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REVIEW ARTICLE

A Comprehensive Review on the Therapeutic Potential of Chromolaena Odorata for the Management of Foot Ulceration and Chronic Wounds

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SUMMARY

The practice of plant derived traditional medicines are considered as one of the excellent tools to enhance the wound healing by reducing healing time and financial burden to the affected ones. In recent years, attention on wound healing medicinal herbs have tremendously improved with the incorporation of multidisciplinary systematic exploratory approach. It is known that many bioactive principles are participated in the healing process with the participation of radical scavenging and anti-pathogenic activities. Though numerous pharmaceutical formulations and preparations are in place and employed for wound repair management, yet the search continues for efficient options, as certain existing therapeutic formulations produce undesirable effects or absence of effectiveness. Phytochemical metabolites from various medicinal plants exhibited abundant ability on various stages of the wound healing shown by numerous molecular mechanisms, thus they are designated as prospective drugs or drug leads of traditional medicine source. Chromolaena odorata (CO) (L.) R.M. King and H. Robinson is recognised as a neglected temperate weed plant. It demonstrated different medicinal properties, which include cytotoxic and other significant actions against pyretic, inflammation, microbes, and analgesic. Besides, in many parts of world it is used for various ailments. To understand its precise role in wound healing and its impact on reasonable health management, this herb requires scientific evaluation based on the existing reports, which are vital for drug design and development. In conclusion, the current review signifies the importance of CO derived phytocompounds for their wound healing potential especially on foot ulceration and chronic wounds. This review highlights the importance and clinical significance of CO which may be benefit the drug screening and pharmaceutical advancement in the field of human and animal medicine.
Keywords: C. odorata, CO, foot ulceration, chronic wounds, wound healing, medicinal herbs

INTRODUCTION

Wounds categorized either as open or closed wounds based on their cause and healing [1]. A wound is an interruption of morphological as well as functional continuity of the skin instigated by physical damage [2]. Most wounds are commonly classified by their level of severity such as chronic or acute wounds[3]. In agreement with the current wound forecast, there are 6-7 million individuals worldwide that experience normal chronic wounds[4,5].

According to Menke et al[6], an acute wound is well-defined as tissue damage that typically goes by sequence and prompt renewal process that restores structural and functional integrity over time. Chronic wounds, on the other hand, result in a state of pathologic inflammation when they are unable to heal through the normal stages. The most prevalent sources of chronic wounds include hypoxic condition, injury, foreign agents, and systemic problems like diabetes mellitus, food deficiency, immunodeficiency, or pharmaceutical consequences[6,7]. Pressure ulcers, diabetic foot ulceration, and venous leg ulceration are few examples of chronic wounds[8]. There is currently no agreed system available for wound classification, yet many kinds of wounds are registered, extending from minor to fatal ones. In addition, wounds can also be identified by their anatomical location, such as an axillary or abdominal wound, as well as by the underlying etiology of the wound.

On the other hand, in the open type of wounds, hemorrhage is noticeable as blood leakage from the affected parts. In accord with Schultz [9], it is categorized as laceration, puncture, gunshot, abrasions or superficial wounds, and incised wounds. A scrape or graze is called an abrasion [10]. This form of wound usually involves an apparent external wound including a part in the dermis as well as in the epidermis. Friction injuries and falling off bikes are among the major causes of this type of wound.[10] Lacerations are defined as wounds caused by blunt objects that frequently need significant power. As the skin has been ruptured rather than sliced, the borders of these wounds are typically split or ripped, leaving ragged edges[11]. Following severe trauma, internal organs such the liver, kidneys, and spleen may also sustain lacerations.

The other types of wounds are incised ones with cuts made by sharp objects. These wounds typically have a clean appearance. Deeper anatomical features like tendons, blood veins, and nerves are examples of incised wounds[12]. Often, puncture wounds are falsely classified as little or penetrating wounds. They are mostly produced with sharp or pointed items, and in addition, infection is a risk, the edges may be sealed over bacterially contaminated areas. Furthermore, puncture wounds have the potential to penetrate down into vital structures like blood vessels or bodily cavities[13].

In addition, gunshot type of injuries is instigated by a bullet or other similar projectile entering or passing through body parts, whereas penetration wounds are produced by an item like knife, inserting and exiting body mostly the skin[14,15]. According to Ahmad Khan et al[16], fish-hook wounds are caused by fishhooks that are embedded in soft tissue, whereas in closed wounds, blood leaks the vascular system but stays in the wound [17]. On the other hand, crush injuries require the application of a great deal of force over an extended period to the skin[18].

Further, contusion is usually known as an abrasion instigated by a blunt blow, where covering skin is uninterrupted however neighboring blood vessels and tissues are broken and evident with discoloration [19]. Besides, wounds can be categorized into wounds with tissue loss (e.g., burn wounds) and absence of tissue loss (e.g., in surgery) [20]. Avulsion is a wound with tissue damage, which prevent gouge induced wound closure [21], whereas stretching forces induced strain injuries to fascia/tendons and muscles are few examples for without tissue loss[22] Strain injuries are resolved mostly with rest and progressive mobilization, but the sprain occurs to fibrous tissues and ligaments by excessive movements[23]. Most of mild sprains are apparent with haematoma formation and takes longer time to recover when compared with strains.

Foot ulceration: A diabetic foot ulceration (DFU) is an open type of sore/wound that occurs 15% of patients with diabetes and is normally termed as foot ulcer or ailment of the lower limb and recognized as a severe peripheral arterial disease (PAD), regularly resulted in amputation by the combined complications of infection and neuropathy. On the other hand, diabetic foot infection (DFI) mostly seen with diabetics is defined as the invasion by pathogenic microbes like P. aeruginosa, S. pyrogens, S. aureus, K. pneumonia, P. mirabilis, E. coli and related injuries caused by them[24,25,26]. Besides, few anaerobic pathogens such as B. fragilis, C. perfringens and yeast C. Albicans also involved in the DFI[27].

The foot ulceration incidence has been observed among diabetes mellitus (DM) patients 4-10%; but the complaint is severe among elder ones[28,29,30] as 85% of amputations are witnessed with them[31, 32]. One of the most probable causes of foot ulceration is from neuropathic origins and takes brief time (about 20 weeks) to cure this type of ulceration than the neuro-ischemic types and they take longer duration and mostly resulted in limb amputation[33].

Pathophysiology and normal wound healing processes: Vascular problems, interruption in the completion of healing at distinct phases and failure are the main factors responsible for the surge of DM cases world-wide [34, 35]. Many reports have established that aberrations in the connective tissue are key factor accountable either for the delay or inadequate wound healing as witnessed mostly in the chronic ulcer and diabetes[36] together with various other contributing reasons like microbial infections, affected site, nutrition, therapeutic drugs, and hormones diabetes[37,38,39]. The following well demonstrated overlapping wound healing processes like hemostasis, inflammation, proliferation, and tissue remodeling or restoration are involved[40,41,42]. This tissue reparative machinery requires the management of diverse immune cells, growth factors, and immune molecules like cytokines[37].

Although the precise pathogenesis of diabetic wounds is not sufficiently addressed, however, the hindrance mechanisms have been recognized[43,44] like delay in collagen synthesis, angiogenesis, and impairment in epithelial development especially in the proliferative phase[45,46,47,48]. Moreover, reduced production of VEGF and decreased nitric oxide synthase (NOS) activity was seen, however increased protease enzyme activity[49,50] was established in various wound healing phases[51,55] but not described in detail. Once the inflammatory response begins, fibroblasts initiate proliferation and travel into the injured area. Collagen and fibronectin are consequently deposited in the wound bed, serving as a transitory matrix, where epithelial cells migrate as groups[56,57]. Despite advances made in the pharmacological industry, the quest for low-cost drug and drug leads to treat wounds remains a challenge[58,59,60]. Numerous novel methodologies like therapeutic gene treatment [61] and transplantation of tissue-engineered skin substitutes have shown insufficient achievement and the current option available is antibiotics only for remedy.

Foot ulceration therapeutic by medicinal plants: The application of phytomedicine is one of the traditional approaches to treat various kinds of wounds including foot ulceration[62]. Plant derived secondary metabolites obtained from numerous herbs play a key role in wound management [63]. The World Health Organization (WHO) has also recommended their application for the treatment of diabetes/hypoglycemic activities [64] and recognized in various tropical Asian as well as African countries as a reserve basin ~~of~~ for medicinal herbs [38, 65, 66]. Ten to fifteen percent of medicinal plants distributed all over the word but mostly found in tropical and African and Asian nations, approximately “three hundred thousand” species are well recognized for their therapeutic attribution[38,65,66 67,68,69]. It is known that diabetic foot wound healing is one of the long awaiting scientific developments in health care systems[70,71]. Traditional medicine practitioners have employed herbal extracts from plants to heal the wound to prevent microbial infection and side effects[72,73,74,75,76,77]. Some of the well-recognized medicinal herbals are Aloe vera; korphad, Anredera cordifolia, Madeira vines, Ixora coccinea, jungle geranium, Morinda pubescens, Indian mulberry; peacock chaste tree, Vitex trifolia, Vitex altissima [78, 79, 80, 81, 82]. In this list CO also added and the current review intent to elaborate the properties of *C. odorata*, as it has diverse pharmacological activities, however, still a lot need to be elucidated more in detail especially the wound healing potential.

Chromolaena odorata plant general description: Asteraceae/Compositae is the major and best-known family of flowering plants, comprising 1,000 genera with 15,000 species. C. odorata (L.) King and Robinson is commonly termed Eupatorium odoratum L. is an ornamental plant as well as one of invasive environmental desert weed (Figure 1). This plant has various other names like Eupatorium brachiatum Sw. ex Wiestr, Eupatorium conyzoides Vahl, Eupatorium atriplicifolium Vahl but Osmia odorata (L.) Schultz-Bip found in the Americas Hawaii region and Guam[83]. France in Europe, African countries like Nigeria and found in the roadsides of South Asia nations including Sri Lanka, India, Nepal and in Southeast Asian (SEA) countries like Thailand, Vietnam, and Malaysia[84,85,86] and is generally considered for its conventional remedial value and versatile pharmacologic actions which include treating burns, wounds, skin infections and inflammations[87,88] (Table. 1).

The wound healing potential of the leaves has been examined using in vivo models so far, as there are no reports to scientifically assess the claimed wound healing property of C. odorata leaf extract in traditional medicine. An attempt was made to discuss the supporting functions such as antibacterial and antioxidant activities to obtain scientific evidence and understand the healing mechanism of action of C. odorata.

Phytochemical constituents of C. odorata and their pharmacological properties: Numerous pharmacological investigations and validation reports have shown that plant extracts from different plants expedite healing process than the standard controls [75, 89]. Several natural products obtained from therapeutic plants have proven to be active compounds involved in healing mechanisms using animal models[90,91]. These metabolites can influence multiple stages of the healing course[92]. Moreover, these phytochemical profiling support identifying the compounds responsible for the healing process.

Several studies have employed chemical analysis on C. odoratum L and identified numerous chemical groups which are hydrocarbons, triterpenes/steroids, monoterpenes, sesquiterpene and alkaloids. The aqueous extract of the leaves contains abundance of flavonoids like salvigenin, sakuranetin, isosakuranetin, kaempferide, betulenol, 2-5-7-3-tetra-o-methylkertetetin, tamarxetin, two chalcones and odoratin and its alcohol components, essential oils (geyren, bornyl acetate and beta-eubedene), saponin triterpenoids, tannins, organic acids, phenolic compounds (protocatechuic, p-hydroxybenzoic, p-coumaric, ferulic and vanillic acids) and many other trace elements[93,94]. As on this date, 17 compounds have been isolated and listed, they are 5aα,6,9,9aβ,10-pentahydro-10β-hydroxy-7-methylanthra [1,2-d][1,3]dioxol-5-one, 1,2-methylenedioxy-6-methylanthraquinone, 3-hydroxy-1,2,4-trimethoxy-6-methylanthraquinone, 3-hydroxy-1,2-dimethoxy-6-methylanthraquinone, and 7-methoxy-7-epi-medioresinol. Additionally, 12 more secondary metabolites obtained from this medicinal herb have been identified, they are odoratin, 3β-acetyloleanolic acid, ursolic acid, ombuin, 4,2'-dihydroxy-4',5',6'-trimethoxychalcone, (-)-pinoresinol, austrocortinin, tianshic acid, cleomiscosin D, (-)-medioresinol, (-), syringaresinol, and cleomiscosin A[94,95].

One of the main roles of CO in traditional curative practice is treating wounds [96, 97]. It is well demonstrated that the wound care comprised the following such as (a) preventing excessive blood loss without compromising circulation at the injured place. (b). averting or eliminating remaining microbial infection. (c). promotes the growth of fibroblast cells at the injured site[98,99, 00]. In line with this, C. odorata leaf extracts have been shown to promote fibroblast proliferation and delay aging related symptoms like wrinkles, hyperpigmentation, etc[100] and exhibit antimicrobial properties[75,97,101].

Numerous investigations have established phytochemical screening of CO using both ethanoic and aqueous extracts revealed the existence of numerous secondary metabolites such as anthraquinones triterpenes, tannins, saponins, and flavonoids[97,02,03]. The ethanol extract was rich in cardiac glycosides, steroids, terpenoids, alkaloids and saponins in the aqueous extract rather than quinones and betacyanins as they present moderate amount in the ethanol extracts than in the aqueous fractions. Besides, the leaf extract of CO[104] also contains flavonols and flavonones like quercetin 7, 4'-dimethyl ether, naringenin 4'-methyl ether, kaempferol 4'-methyl ether, etc. Several studies have obtained six to eleven types of flavonoids from the CO leaves[75,102,104]. Besides, phenolic terpenes detected both in the ethanol and aqueous extracts 105 but found more in the ethanol extract and accounted for antioxidant activity[106]. Tannins are known to prevent the growth of microbes by precipitating microbial proteins and provide nutritious value [107]. In addition, flavonoids and terpenes are used as plant classification indicators for the Asteraceae family[108]. In fact, the predominance of flavonoids in the CO leaves are attributed for their medicinal properties[102]. More importantly phytochemicals of the leaf extract interaction with one another in various combinations produce therapeutic effects as it is a common synergistic effect found in herbal medicine[108]. Thus, CO plant contains all the necessary properties for effective wound management[107].

The goal of wound management is to repair the injury or wound in a short span of period, so that the affected persons experience as little pain, distress and scarring as possible or minimize unwanted consequences[109]. Care should be taken to find an agent that accelerates wound healing or as it progresses. Treatment of wounds, especially those that are poorly healed, is a complex and expensive program. The study of wound healing using drug leads is one of the emerging fields of modern biomedicine [110, 111]. Phytochemical screening is now considered the first step in finding useful drugs[112].

However, the major challenge still exists in wound healing development is the molecular mechanism. Most of the previous studies focused on plants wound healing effects only not investigated their molecular mechanism of action. It is well established that wound healing mechanism is a complex one with the involvement of, various stages including inflammation, epithelialization, protection from free radical and changes in biochemical pathways (proline and hydroxyproline), granulation, neo-vascularization, and wound reduction [113]. Therefore, this comprehensive review aimed at improving the understanding of the current data and available experimental evidence about a neglected but an underutilized herbal weed plant CO and its detailed molecular mechanisms both in vitro and in vivo. In addition, we hope to strengthen and support the ethno pharmacological rights and benefits of this tropical weed and promote the global recognition of herbal wound remedies and their rightful role as a gift of nature in wound healing [114].

CO is well-known for its various biological properties against protozoa, trypanosome, fungus, bacterium, plasmodium, hypertension, inflammation, and hepatotropic [115]. Besides, CO is recognized as an immunomodulatory [116] and anti-cancerous agent [117, 118]. Traditionally root extracts were used to reduce fever and pain, whereas salt containing leaf extract is used to prevent throat and cold diseases [102]. Furthermore, few countries like Vietnam uses decoction from fresh leaves to treat leech bites, soft injuries, skin infections and rashes[119] and many occasions gummy bears are conventionally applied by the medical practioners into cuts or wounds to prevent bleeding[120]. In fact, a produce from this plant called “eupolino” is already available for clinical use in Vietnam for wounds and burns[121,122].

Wound healing is a normal biological phenomenon in the human body and is accomplished through four precisely programmed stages of hemostasis, inflammation, proliferation, and regeneration [123, 124]. Normally the healing mechanisms are well-orchestrated cellular and molecular actions that led to the formation and growth of new cells and repair of affected sites in a specific manner with the incorporation of blood cells, immune cytokines, and various growth factors that eventually restore the damaged skin or tissue to a normal state[56,125].

The wound healing mechanism is promoted by several natural products consisting of active substances such as triterpenes, alkaloids, flavonoids, and biomolecules[126] have free radical scavenging properties[127], which can support healing process—by increased levels of antioxidant enzymes in granulomatous tissues. These phytocompounds were proven to be powerful antioxidants as evident from the protection of laboratory cultured skin cells from the oxidative injury[101,128].

Free radicals are normally harmful to the healing process because they negatively affect the cellular structures and absorbable synthetic biomaterials[129]. In general, antioxidants play a key role by creating a favorable environment and significantly enhancing the repair mechanism to protect the cells and tissues from the oxidative bombardment[130]. Enzymes like superoxide dismutase (SOD) and catalase are known to reduce free radicals. It is evident now that some of the natural wound medicines consisting of active substances such as triterpenes, alkaloids, flavonoids, and biomolecules [131] have also exhibited their antioxidant effects[128] and therefore can support wound improvement. The increased levels of antioxidant enzymes in granulomatous tissues may be responsible for this free radical scavenging effect. Hence, compounds with antioxidant activity isolated from natural plant sources including CO may be useful to prevent or modulate PMNL-derived ROS-related oxidative damage [116].

Anti-microbial potency of CO: Infectious diseases are health problems caused by microbial infections worldwide, especially in developing countries because of poor living conditions, less sanitation, overcrowding and deficiency of awareness[132]. Many available reports are alarming that approximately 25% of the 57 million annual deaths are due to communicable infections[133] and most of pathogens have developed resistance to antibiotics[134-135]. It is a known phenomenon that pathogen infected wounds restore slowly as most of the living bacteria in the infected site secrete exotoxins. These substances are poisonous and prevent normal functioning of the surrounding cells and tissues including protein synthesis. Antimicrobial therapy is one of the most important wound care methods[136]. Open wounds are more vulnerable to infection, specifically for bacterial infections, as they are the point of entry for systemic infection. This type of wounds heal more slowly, often results in the production of unpleasant secretions and toxins, as well as the death of regenerative cells. Antibacterial and antifungal agents used in traditional medicine can prevent this occurrence and provide a basis for their use in wound care[137].

Recently, bacterial skin infections have frequently been seen with hospitalized patients, producing nosocomial infections[138,139,140]. The causative includes Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa[138,139,140]. According to FDA, the skin infections are associated with S. aureus, B. cereus and B subtilis[141]. Many studies elaborated the antimicrobial activity of medicinal plants[142,143,144,145] along with wound healing potency[102,146] have been reported. Plant derived antimicrobials are a huge source of untapped pharmaceutics and further research on plant antimicrobials is much required as they have enormous therapeutic potential[147,148,149]. In this list, CO is reported to have good antibacterial effect against Vibrio cholera[150], Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa and Enterococcus faecalis[151,152]. To support further, Vijayaraghavan et al. [75] showed the multi-spectral antimicrobial properties of CO leaf extracts against Staphylococcus aureus, Bacillus cereus and Bacillus subtilis (Gram positive) and Pseudomonas aeruginosa and E. coli (Gram negative) bacteria. CO was bactericidal to all microorganisms but P. aeruginosa among bacteria that often infect wounds[153]. The antimicrobial efficacy results of this study showed that CO leaf extracts showed promising and powerful antibacterial activity against the five tested bacterial strains. In clinical use, an aqueous extract of CO has also been found to increase hemostasis[154,155] and its astringent properties, explaining its usage in the therapeutics of wounds/injuries. The wound healing efficiency can be attributed to the antimicrobial and hemostatic effects of CO.

It is established that the multi-spectral antimicrobial attribution of the herbal plants is owing to the existence of variety of NPs like flavonoids, glycosides, phenols, saponins, alkaloids and steroids[156,157]. To substantiate the above, from like flavonoids from CO can effectively inhibit bacterial growth by binding to cell wall and inhibit biosynthesis of cell wall [151, 158]. Similarly, another compound tannins inhibit the growth of many other microbes like fungi, yeasts, and viruses[159]. Furthermore, the occurrence of alkaloids and saponins in the leaf extract of CO also involved in microbial inhibition [75, 160]. These the phytoconstituents screening and identification of bioactive compounds from CO are beneficial for the antimicrobial drug discovery and development[161].

To support the above, previous reports have shown that the extracts from Aloe Vera and H. rosasinensis played a key role in wound healing process through various mechanisms like up-regulation of transforming growth factor beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), activation of nuclear factor-кappa B (NF-κB) and interleukin-8 (IL8) and further the expression of alpha-1 (type-1) collagen and increased iNOS activity [162, 163, 164]. It is well established that VEGF is responsible for angiogenesis[165,166]. This growth factor acts on the respective receptors on keratinocytes and macrophages and performs various vital functions during wound healing process. Inadequate vasculogenic condition is generally apparent both in the chronic as well as in the non-healing wounds[167]. Deferred wound amelioration has been proven in diabetic animal models, where insufficient vascularization is the cause of poor epithelialization, granuloma tissue formation and delayed wound closure[168]. It is known that TGF-β is one of the most vital players for cell proliferation and it acts through intracellular serine/threonine kinase receptors using SMAD pathway as it controls cell proliferation[169]. TGF-β stimulates leukocytes to migrate into the damaged site[170], consequently monocytes become macrophages and involve in the clearance of debris with the incorporation of TGF-β and other necessary growth factors, which in turn contribute to the establishment of granulation[171].

On the other hand, the activation of phosphatidylinositol 3-kinase (PI3K) leads to phosphorylation of Akt (serine/threonine specific protein kinase) at serine 473 residue is also involved in healing process as shown to be important for the precise guided migration of corneal and dermal epithelial cells in response to wounds or injury[172,173]. Many medicinal plants like C. officinalis tincture have been reported to stimulate wound healing process through PI3K[174]. Besides, aqueous extract of Korean red ginseng also activates PI3-K/Akt pathways and stimulate angiogenesis in vivo and in vitro[175].

NF-κB signaling plays a significant role in maintaining immune homeostasis in epithelial cells[176]. Many reports have shown the activation of NF-κB increases the expression of pro-inflammatory mediators that orchestrate and involve in chronic inflammatory processes leading to tissue damage both in immune and non-immune cells[177, 178, 179]. On the other hand, the inhibition of NF-κB can have detrimental effects and can lead to inflammatory diseases[180]. The n-hexane extract of C. officinalis plant has been reported to increase the activity of the transcription factor NF-κB in immortalized human keratinocytes and skin fibroblast cells and promote healing process[162,181].

Besides, increased synthesis of nitric oxide (NO) by Pang et al[182] inducible nitric oxide synthase (iNOS) is reported in the proliferative phase of the wound healing[37,160,182] as it manages keratinocyte proliferation, collagen formation, and wound reduction [183]. To support the above, polysaccharide-rich extract of C. ferrea increased the expression of iNOS[184,185]. In addition, Rho family GTPases such as Rac-1, Rho-A and Cdc-42 play a vital role in the proliferation and migration of fibroblast cells [186,187]. Cell cycle regulators such as cyclins and cyclin-dependent kinases 1 and 2 are involved in cytoskeleton formation in fibroblasts[188]. In fact, C. tamurana has been reported to increase the migration of mammalian cells towards the injured area through activation of Rac-1, Rho-A, Cdc-42 mRNA, Cdk-1 and Cdk-2 genes[189].

Much evidence indicates that an increased radical species generation by neutrophils and myeloperoxidase enzyme (MPO) activity are responsible for long-lasting chronic wound damage by producing cellular toxicity through oxidative stress and slows down wound healing [190, 191]. The presence of various phytochemicals possesses the antioxidant activity and promotes healing mechanisms [192]. In support of this claim, topical application of L. macrophylla ethanol extract (5% w/v) in bio-adhesive gel increased various scavenging enzymes like superoxide dismutase catalase, and glutathione activity but decreased MPO activity[193].

The wound amelioration procedure consists of four well integrated phases, such as hemostasis, inflammation, proliferation, and remodeling[194,195]. Hemostasis is primarily regulated by thromboxane synthetase, which alters prostaglandin H2 to thromboxane A2, a well-known effective vasoconstrictor and platelet aggregator[196]. Furthermore, plasminogen activator inhibitor type 1 (PAI-1) also affects hemostasis by preventing fibrinolysis[197]. During inflammatory phase, heme proteins accumulate in the wound site and neutrophils release radical species to target bacteria[198]. Heme and heme proteins have both pro-oxidative and anti-inflammatory properties and induce adhesion molecules, which leads to vascular permeability and leukocyte infiltration, which initiates wound healing[199]. Heme oxygenase-1 (HO-1) has anti-inflammatory and antioxidant effects and is responsible for several wound healing functions including the conversion of heme to iron, carbon monoxide and bilirubin and biliverdin[200]. HO-1 overexpression promotes accelerated healing process by attenuating inflammation, inducing cell proliferation, and protecting endothelial cells from apoptosis[201]. Besides, matrix metalloproteinase (MMPs) also plays a vital role in extracellular matrix (ECM) remodeling in wound healing[202], and matrix metalloproteinase (MMP-9) is a key effector among these proteins[203].

To support the above, various investigations have shown that Siamese herb extract which includes its biomarkers Scu and stigmasterol accelerates hemostasis[154, 204] thereby wound healing[205,206] and anti-inflammatory properties[207]. The phytoprofen compound chromoic acid C-I was identified as a strong inducer of the activity of the transcription factor of CO, NFE2L2 (Nrf2), which is a key regulator of several genes with protective, anti-inflammatory and detoxification functions[95].

In the healing procedure, inflammation is a part of acute response as it permits the influx of neutrophils into the affected site [208] and these cells produce free radicals through their characteristic "respiratory burst"[209]. Non-phagocytic cells associated with the wound also produce free radicals through processes involving the nicotinamide adenine dinucleotide phosphate (NAD (P) H) oxidase is normally considered as a non-phagocytic machinery[210] at the wound site. The abundant surge of oxygen and nitrogen radicals at the wound site leads to DNA damage, enzyme deactivation and lipid peroxidation. Topical administration of plant derived NPs having ROS scavenging properties significantly improve the healing process and defend the tissues from radical injury[211].

Inflammation regulates several proinflammatory enzymes like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) and cytokines as they play a critical role in inflammation [212]. Proinflammatory enzymes produce mediators like prostaglandin E2 (PGE2) and nitric oxide (NO), which in turn activate the expression of tumor necrosis factor (TNF)-α and interleukin (IL)-1β. In line with this, CO is reported to have anti-inflammatory effects both in vitro and in vivo [102, 213] especially the metabolites like Scutellarein tetramethylether (Scu) (4', 5, 6, 7-tetramethoxyflavone), Isosakuranetin and Stigmasterol have exhibited these properties[208, 214].

It is well accepted that wound restoration also involves immune facilitated physiological mechanisms[215]. Numerous therapeutic plants employed in traditional medicine to treat various skin diseases, comprising ulcerative lesions[216]. Similarly, enhanced healing activity has been attributed for the increased collagen synthesis and angiogenesis [217] process. Collagen plays a vital role in wound repair as it is a part of connective tissue and provides structural basis for tissue regeneration [218]. In addition, in the granulation phase, angiogenesis increases blood flow at the injured site to supply nutrients and oxygen as they require for re-epithelialization[219] process, which in turn stimulates epithelial cell proliferation in the healing process[220]. To support this, various reports demonstrated that CO treated have shown significant increase of fibroblasts[37,101,119], synthesis of collagen and neovascularization, leading to augmented wound tensile strength and healing process[119,160,221], whereas, the proliferative phase usually follows and overlaps with the inflammatory phase, characterized by epithelial proliferation and migration across by creating the temporary matrix/re-epithelialization in the wound. Many studies have demonstrated that CO is known to involve in the growth and proliferation of skin fibroblasts and other cells like endothelial and epidermal keratinocytes[205,206,221] and this may partly explain the beneficial therapeutic properties observed in the wound healing process.

Figure 1. Image of Chromolaena odorata plant (Ref: 37)

Table 1: General Description of the plant (Ref: 86)

		C. odorata **Synonyms**	**Distribution**
Kingdom	Plantae - Plants	Eupatorium odoratum L., Eupatorium sabeanum Buckley, Eupatorium stigmatosum Meyen & Walp., Osmia conyzoides (Vahl) Sch.-Bip., Osmia divergens (Less.) Schultz-Bip., Osmia floribunda (Kunth) Schultz-Bip., Osmia graciliflora (DC.) Sch. Bip., Osmiaodorata (L.) Schultz-Bip. Eupatorium affine Hook & Arn. Eupatorium brachiatum Wikstrom, Eupatorium clematitis DC., Eupatorium conyzoides M. Vahl, Eupatorium divergens Less., Eupatorium floribundum Kunth, Eupatorium graciliflorum DC.	In North America, various parts from Florida and Texas to Mexico and the Caribbean. Also found in tropical Asia, west Africa, and parts of Australia.
Sub Kingdom	Tracheobionta - Vascular plants		
Super division	Spermatophyta - Seed plants		
Divison	Magnoliophyta - Flowering plants		
Class	Magnoliopsida – Dicotyledons		
Subclass	Asteridae		
Order	Asterales		
Family	Asteraceae - Aster family (Sunflower family)		
Genus	Chromolaena DC. – thoroughwort		

CONCLUSION

In summary, wounds specifically foot ulceration is a devastating condition that significantly compromises the affected persons quality of life. Though interest in foot ulceration increased recently but the current available therapeutics are not effective as they have produced a meagre clinical outcome. This is explained by inadequate information of the causal molecular mechanisms and treatments. Hence the complexity of foot ulceration must be addressed by implementing multidisciplinary methods, which include the adaptation of herbal medicines through a rigorous research method and appropriate methods, which should bring together all the necessary knowledge to optimally manage every aspect of foot ulcer complications. Since wound care is one of the most significant areas in clinical medicine, which is clarified in various traditional and folk medicine practices. Plants have enormous potential for wound healing and traditional medicine practioners around the world use plants to treat wounds and burns. The natural substances derived from medicinal plants promote the healing and regeneration of lost tissue through various mechanisms as these phytomedicines are not only cheap and affordable but also safe.

Herbal medicines play vital roles in the management of many diseases including foot ulceration caused by various microbial pathogens and radical species because they are nature's gift not only for wound healing but also for affordable health care. Identification and isolation of NPs offers enormous opportunities for better therapeutic use in the treatment of human diseases, microbial complications due to infections. This is crucial for the drug discovery and development with the inclusion of higher quality research, not only in the field of foot ulceration, but also on every field in the basic research till the clinical trial with the careful consideration of batch-to-batch reproducibility of topical botanicals used in the clinic. Despite the limitations of the scale and scope of the use of phytomedicines for the management of foot ulceration, it is still promising and may certainly provide an exciting therapeutic opportunity for wound healing. However, additional investigation and extensive scientific verifications are highly required to confirm the safety and efficacy of certain herbs, their mechanisms of action.

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