107}\].
Elephantopus scaber L. belonging to family Asteraceae. Plant promotes the wound healing when after maceration plant extract is applied over the surfaces of wounds [116]. Leaf paste of Myrsinaceae member Embelia ribes Burm. is used to cure the wounds [117]. Hibiscus rosa sinensis L. (Malvaceae) is a herb used to rejuvenate the inflamed skin and for the treatment of wounds [115]. Jasminum auriculatum Vahl. Member of Oleaceae also has remarkable effects on wounds. When extract of leaves of J. auriculatum is applied over the wounds in the form of jelly beneficial effects have been observed in form of endorse wound healing [122]. Lycopodium serratum is the plant especially useful in the treatment of burns, sores, cuts and wounds. This is member of family Lycopodiaceae, thick paste of plant prepared by boiling in water has widely been used by the tribes for treating wounds [78]. Rafflesia hasseltii buds and flowers extract is very effective in accelerating the wound healing process [166].

Herbal remedies are fruitful to treat wounds like scrapes and scratches; bug bites and bruises and several of the plants used for such type of conditions are also fruitful in treating other conditions as well. Calendula officinalis is found to be useful in treating acne and this plant along with aloe vera and Melaleuca alternifolia tea tree are used often for treating scrapes as well as scratches and bug bites. Bruising can be limited effectively by using Symphytum officinale (Comfrey) topically and is a common salve ingredient in case of herbal burn salve. Nepeta cataria (Catni) and Matricaria recuitita (Chamomile) can be used without even the risk of any side effects [9,167].

Other conventional/traditional and emerging therapies-

Traditional medicine usually called as indigenous or folk medicine encompasses the knowledge developed over generations before the era of modern medicine. Folk medicine sometimes referred as traditional medicine is often called complementary and alternative medicine (CAM) when used for diversified health conditions that is broad set of health-care practices other than the realm of conventional therapy, it includes long standing remedies passed on to generations to be practiced by common people [168]. Such practices include Herbal, Ayurveda, Siddha, Iranian, Unani, Islamic, Chinese, Acupuncture, Vietnamese and African health care practices all over the globe. Historical evidences suggest that in ancient time honey, wine, vinegar, turmeric, indigenous herbs, dietary therapy were very successfully used for the management of wound [169].
parts of plants are used as a part of diet to support and hasten the healing process such as turmeric in lukewarm milk, citrous fruits to yield Vitamins in order to boost the formation of healthy granulation tissue network [136]. At the time of war, to treat gunshot wounds boiling oil, egg yolk, turpentine, yogurt, oil from tea leaves, honey, palm oil and thin peelings of potato have been widely used as therapeutic agents [170,171,172]. The use of honey in wound management has even been described in the Bible and the Quran to treat wounds, burns, cataracts, skin ulcers and diarrhoea. The first documentary proof of the use of honey in wound management is 2000 BC old from the Egypt. In the 20th century many reports have confirmed the advantages of using honey as a natural remedy for wounds. Now at present as there is decrease in the introduction of newer antibiotics and antibiotic resistance is gradually spreading the interest of using sterilized honey for wound management is re-initiated [173,174,175]. Honey in combination with Azadirachata indica (neem) bark decoction can be used for the treatment of chronic wounds [176].

Being viscous and hypertonic in nature honey shows effective antiseptic as well as anti-inflammatory action, because of hyperosmolarity of honey, it absorb the exudates from the wound and enhance the healing process [177]. Honey is rich in antibacterial, antifungal and anti-inflammatory properties especially against Staphylococcus aureus, coagulase negative staphylococci even community-acquired methicillin-resistant Staphylococcus aureus, Escherichia coli O157:H7 and Salmonella typhimurium infections [178,179]. The anti-bacterial properties are minly due to the multifarious interaction of the various components of honey viz. hydrogen peroxide, bee defensin-1 and methylglyoxal. Honey shows inherent capacity to reduce edema, inflammation and the synthesis of collagen and thereby augment the formation of granulation tissue, increase wound contraction, wound epithelialization and stimulate tissue growth by deodorizing the wound and reducing pain in animals as well as in human beings [180]. More concentrated honey has greater anti-bacterial action [181].

In recent years researchers have shown their interest in the use of cow urine for healing of wounds [44]. In Wester albino rat the activity of wound healing of cow urine has been studied and its efficacy has been evaluated by excision wound model with wound contraction as the parameter. Such study has revealed that cow urine can hasten the process of wound healing when applied externally [182].
Use of various herbs and traditional medicine is economical also in present situation of escalating health care cost hence an abreast is required to dig out as much as possible from the treasure of nature in order to shore up the good health among the advance techniques of wound care\[^{183}\].

**Conclusion and Future Perspectives**

Wound care and treatment modalities are constantly sprouting with the advances in medicinal science. Emergence of multidrug resistant microorganisms and a decrease in effective antibiotics has driven health/wound care professionals and practitioners to revisit the old ancient healing methods of traditional and alternative medicines involved in wound management since eternity. Several studies in this regards have been acknowledged in wound care management with the encouraging remarkable results across the globe projecting that wound therapy holds good promise in the future. We must exploit the hidden attributes of natural products in modern time because before discovery of synthetic drugs they were very successful in the past. In the management and treatment of wounds plants and their extracts have immense potential thereby increasing the importance of studying and examining all options of improving wound management. Traditional medicinal plants can be recommended for wound healing only after necessary scientific validation as well as standardization and safety evaluation. A thorough reviewing is therefore mandatory in order to observe and describe and at the same time investigate experimentally indigenous drugs along with their biological properties. Along with herbal therapy many traditional remedies and new therapeutic approaches are on the mid-way to be much explored and popularized. To triumph over these hurdles various alternative emerging novel therapies such as herbal medication, ethno-veterinary medicines, bacteriophage therapy, cytokine therapy, mycophage therapy, panchgavya therapies etc. are in the picture which are opening new avenues to prevail over these superbugs. Thus focus should be made on studying the actual etiology of various wounds and skin infections and their sensitivity pattern to different concentration of herbal by products.

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For Correspondence:
Sandip Chakraborty
Email: sandipchakraborty53@yahoo.com