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## Medicinal Plants and Natural Products with Demonstrated Wound Healing Properties

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Additional information is available at the end of the chapter

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### Abstract

This section reviews the current literature on medicinal plants including extracts, fractions, isolated compounds and natural products that have been demonstrated to have wound healing properties. Various electronic databases such as PubMed, Science Direct, SciFinder and Google Scholar were employed to search for plants, natural plant constituents and natural products that have been scientifically demonstrated to have wound healing activity using *in vivo* and *in vitro* wound models. Parameters used in the evaluation of an agent with wound healing properties include rate of wound contraction, tensile strength, antioxidant and antimicrobial activities, hydroxyproline content assay and histological investigations including re-epithelization, collagen synthesis, granulation, proliferation and differentiation of fibroblasts and keratinocytes in excision and incision wound model studies. Eighty-five medicinal plants belonging to 45 families, phytoconstituents including phenolics, oils and other substances including honey were identified as potential wound healing agents or possess wound healing properties using various wound healing models.

**Keywords:** wounds, wound healing, medicinal plants, natural products, incision, excision

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### 1. Introduction

Wounds are physical injuries that result in an opening or break of the skin that causes disturbance in the normal skin anatomy and function. They result in the loss of continuity of epithelium with

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or without the loss of underlying connective tissue [1, 2]. Wounds that are most difficult to heal include delayed acute wounds and chronic wounds. Current estimates indicate that nearly 6 million people suffer from chronic wounds worldwide [3, 4]. Foot and leg ulcer is a common disorder, and approximately 1% of the European population suffers from such chronic and recurrent ulceration [3, 5]. Non-healing or chronic wounds result in enormous health care expenditures, with the total cost estimated at more than \$3 billion *per year* [3, 4]. Wounds such as injuries, cuts, pressure, diabetic, burns, gastric and duodenal ulcers continue to have severe impact on the cost of health care to patients as well as their families, dependents and health care institutions globally with increasing aging population.

Over the last decades, the search for newer and potent agents from nature (plants, marine environment, fungi and other microorganisms) to manage chronic wounds especially, in patients with underlying metabolic disorders has increased immensely. This is mainly due to the high risk of loss of function, loss of mobility, amputations and huge financial cost as well as death in some cases associated with chronic wounds [6, 7]. The situation is also compounded by the increase in the number of non-communicable diseases such as diabetes and ulcers and longer life expectancy in most developed countries where the prevalence and impact of chronic wounds are on the increase [8].

Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, venous stasis disease, or pressure. Between 70% and 80% of people living in the developing countries especially in Africa and Asia depend on herbal medicine for their health needs including wounds, infectious and metabolic diseases [5]. For some time now, there have been increased use of herbal and natural products for the management and treatment of various disease conditions among people in the developed countries including the United States, Europe and Japan.

With respect to the use of medicinal plants and natural products for the treatment of various diseases including metabolic and infectious diseases, specific diagnoses using various modern tools and equipment are not normally made but the treatment is based on the signs and symptoms of the diseases with which these products have been used for over a long period of time with successful treatment outcomes.

This section highlights the importance of medicinal plants and natural products as a major source of wound healing agents with the potential to be developed into phytotherapeutic agents to treat and/or manage wounds and their associated complications. This will also provide a starting point for future studies aimed at isolation, purification, and characterization of bioactive compounds present in these plants as well as exploring the underlying pharmacological mechanisms of action and potential niche market of these medicinal plants and natural products.

## **2. Properties of a good wound healing agent from herbal or natural product**

Wound healing agents are agents that can stimulate fibroblast proliferation, induce keratinocytes proliferation and differentiation, increase collagen formation, exhibit antimicrobial,

antioxidant and anti-inflammatory properties. In most cases, for an agent from medicinal plants or natural product to be classified as a good wound healing agent, it should possess two or more of the above properties [9, 10].

### **3. *In vivo* models for assessing wound healing activity**

*In vivo* models include both artificial and tissue models. Artificial models include subcutaneous chamber/sponges and subcutaneous tubes. Tissue models such as excision wounds, incision wounds, superficial wounds, dead space and burn wounds are usually used to determine the degree of re-epithelialization, collagenation, neovascularization and tensile or breaking strength of wounds [11–13]. Models such as rabbit ear chamber, the hamster cheek pouch, the rabbit corneal pocket and the chick chorioallantoic membrane can also be employed to investigate the extent of re-epithelialization, neovascularization and dermal reconstitution [14].

### **4. *In vitro* models for assessing wound healing activity**

*In vitro* models are generally simple, rapid and involve minimal ethical consideration compared to whole animal work and allow insight into the biochemical and physiological processes induced by the test agent. Many pharmacological agents at different concentrations can be evaluated concurrently without intrinsic heterogeneity associated with *in vivo* models [14]. As regenerative skin is characterized by connective as well as epithelial tissues, both cell types, dermal fibroblasts as well as human fibroblasts (either primary cells or cell lines), should be used for complete assessment of wound healing activity. *In vitro* models are relevant in study of cell-cell and cell-matrix interaction to mimic cell migration during wound healing. *In vitro* models can employ single cell systems, three dimensional systems, multicellular systems or organ cultures in assessing the wound healing properties of wound healing agents or compounds [14, 15].

### **5. Methods used for pinpointing herbal materials and natural products with wound healing property**

Electronic databases such as PubMed, Scifinder® and Google Scholar were used to search medicinal plants that have been evaluated for wound healing. All filtered articles were appraised to determine whether they contain any validated *in vitro* or *in vivo* wound model. Primary search results were independently screened by two investigators. Included articles were reviewed concerning plant botanical names, part of plants used in the respective study and type of plant extracts, active constituents or compounds and wound models used (*in vivo* or *in vitro*) or standardized clinical trials with clearly demonstrated wound healing activity in

the models used. Consideration was given to the significant differences between test group and control group with respect to wound contraction, wound tensile strength, period of epithelialization, neovascularization, collagenation, keratinization and fibrosis. In case of clinical studies, the respective design, number of patients, interventions, duration of treatment, and data related to the efficacy and tolerability of the patients to treatment were also monitored.

## 6. Medicinal plants used in wound care

### 6.1. Acanthaceae

*Justicia flava* (Forssk.) Vahl has widespread uses in tropical Africa. It is used in traditional medicine for the treatment of cough, paralysis, fever, epilepsy, convulsion and spasm, and skin infections and disorders. The roots are also used for diarrhea and dysentery [16, 17]. The methanol leaf extract of *J. flava* (7.5% w/w) has been found to reduce wound size significantly ( $p < 0.01$ ) as compared to the untreated wounds in rats excision wound model. The extract also significantly ( $p < 0.01$ ) increased the tensile strength of wounds compared to the untreated wounds. Wound tissues from animals treated with the test extract showed improved angiogenesis, collagenation, and re-epithelialization compared to the untreated wound tissue [16].

*Adhatoda vasica* L., commonly known as Chue Mue, grows in India. Leaves and stems of the plant have been reported to contain an alkaloid mimosine. Leaves also contain mucilage and root contains tannins. The methanol, chloroform and diethyl ether extract ointment (10% w/w) of *A. vasica* showed significant effect when compared to standard drug in excision wound model [18].

### 6.2. Amaranthaceae

*Achyranthes aspera* L., locally known as "Telenge or ambulale," is one of the traditionally used plants in the indigenous health care delivery system for the treatment of various kinds of wounds especially in Ethiopia and India. The leaves of *A. aspera* (2.5%, 5% and 10% w/w) simple ointment when applied topically have been shown to significantly ( $p < 0.05$ ) enhance the rate of wound contraction, breaking strength and epithelization in excision wound model compared to the control. Histological evaluation of *A. aspera*-treated wound tissues revealed well organized epidermal layer, increased number of fibrocytes, improved neovascularization and epithelialization compared to the control group [19]. Barua et al. [20] further reported that 5% ointment of methanol leaf extract of *A. aspera* significantly ( $p < 0.05$ ) increased the wound contraction rate, hydroproline and protein production, vitamin C content as well as elevates antioxidant enzymes such as superoxide dismutase and catalase levels in burn wound bed compared to control. The study via gelatin zymography also revealed an increased expression of matrix metalloproteinases (MMP-2 and 9) and improved granulation tissues, collagen and fibroblast deposition in wound bed of *A. aspera*-treated animals compared to control group in subsequent histological examinations.

*Alternanthera sessilis* (L.) R. Br. ex DC is a tropical plant which is traditionally used for the treatment of ulcers and cuts and wounds, fevers, ophthalmia, gonorrhea, pruritis, burning sensations, diarrhea, skin diseases, dyspepsia, hemorrhoids, liver and spleen diseases [21]. The oral application of chloroform extract from the leaves of *A. sessilis* at a dose of 200 mg/kg body weight significantly reduced wound area ( $p < 0.005$ ) and increased re-epithelialization ( $p < 0.0001$ ) compared to the untreated wound tissues. Furthermore, in excision wound model, scar area after complete epithelialization ( $p < 0.0008$ ) with increased wound breaking strength ( $p < 0.0001$ ) compared with the untreated wounds in incision wound model [22]. Antibacterial property of the leaves and aerial parts of *A. sessilis* has been reported by [23] and antibacterial activity is an ideal property of good wound healing agent [9].

*Pupalia lappacea* (L.) Juss is an annual or perennial herb found widespread in the tropics and subtropical regions in Africa and it is used in folklore medicine for treatment of boils, chronic wounds and skin infections [10, 24]. Histological studies of wound tissues treated with extracts revealed appreciable collagenation, re-epithelialization, granular tissue formation and angiogenesis for wounds treated with 2% and 10% (v/w) of ethanol leaf extract creams as well as 1% chloroform extract creams to untreated control wound tissues. The ethanol and chloroform extracts also exhibited high rate of wound closure [25]. However, Udegbumam et al. [26] also reported that higher concentrations (10% and 20% (w/v) ointment of methanol leaf extract of *P. lappacea*) significantly ( $p < 0.05$ ) accelerated wound healing, thereby the 20% ointment having the highest percentage wound contraction and rate of epithelialization. The extract also exhibited antimicrobial activity with MIC of 3.0–9.0 mg/mL and MBC of 7–10 mg/mL against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*.

### 6.3. Anacardiaceae

*Buchanania lanzan* Spreng, commonly known as char, achar and chironji, is an evergreen tree commonly found in the dry deciduous tropical forests of India and it is used to treat cough, constipation, skin disorders and stomach disorders [27]. Topical application of methanol root extract of *B. lanzan* (10% (w/w) ointment) significantly ( $p < 0.05$ ) increased the tensile strength in the incision wound model. *B. lanzan* also showed significant wound healing activity in excision wound model [28]. However, a study conducted by Chitra et al. [29] showed that the methanol fruit extract of *B. lanzan* did not significantly ( $p > 0.05$ ) promote wound healing when compared to the control in excision, incision and dead space wound models.

*Lannea welwitschii* (Hiern.) Engl. is found growing in deciduous and secondary forests of Africa from Cote d'Ivoire to Cameroon and extending to Uganda and Angola. Decoction of the leaves is used traditionally for the treatment of diarrhea, dysentery, swellings, gout, gingivitis, topical infections, and wounds [10]. Methanol leaf extract of *L. welwitschii* (7.5%, w/w) significantly ( $p < 0.05$ ) reduced wound size as compared to the untreated in excision wound model in rats. The extract also significantly ( $p < 0.01$ ) increased the tensile strength, improved angiogenesis, collagenation, and re-epithelialization of wounds compared to the untreated wounds [16].

#### 6.4. Apiaceae

*Centella asiatica* (L.) Urban is a tropical plant native to Southeast Asian countries such as India, Sri Lanka, China, Indonesia, and Malaysia as well as South Africa and Madagascar [30]. It is used for treatment of burns and postoperative hypertrophic scars [31, 32]. Asiaticoside, isolated from *C. asiatica*, has been studied in normal as well as delayed-type wound healing in guinea pigs. Topical applications of 0.2% (v/w) asiaticoside on wounds induced a 56% increase in hydroxyproline, 57% increment in tensile strength, increased collagen formation and improved re-epithelialization. Also in streptozotocin-diabetic rats, where wound healing is typically delayed, topical application of 0.4% (v/w) asiaticoside over punch wounds increased hydroxyproline content, tensile strength, collagen content and epithelialization thereby facilitating the healing. Asiaticoside was also found to be active by the oral route at a dose of 1 mg/kg in the guinea pig punch wound model. It promoted angiogenesis in the chick chorioallantoic membrane model at 40 µg/disk concentration [33]. Triterpene compounds such as asiatic acid, madecassic acid and madecassoside are the principal components of *C. asiatica*, responsible for wound healing. The action has been demonstrated both for the extracts as well as for the triterpene *in vitro* and *in vivo* studies [31, 32].

*Cuminum cyminum* L. is one of the oldest cultivated medicinal food herbs in Africa, Asia and Europe and seeds have been commonly used for culinary and flavoring purposes and folklore therapy since antiquity in various countries [34–36]. Alcoholic extract of the seeds and its petroleum ether fraction showed better re-epithelialization ( $p < 0.001$ ), therefore promoted wound healing compared to the untreated wounds [37].

#### 6.5. Apocyanaceae

*Catharanthus roseus* L. is native to the Caribbean Basin, Madagascar and has been found growing in tropical Africa. The fresh juice from the flowers of *C. roseus* made into a tea has been used by Ayurvedic physicians in India to treat skin infections, dermatitis, eczema and acne. Ethanol flower extract of *C. roseus* significantly ( $p < 0.001$ ) increased the wound breaking strength in the incision wound model compared to controls. The extract-treated wounds were found to epithelialize faster, and wound contraction was significantly ( $p < 0.001$ ) increased in comparison to control wounds and hydroxyproline content in a dead space wound model increased significantly ( $p < 0.05$ ) [38].

*Strophanthus hispidus* DC. is found all over Africa including savannah forests in Ghana, Senegal, Sudan, Congo DR, Uganda, and Tanzania. It is used for the treatment of syphilis ulcers, bony syphilis, and guinea worm sores and wounds [39]. The influence of the leaf and root extracts of *S. hispidus* on rate of wound closure was investigated using the excision wound model. The extract (7.5%, w/w) showed significantly ( $p < 0.05$ ) improved wound contraction compared to the untreated wounds. Extract-treated wound tissues with showed improved collagenation, re-epithelialization and rapid granulation formation compared with untreated wound tissues [40].

*Wrightia tinctoria* R. Br., commonly known as Indrajauis, is a small deciduous tree distributed in Asia and some tropical countries in Africa such as Ghana, Nigeria and Cameroun. It is used

traditionally to treat various skin diseases and wounds [41–43]. *In vivo* investigations revealed that ethanol stem bark extract of *W. tinctoria* exhibited significant wound healing activity. The extract improved breaking strength ( $p < 0.01$ ) increased the percentage wound closure and decreased epithelialization time ( $p < 0.001$ ) compared to the control. It also significantly increased ( $p < 0.001$ ) hydroxyproline content of ten-day-old granuloma of extract-treated animals compared to control animals in dead space wound model. The pro-healing action seems to be due to the increased synthesis of collagen and its cross-linking as well as better alignment and maturation [44].

*Saba florida* (Benth.) is widely distributed in tropical Africa in countries such as Senegal, Nigeria, Cameroon, Sudan and Tanzania. It is used to treat rheumatism, diarrhea, gonorrhoea and as antidote against food poisoning as well as snake bites [45]. Alcohol extract of *S. florida* when administered topically (10%, w/w) and orally (100–400 mg/kg body weight) significantly stimulate wound healing in excision and incision wound models [46].

## 6.6. Asclepiadaceae

*Calotropis gigantea* R. Br. is a perennial under-shrub found chiefly in wastelands throughout India, and in some African countries such as Angola, Gabon, DR Congo, Kenya, Sudan, Tanzania and Mozambique. The whole plant is used for treatment of skin diseases, boils and sores. *C. gigantea* is also used in some parts of India for wound healing in combination with other plants [47–49]. The whole plant extract increased the percentage of wound contraction, scar area and decreased re-epithelialization time. Breaking strength of extract-treated wounds and hydroxyproline content increased compared to untreated [50].

*Calotropis procera* W. T. Aiton is a well-known plant in the Ayurvedic system of medicine. *C. procera* originated from the Afro-Asian monsoonal regions. It spreads on an arc expanding from north western Africa including Mauritania, Senegal, through the Arabian Peninsula and Middle-East to the Indian subcontinent. It was introduced to subtropical America, the Mascarene Islands, drier parts of Australia and probably Southeast Asia [51]. The latex of *C. procera* (1%, w/v) significantly facilitated the wound healing process by increasing collagen, DNA and protein synthesis and epithelialization leading to a marked reduction in wound area compared to the control [52].

## 6.7. Asteraceae

*Achillea biebersteinii* Afan is a perennial herb which is used in folkloric medicine in Turkey to treat abdominal pain, wounds and stomachache. N-hexane aerial parts extract of *A. biebersteinii* showed marked increase in wound contraction rate and tensile strength in excision and incision wound models, respectively. However ointment incorporated with 1% chloroform, ethyl acetate and methanol extract showed no significant influence on the wound healing process in both excision and incision wound models [53].

*Ageratum conyzoides* L. has long been known in herbal medicine as a remedy for various ailments in Africa [54], Asia, and South America [55, 56]. It is used by the Fipa in South Africa and central Africa for the treatment of fresh wounds and burns [57]. The wound healing



activities of petroleum ether, chloroform, methanol and aqueous extracts of *A. conyzoides* were evaluated using the excision, incision and dead space wound models. Methanol and aqueous leaf extracts of *A. conyzoides* showed faster rate of wound healing compared to other extracts [58].

*Chromolaena odorata* L. is a perennial shrub that is native in Africa [59, 60]. Extracts from the leaves of *C. odorata* have been shown to be beneficial for treatment of wounds. The crude ethanol extract of the plant had been demonstrated to be a powerful antioxidant in protecting fibroblasts and keratinocytes *in vitro*. Phenolic acids including protocatechuic, p-hydroxybenzoic, p-coumaric, ferulic and vanillic acids and complex mixtures of lipophilic flavonoid aglycones (flavanones, flavonols, flavones and chalcones) were antioxidants found to protect cultured skin cells against oxidative damage in colorimetric and lactate dehydrogenase release assay [61].

*Centaurea iberica* Trev. ex Spreng also called Iberian star thistle is native to the Mediterranean region, southern Europe and northern Africa. Several *Centaurea* species are used in Turkish folk medicine to alleviate pain and inflammatory symptoms in rheumatoid arthritis, high fever, headache and wounds. Particularly, the aerial parts have found to improve wound healing. Histopathological evaluation of both ointment of aqueous and methanol extracts treated and untreated wound tissues from rats supported the healing process with remarkable increase in the proliferation of fibroblasts, differentiation of keratinocytes, re-epithilization and remodeling [62].

*Sphaeranthus indicus* L. is distributed throughout Africa, India, Sri Lanka and Australia. It is an important medicinal plant used for the treatment of styptic gastric disorders, skin diseases, anthelmintic, glandular swelling, and nervous depression. The decoction and powdered material of the plant are used for the treatment of bronchitis, asthma, leucoderma, jaundice, piles and scabies [63–65]. Extract of the aerial parts of *S. indicus* significantly enhanced the rate of wound contraction and the period of epithelialization comparable to neomycin in pigs [66].

*Tridax procumbens* L. is commonly known as 'coat buttons' among English folks. The plant is native to tropical America and naturalized in tropical Africa, Asia, Australia and India. The influence of whole plant extract and aqueous extract of *T. procumbens* on lysyl oxidase activity, protein and nucleic acid contents as well as the tensile strength which are relevant to wound healing resulted in significant ( $p < 0.01$ ) increment in the above parameters in albino rat treated with whole plant aqueous extract and aqueous extract fractions compared to the untreated in dead space wound healing model. Butanol and petroleum ether fractions treated wound tissues showed a decrease in all these parameters except tensile strength. In these two groups, the hexosamine levels were increased ( $p < 0.001$ ). Whole plant extract were more active as compared to the other extracts in dead space wound model [67]. Yaduvanshi et al. [68] reported that, excision wounds treated with extract of the juice of *T. procumbens* (1 mg/g) and VEGF (1  $\mu\text{g}/\text{mL}$ ) exhibited a significant ( $p < 0.05$ ) increase of 38.81% and 47%, respectively in collagen biosynthesis compared to the vehicle-treated wounds. Histological investigations also showed increased infiltration of inflammatory cells, fibroblast proliferation and re-epithelialization with moderate vascularity in dermal wound tissues treated with extract of the juice of *T. procumbens*. However, dermal wounds treated with

extract of the juice of *T. procumbens* at a dose of 4 mg/g induced inflammation, edematous tissue and decreased vascularity. Ethanolic and aqueous leaf extract *T. procumbens* significantly ( $p < 0.05$ ) increase in wound tensile strength. In the excision model, biochemical markers such as hydroxyproline, collagen and hexosamine increased significantly ( $p < 0.05$ ) compared to the untreated control group [69].

*Calendula officinalis* L., also known as pot marigold or garden marigold, is a common garden plant which is native to Southern Europe and Egypt. Traditionally it is used to treat various skin disorders such as burns and wounds, eczema, psoriasis and variety of skin infections. It can also be used to treat seizures, haemorrhoids and lungs, mouth and throat infections [70]. The effects of oral application of *C. officinalis* flower ethanol extract at dose of 20 and 100 mg/kg body weight have been reported to significantly ( $p < 0.01$ ) promote wound closure and re-epithelialization compared to the control group in excision wound model. In addition, there was significant ( $p < 0.05$ ) increases in hydroxyproline and hexosamine content in the 100 mg/kg extract-treated wounds compared with the untreated animals [71].

## 6.8. Bignoniaceae

*Kigelia africana* (Lam.) Benth. is found widespread across tropical Africa including Ghana, Sierra Leone, Gambia, Sudan and Nigeria and also found growing in wet savannah and near river bodies where it occurs in abundance [72]. It is used to treat skin ailments including fungal infections, boils, psoriasis and eczema, leprosy, syphilis, and cancer. The roots, wood and leaves have been found to contain kigelinone, vernolic acid, kigelin, iridoids, luteolin, and 6-hydroxyluteolin [73]. The iridoids have antibacterial property [74]. The methanol stem bark extract of *K. africana* (7.5%, w/w aqueous cream) in rat excision wound model showed significant ( $p < 0.05$ ) wound contraction on day 7 with 72% of wound closure compared to the untreated control group. Wound tissues treated with the extracts showed improved collagenation, re-epithelialization and rapid granulation formation compared to untreated wound tissues [40].

*Spathodea campanulata* P. Beauv. is used in folkloric medicine in Ghana and several African countries to treat various forms of wounds [9, 10, 75]. Excision wounds treated with 20% (w/w) *S. campanulata* cream and Cicatrin® cream showed a rapid and comparable decrease ( $p < 0.05$ ) in wound size in rats. In uninfected wounds, both 20% (w/w) *S. campanulata* cream and Cicatrin® cream application resulted in 95% wound closure seen on day 20, and a complete closure seen on day 24. In infected wounds, both 20% (w/w) *S. campanulata* cream and Cicatrin® cream administration led to approximately 91% wound closure on day 24 and a complete wound contraction on day 28 [76].

*Tecoma capensis* Thumb. Lindl, commonly called Cape honeysuckle, is a shrub which is native of South Africa. The leaf extract of *T. capensis* (5% and 10%, w/w ointment) have been reported to exert significant increase rate wound closure and wound breaking strength in excision and incision wound models, respectively. Again, oral administration of 200 and 400 mg/kg leaf extract significantly increased granuloma breaking strength and hydroxyproline contents in dead space wound model [77].

### 6.9. Boraginaceae

*Heliotropium indicum* L. has a pantropical African distribution, but is probably native of tropical America and it is widespread throughout Africa. It is used as an analgesic (rheumatism), diuretic and for treatment of skin problems including yaws, urticaria, scabies, ulcers, eczema, impetigo and wounds [17, 78, 79]. *H. indicum* extracts (petroleum ether, chloroform, methanol and aqueous) promoted wound healing activity. The highest activity was observed with the methanol fraction. Significant increase in the granulation tissue weight, increased hydroxyproline content, and increased activity of superoxide dismutase and catalase level with the animals treated with methanol extract in dead space wound model further augmented the wound healing potential of *H. Indicum* [80].

### 6.10. Cactaceae

*Opuntia ficus-indica* (L.), commonly known as cactus or prickly pear, is a tropical and subtropical plant that grows in arid and semi-arid climates with a geographical distribution encompassing Mexico, Latin America, South Africa and Mediterranean countries [81, 82]. It has been used in folklore medicine for the treatment of diseases including inhibition of stomach ulceration [83]. The methanol stems extract of *O. ficus-indica* and its hexane, ethyl acetate, *n*-butanol and aqueous fractions were evaluated for their wound healing activity in rats. The extract and less polar fractions showed significant ( $p < 0.05$ ) wound healing effects compared to the untreated wounds [84]. The wound-healing potential of two lyophilized polysaccharide extracts obtained from *O. ficus-indica* (L.) cladodes applied on large full-thickness wounds in the rat have been reported. When topically applied for 6 days, polysaccharides with a molecular weight  $>10(4)$  Da accelerated the re-epithelialization and remodeling phases, also by affecting cell-matrix interactions and by modulating laminin deposition. However, the wound-healing activity is high with polysaccharides with a MW ranging between  $10(4)$  and  $10(6)$  Da than for those with molecular weight  $>10(6)$  Da [85].

### 6.11. Caricaceae

*Carica papaya* L. is commonly known as pawpaw. The edible part of *C. papaya* is widely used all over the world and is cultivated in most tropical countries. The leaves are used traditionally as a dressing component for wounds [86]. The aqueous leaf extract of *C. papaya* (5% and 10%, w/v extract in vaseline and solcoseryl jelly) accelerated wound healing compared to the wounds treated with blank vaseline [87]. In streptozotocin-induced diabetic rats using excision and dead space wound models, the aqueous extract exhibited 77% reduction in the wound area compared to the controls. The wet and dry granulation tissue weight and hydroxyproline content increased significantly when compared to controls [88]. Carbopol gel containing 1.0% and 2.5% (w/w) of dried papaya latex have been found to accelerate wound closure, increase hydroxyproline content and stimulate epithelialization compared to the control in burn wound model [89].

## 6.12. Cecropiaceae

*Myrianthus arboreus* P. Beauv is a dioecious shrub or tree which grows up to 20 m tall. It is found growing in forest zones of tropical Africa including Ghana, Sierra Leone, Sudan, Ethiopia, southern part of DR Congo, Tanzania and Angola. Extracts of the leaves and leafy shoots of *M. arboreus* are used in the treatment of dysentery, diarrhea, wounds, boils, dysmenorrhea and incipient hernia and vomiting. The study revealed that 5% (w/w) methanol leaf extracts of *M. arboreus* cream has potent wound healing capacity with better wound closure ( $p < 0.05$ ) on day 1 and day 9 ( $p < 0.001$ ) compared with untreated wounds in excision wound model. Histological investigations showed enhanced wound tissue proliferation, fibrosis and re-epithelialization compared with the untreated wound tissues [90].

## 6.13. Combretaceae

*Terminalia arjuna* (Roxb. Ex DC) Wight and Arn. is native to India and Sri Lanka but it has been planted and naturalized in many African countries. In Mauritius, it is traditionally used in the management of dysentery and rheumatism. The effect of topical application of fractions (fractions I, II and III) obtained from a hydro-alcoholic extract of the stem bark were assessed on the healing of rat dermal wounds. The fractions significantly increased the tensile strength of the incision wounds and degree of re-epithelialization of excision wounds compared to control animals ( $p < 0.05$ ). However, topical treatment with fraction I, consisting mainly of tannins, was found to demonstrate a comparatively high increase in the tensile strength of incision wounds and exhibited the fastest rate of epithelialization and increased hexosamine content [91].

*Combretum mucronatum* Schum. & Thonn. grows in west Africa in countries such as Ghana Senegal, DR Congo and Gabon. The leaves are traditionally used for treatment of wounds and skin infections. Aqueous leaf extract of *C. mucronatum* has been shown to stimulate viability of human keratinocytes and dermal fibroblasts. The extract stimulated cellular differentiation of primary keratinocytes significantly at 1 and 10  $\mu\text{g/mL}$ . An isolate, procyanidin B2 from *C. mucronatum* at 1 and 10  $\mu\text{M}$  was shown to be responsible for the induction of this cellular differentiation, while epicatechin and procyanidins B5, C1 and D1 also isolated from the extract were inactive [92].

## 6.14. Crassulaceae

*Bryophyllum pinnatum* Lam. is a perennial herb that grows in the tropical, subtropical and temperate regions of the world. The plant is well known as an agent for wound healing in folkloric medicine in most part of Asia especially in India. Petroleum ether, alcohol and aqueous leaf extract of *B. pinnatum* at an oral dose of 400 mg/kg showed significant ( $p < 0.001$ ) increase in the breaking strength of incision wound as compared to control group. In the dead space wound healing, granuloma breaking strength and hydroxyproline content of granulation tissue increased significantly ( $p < 0.001$ ) compared to control group. The aqueous extract of *B. pinnatum* also showed significant ( $p < 0.001$ ) increase in wound contraction and formation of scars compared to the control in excision wound model [93].

### 6.15. Curcubitaceae

*Momordica charantia* L. also known as bitter gourd or bitter lemon is found in tropical regions including west Africa and it is used in the management of wounds, peptic ulcer, fever, piles and skin infections and parasitic infections [86, 94]. In excision wound model, the methanol leaf extract of *M. charantia* showed significant ( $p < 0.05$ ) wound closure and histological investigation of the wound tissues revealed high fibrosis and collagenation compared to the untreated wound tissues in rats [94].

### 6.16. Cyperaceae

*Cyperus rotundus* L. is indigenous to India, but now it is found in tropical, subtropical and temperate regions from Asia, Africa and South America [95]. *C. rotundus* is used in folkloric medicine for the treatment of dyspepsia, fever, pruritis, wounds and pains [64, 96]. An alcoholic extract of tuber parts of *C. rotundus* ointments showed an increase in wound contracting ability, tensile strength and a decrease in wound closure time [97].

### 6.17. Euphorbiacea

*Phyllanthus muellerianus* (Kuntze) Exell. is found growing in most tropical region including Africa and Asia and it is used for the treatment of boils, wounds, stomach sores, menstrual disorders, fevers and other skin eruptions. Geraniin is the major phytochemical constituents in the leaves of *P. Mullerianus* [98]. In the excision wound healing, aqueous extract (PLE) of *P. muellerianus* (0.25%, 0.5% and 1%, w/w) and geraniin (0.1%, 0.2% and 0.4%, w/w) significantly ( $p < 0.001$ ) reduced wound area, increased hydroxyproline content and tensile strength compared to the untreated wounds. Histological studies of wound tissues showed high number of fibroblasts and increased collagenation in PLE and geraniin-treated wound tissues. Immunohistochemical investigations revealed high levels of TGF- $\beta_1$  in PLE (0.25%, 0.5% and 1%, w/w) and geraniin-treated (0.1%, 0.2% and 0.4%, w/w) wound tissues compared to the untreated wound tissues. Protein band analysis of coomassie stained SDS-PAGE showed significantly ( $p < 0.001$ ) high levels of TGF- $\beta_1$  in both PLE (0.25%, 0.5% and 1%, w/w) and geraniin-treated (0.1%, 0.2% and 0.4%, w/w) wound tissues compared to the untreated wound tissues. SOD activity increased significantly ( $p < 0.001$ ) in both PLE (0.25%, 0.5% and 1%, w/w) and geraniin-treated (0.1%, 0.2% and 0.4%, w/w) wound tissues compared to the untreated wound tissues. SOD, CAT and APx activity increased significantly ( $p < 0.01$ ) in both PLE (0.25%, 0.5% and 1%, w/w) and geraniin-treated (0.1%, 0.2% and 0.4%, w/w) wound tissues compared to the untreated tissues. However, MPO activity decreased significantly ( $p < 0.01$ ) in PLE (0.25%, 0.5% and 1%, w/w) and 0.2% and 0.4% (w/w) geraniin-treated wound tissues compared to the untreated wound tissues [99]. Hydrophilic extracts from *P. muellerianus* and especially the major isolate, geraniin, exhibited stimulating activity on dermal fibroblasts and keratinocytes, leading to increased cell proliferation, barrier formation and formation of extracellular matrix proteins [98].

*Alchornea cordifolia* (Schum. & Thonn.) Muell. Arg. is an evergreen dioecious shrub which grows in the eastern part of Senegal to Kenya and Tanzania and throughout Central Africa to Angola.

The poultice of the leaves is used for the treatment of wounds. The leaves and root bark of *A. cordifolia* are externally applied to treat leprosy and as antidote to snake venom [10, 86]. Aqueous leaf extracts of *A. cordifolia* cream (10%, w/w) in an excision wound model, exhibited potent wound healing capacity with better wound closure ( $p < 0.05$ ) at day 1 and day 9 ( $p < 0.001$ ) compared with untreated wounds. Histological investigations showed enhanced wound tissue proliferation, fibrosis and re-epithelialization compared with the untreated wound tissues [90].

*Jatropha curcas* L. also called physic nut is a perennial poisonous shrub originated from Central America but has spread to other tropical and subtropical countries and mainly grows in Asia and Africa. The plant has been employed in the management of many ailments including ulcer and sores in some parts of Africa [99, 100]. The leaf and stem bark extracts of *J. curcas* have been found to accelerate the healing process by increasing the skin breaking strength, granulation tissue breaking strength, wound contraction, dry granulation tissue weight and hydroxyproline levels. A marked decrease in epithelialization period was also observed. The histological examination of granulation tissue also showed the presence of more collagen, which has organized to form bundles indicative of advance wound healing [101].

Arabinogalactan protein (JC) from *J. curcas* seed endosperm (mean molecular weight 140 kDa) was isolated by cold water extraction and characterized concerning sugar and amino acid composition. At 10 and 100  $\mu\text{g/mL}$  JC stimulated mitochondrial activity (MTT assay) of HaCaT keratinocytes and dermal fibroblasts and the ATP status of primary keratinocytes. JC did not influence the cellular proliferation, while primary keratinocytes were triggered into differentiation status. Investigations on a potential mode of action of JC were performed on complex organotypic skin equivalents. JC induced HGF, KGF and TGF- $\beta$  expression, with TGF- $\beta$  being the main inducer for the differentiation-inducing effect of JC. Also the expression of GM-CSF was stimulated strongly by JC. This *in vitro* activity profile indicated JC to be a potent inducer of cellular differentiation via stimulation of growth hormones and TGF- $\beta$ -induced cell signaling [102].

*Mallotus oppositifolius* (Geiseler) Müll. Arg. is found growing in tropical African region regions including Ghana and Nigeria. A leaf or stem bark infusion is applied to cuts and sores as haemostatic and used to treat burns, skin eruptions and rashes [78, 86, 103]. Methanol leaf extract of *M. oppositifolius* showed significant ( $p < 0.05$ ) wound closure, fibrosis and collagenation in excision wound model [94].

*Phyllanthus emblica* L. also known as *Emblica officinalis* is a native plant from Asia. It is used in folkloric medicine as a wound healing agent either in single formulation or in combination with other medicinal plants. Topical application of ethanol fruit extract (200  $\mu\text{L}$ ) of *P. emblica* increases cellular proliferation and cross-linking of collagen at the wound site, which is evidenced by an increase in the activity of extracellular signal-regulated kinase 1/2, along with an increase in DNA, type III collagen, acid-soluble collagen, aldehyde content, shrinkage temperature and tensile strength. Higher levels of tissue ascorbic acid, alpha-tocopherol, reduced glutathione, superoxide dismutase, catalase and glutathione peroxidase support the fact that *P. emblica* promotes antioxidant activity at the wound site in excision wound model [104]. Again, aqueous extract of the fruit of *P. emblica* (0.1  $\mu\text{g/mL}$ ) in scratch assay using human

umbilical vein endothelial cells (HUVEC) was shown to promote endothelial cell function and wound healing by significantly ( $p < 0.05$ ) promoting NO production, endothelial wound closure, endothelial sprouting, and VEGF mRNA expression which provides further evidence to support the traditional use of *P. emblica* as a wound healing agent [105].

### 6.18. Fabaceae

*Mimosa pudica* L. originated in tropical Central and South America and naturalized throughout the tropics including Africa. Its wound healing properties were studied in three different wound models in rats (excision, incision and estimation of biochemical parameter) using both aqueous and methanol root bark extract. Treatment of wounds with ointment containing 2% (w/w) of methanol and aqueous extract exhibited significant ( $p < 0.001$ ) wound healing activity by increasing rate of wound contraction, tensile strength and hydroxyproline content compared to the control. The period for re-epithelialization was reduced compared to the control [106].

*Indigofera enneaphylla* L. is an under-shrub widely grown throughout India. The plant is used traditionally to treat scurvy, stomach disorders, pain, skin infections and wounds. showed that Ethanol extract of the whole plant extract of *I. enneaphylla* (0.5% and 1%, w/w ointments) significantly increased ( $p < 0.001$ ) rate of wound contraction on day 18 post wounding in excision wound model when compared to the control group. In the incision wound model, both doses of extract also exhibited significant ( $p < 0.001$ ) increase in tensile strength [107].

*Tephrosia purpurea* L. is an herb which grows in the tropical regions. It is traditionally used in the treatment of bronchitis, boils, bleeding piles, pimples, roots and seeds are used as insecticidal, vermifuge, leprous wound and the juice is used for the eruption on skin. It has found to contain glycosides, rotenoids, isoflavones, flavones, chalcones, flavonoids and sterols. Ethanol aerial parts extract of *T. purpurea* formulated into a 5% (w/w) simple ointment stimulated ( $p < 0.05$ ) wound contraction, tensile strength, hydroxyproline content, protein level in excision, incision and dead space wound models. Histological examination of the wound tissue showed significant ( $p < 0.05$ ) increase in fibroblast cells, collagen fibers and blood vessels formation [104].

### 6.19. Fagaceae

*Quercus infectoria* Olivier is a small tree found in Greece, Asia and Iran. The galls of *Q. infectoria* are used traditionally to treat inflammatory diseases including toothache and gingivitis. The wound healing activity of ethanol extract of the galls of *Q. infectoria* was investigated using the incision, dead space and excision wound models in rats. The study revealed a (400 and 800 mg/kg body weight) significantly ( $p < 0.05$ ) increase in tensile strength in extract-treated wound tissues compared to the control group in the incision wound model. In the dead-space wound model the extract significantly ( $p < 0.05$ ) increased dry granuloma weight, granuloma breaking strength and hydroxyproline content compared to the control group. *Q. infectoria* was also identified to significantly ( $p < 0.05$ ) promote wound contraction rate as well as increase levels of superoxide dismutase and catalase activity in wound bed compared to the control in the excision wound model [108].

## 6.20. Flacourtiaceae

*Hydnorcarpus wightiana* Blume is widely distributed in India and its neighboring countries. The oil referred to as “chaulmoogra” which is extracted from *H. wightiana* and other species is well known for its anti-leprosy activity. The oil at a dose of 45 mg/kg is also reported to significantly ( $p < 0.01$ ) enhance wound healing by increasing breaking strength and collagen and hydroxyproline contents of wounds compared to the control in incision and dead space wound models, respectively. *H. wightiana* oil administered orally significantly ( $p < 0.001$ ) promoted epithelialization, but not wound contraction rate in excision wound model [109, 110].

## 6.21. Gentianaceae

*Anthocleista nobilis* G. Don is used in local medicine in Ghana and other parts of West Africa for curing fever, stomach ache, diarrhea, gonorrhoea and also as poultice for sores [72, 111]. Methanol extract of *A. nobilis* at concentration of 33.3% (w/w) significantly ( $p < 0.02$ ) enhanced wound closure and hydroxyproline production compared to the control in the excision wound model in rats. In the incision wound model, the extract significantly increased tensile strength of *A. nobilis* treated-wounds compared to the control. However, the methanol extract of *A. nobilis* had no significant effect on the proliferation of human dermal fibroblast at concentrations as high 50  $\mu\text{g/mL}$ . Doses over 50  $\mu\text{g/mL}$  showed cytotoxic effects on the human dermal fibroblasts [112].

## 6.22. Ginkgoaceae

*Ginkgo biloba* L. also known as maiden hair tree is believed to be native of China. The plant has been used in folkloric medicine for its therapeutic purposes especially in mental sicknesses. Bairy and Rao [113] reported that intraperitoneal administration of the 50 mg/kg dried leaf extract of *G. biloba* significantly ( $p < 0.01$ ) promoted the breaking strength and hydroxyproline content of granulation tissue in dead space wounds in rats. However, in excision wounds while it did not affect the wound contraction but epithelization period was significantly ( $p < 0.01$ ) shortened compared to the control.

## 6.23. Hypericaceae

*Hypericum patulum* Thumb. is a perennial plant distributed in Southern Africa, Asia and North America. It is used traditionally to treat dog bites and bee sting [114]. Methanol leaf extract of *H. patulum* in the form of an ointment (5% and 10%, w/w) enhanced wound contraction rate, re-epithelialization, tissue granulation and increased tensile strength in rats compared with the control group [115].

*Hypericum perforatum* L., commonly called St John Worts, Klamath weed, tipton weed, goat weed, and enola weed, is a perennial flowering herb native to Europe, but has spread to temperate locations in Asia, Africa, Australia, Europe and North and South America [116]. Olive oil extracted from the aerial parts of *H. perforatum* is a popular folk remedy for the treatment of wounds in Europe. Aerial parts of *H. perforatum* have been found to possess remarkable wound healing activities. Flavonoids including hyperoside, isoquercitrin, rutin



and (-)-epicatechin, and naphthoquinones especially hypericins were found as the active components of *H. perforatum* [117]. The total extract of *H. perforatum* in *in vivo* experimental wound models of linear incision, circular excision and thermal burn showed that topical treatment improve wound contraction rate and period of re-epithelialization [118]. A plant-derived wound dressing containing a mixture of hypericum oil and neem oil (*Azadirachta indica* A. Juss.) in scalp wounds with exposed bone [119] and pediatric burn wounds [120] promoted healing in rats by enhancing granulation tissues formation and re-epithelialization.

#### 6.24. Lamiaceae

*Occimum sanctum* L. occurs naturally in tropical America, Africa and Asia. It is used traditionally in the treatment of diverse ailments like infections and skin diseases [121]. The wound healing parameters were evaluated by using incision, excision and dead space wound models in rats. The alcoholic (400 and 800 mg/kg) and aqueous (400 and 800 mg/kg) extracts of *O. sanctum* significantly ( $p < 0.05$ ) increased wound contraction rate, wound breaking strength, hydroxyproline, hexuronic acid, hexosamines, superoxide dismutase, catalase and reduced glutathione levels. Lipid peroxidation was significantly ( $p < 0.05$ ) reduced when compared with the control group [101]. Goel et al. [122] also reported that 10% *O. sanctum* aqueous leaf extract in petroleum jelly increased rate of wound contraction and re-epithelialization compared to the control in excision model of wound repair in Wistar albino rats.

*Occimum gratissimum* L. is an aromatic plant found in tropical Africa including Ghana, Nigeria and Kenya among others. The leaves are rubbed between the palms and sniffed as a treatment for blocked nostrils [115]. Leaf extract of *O. gratissimum* promote wound healing by significant wound contraction ( $p < 0.05$ ) on day 10 in extract-treated rats group compared with the control group. Histology of the healed scar showed non-significant ( $p > 0.05$ ) decrease in the mean fibroblast count for the experimental group compared to the control group [123, 124].

*Hoslundia opposita* Vahl. is used in ethnomedicine to treat sore throats, colds, sores, veneral diseases, herpes and other skin diseases [125], malaria, microbial infections, epilepsy, fever and inflammation [126, 127]. Methanol leaf extract of *H. opposita* at concentration of 33.3% (w/w) significantly ( $p < 0.01$ ) increased wound contraction and hydroxyproline content compared to the control in the excision wound model in rats. In the incision wound model, the extract significantly improved tensile strength of wounds compared to the control. The extract had no significant effect on the growth of human dermal fibroblast up to concentrations of 50  $\mu\text{g/ml}$  and higher concentrations exhibited toxic effects [112].

*Hyptis suaveolens* (Poit), commonly called bush tea, is a native to tropical America, but it is also widespread in tropical Africa, Asia and Australia. *H. suaveolens* is used in traditional medicine for treatment of various diseases including wounds, skin infections etc. Ethanol leaf extract of *H. suaveolens* (400 and 800 mg/kg body weight) increased skin breaking strength, granuloma breaking strength, wound contraction, hydroxyproline content and dry granuloma weight and decreased the re-epithelialization period in rats. A supportive study made on granuloma tissue to estimate the levels of catalase and superoxide dismutase recorded a significant ( $p < 0.05$ ) increase in the level of these antioxidant enzymes which resulted enhanced collagenation [128]. Shenoy et al. [129] also showed the effect of petroleum ether, alcohol, and aqueous leaf

extracts of *H. suaveolens* on excision, incision and dead space wound models using Wistar albino rats. All three extracts at a dose of 500 mg/kg enhanced wound healing by accelerating wound closure and period for re-epithelialization compared to the control. Tensile strength, dry weight granulation tissue, breaking strength of granulation tissue and hydroxyproline content were also increased compared to the control.

*Leucas hirta* is found in East Africa and India [130, 131]. Decoctions of dry and fresh herbs of *L. hirta* are used for skin diseases and as gargle for the treatment of thrush, respectively. Roots are also used for snake bites [132]. A leaf poultice is used on swelling and boils. The latex of *L. hirta* is applied on lower eyelids to cure eye sores. The wound healing effect of aqueous and methanol leaf extracts of *L. hirta* at a dose of 35 mg/kg was evaluated in excision, incision and dead space wound models in rats. The methanol and aqueous leaf extracts were found to possess significant wound healing activity which was evidenced by decrease in the period of re-epithelialization, increase in the rate of wound contraction, skin breaking strength, granulation tissue dry weight, hydroxyproline content and breaking strength of granulation tissue. Histological study of the granulation tissue showed increased collagenation when compared to the respective control group of animals [133].

#### 6.25. Liliaceae

*Allium cepa* L. is a biennial herbaceous plant with edible bulb. It is commonly known as onion. Since ancient times, it has been used traditionally for the treatment of different diseases including various types of wounds, skin problems etc. It contains kampferol,  $\beta$ -sitosterol, ferulic acid, myritic acid, prostaglandins [134]. Shenoy et al. [129] reported that alcohol extract exhibits significant ( $p < 0.05$ ) wound contraction rate, improved tensile strength and increased wound breaking strength, dry weight granuloma and hydroxyproline content compared to the control in excision, incision and dead space wound models in rats.

#### 6.26. Lythraceae

*Lawsonia inermis* L. is widely distributed throughout Africa. It also occurs in the Middle East. Ethanol leaf extract of *L. inermis* (200 mg/kg/day) demonstrated high rate of wound contraction ( $p < 0.001$ ), a decrease in the period of epithelialization ( $p < 0.001$ ), high skin breaking strength ( $p < 0.001$ ), a significant increase in the granulation tissue weight ( $p < 0.001$ ) and hydroxyproline content ( $p < 0.05$ ). The extract-treated rats showed 71% reduction in the wound area when compared with controls which was 58%. Enhanced wound contraction, increased skin breaking strength, hydroxyproline and histological findings suggest the use of *L. inermis* in the management of wounds in humans may be justified [135].

*Punica granatum* L., commonly called pomegranate, originated from Iran. It is widely distributed in Mediterranean, Europe, Africa and Asia. Leaf extract of *P. granatum* possess wound healing activity at concentrations of 2.5% and 5% (w/w) in rats. The amount of hydroxyproline increased by twofold in the group treated with 5.0% gel. The extract was found to contain gallic acid and catechin as major compounds [136].

### 6.27. Malvaceae

*Hibiscus rosa sinensis* L. is native in the tropics and subtropics [137]. It has been used traditionally for the treatment of a variety of diseases as well as to promote wound healing. Ethanol leaf extract (120 mg/kg/day) exhibited an 86% reduction in the wound area compared with controls, which exhibited a 75% reduction in rats. The extract-treated animals showed a significant epithelialization ( $p < 0.002$ ) and had significantly ( $p < 0.002$ ) higher skin-breaking strength than controls. The dry and wet weight of granulation tissue and hydroxyproline content also increased significantly when compared with controls [138]. Bhaskar and Nithya [139] also reported the influence of ethanol flower extract of *H. rosa sinensis* (5% and 10%, w/w) on wound healing in Wistar albino rats using excision, incision and dead space wound model. The extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in DNA, total protein and total collagen content of granulation tissues. The extract significantly ( $p < 0.001$ ) promoted wound healing which was indicated by improved rates of epithelialization and wound contraction as well as increased wound tensile strength and wet and dry granulation tissue weights compared to the control.

*Thespesia populnea* (L.) Soland Ex. Corr, also known as Indian Tulip tree, is found growing from West Bengal to South India. It is used locally to treat skin ailments like scabies, psoriasis, wounds and ulcers. Shivakumar et al. [140] reported that ointments containing 5% (w/w) of petroleum ether, alcohol and aqueous leaf extracts of *T. populnea* promote wound contraction and wound breaking strength significantly ( $p < 0.01$ ) when compared to the control groups in excision and incision wound models in rats, respectively.

### 6.28. Meliaceae

*Carapa guianensis* Aublet is found in Guiana and Africa. The leaves of *C. guianensis* are used to treat ulcers, skin parasites and skin problems. The ethanol leaf extract of *C. guianensis* exhibited significant reduction ( $p < 0.01$ ) in the wound area when compared to controls with significant decrease in the epithelialization period. Skin breaking strength ( $p < 0.001$ ), wet ( $p < 0.002$ ) and dry ( $p < 0.02$ ) granulation tissue and hydroxyproline content ( $p < 0.03$ ) were significantly higher in extract-treated animals. The increased rate of wound contraction, skin breaking strength and hydroxyproline content may support application of *C. guianensis* for treatment of wounds [141].

*Azadirachta indica* A. Juss (Neem tree) is a native of Asia but has now naturalized in West Africa. In excision wound model in rats, aqueous leaf extract of *A. indica* significantly increased ( $p < 0.05$ ) the rate of wound closure of extract-treated group compared to control group [142]. Methanol leaf extract (5%, w/w ointment) of *A. indica* has also been reported to significantly ( $p < 0.05$ ) promote the wound healing activity in both excision and incision wound models in rats [20]. Pandey et al. [143] reported that *A. indica* oil increases wound tensile strength and wound closure rate in animals using incision and excision wound models, respectively.

### 6.29. Moraceae

*Ficus religiosa* L., which is commonly known as bo tree, Pepal tree, Bodhi tree, peepul or sacred fig, is abundantly distributed throughout India, Southeast Asia, Southwest China and the Himalayan foothills. *F. religiosa* is reported to have wound healing, anti-inflammatory, analgesic, antioxidant (lipid peroxidation) properties. Application of simple ointment containing hydro-alcohol leaf extract of *F. religiosa* (5% and 10%, w/w) significantly promoted wound contraction rate, epithelization and wound breaking strength in excision and incision wound models, respectively, when compared to the control [144].

### 6.30. Moringaceae

*Moringa oleifera* Lam. is commonly known as drumstick and is widely distributed in India, Arabia and cultivated in tropical Africa, tropical America, Sri Lanka, India, Mexico and Malaysia [145]. The whole plant is used in the treatment of psychosis, eye diseases and fever and also as an aphrodisiac. Its leaf poultice is used in the management of wounds [146]. Qualitative phytochemical investigation confirmed the presence of phytosterols, glycosides, tannins, and amino acids in the various leaf extracts of *M. oleifera* whereas its seed extracts showed the presence of phytosterols, glycosides, phenolic compounds, carbohydrates and amino acids. The ethanol and ethyl acetate extracts of the seeds showed significant antipyretic activity in rats, whereas ethyl acetate leaf extract exhibited significant wound healing activity (10%, w/w ointment) on excision, incision and dead space (granuloma) wound models in rats [142].

### 6.31. Musaceae

*Musa sapientum* L. originated from native south-western Pacific home and spread to India and to the Islands of the Pacific, then to the West Coast of Africa [147]. It has an ulcer healing activity [148]. Aqueous and methanol extracts (100 mg/kg) have been found to increase wound breaking strength and levels of hydroxyproline, hexuronic acid, hexosamine, superoxide dismutase, reduced glutathione in the granulation tissue and decreased percentage of wound area, scar area and lipid peroxidation when compared with the control group in rats. The wound healing effect of *M. sapientum* may be due to its antioxidant effect and on various wound healing biochemical parameters [149].

### 6.32. Myrsinaceae

*Embelia ribes* Burm. is found in the hilly parts of India and grows in southern China, Indonesia and East Africa [150]. Traditionally the seeds are employed as a remedy for toothache, headache and snakebite. The seeds are mainly used for maintaining healthy skin and to support the digestive function [64]. It is also effective in the treatment of fever, abdominal disorders, lung diseases, constipation, fungus infections, mouth ulcer, sore throat, pneumonia, heart disease and obesity [150]. Ethanol leaf extract of *E. ribes* and its isolated quinone compound, embelin, were screened for wound healing activity in rats. In embelin-treated group (4 mg/mL in a 0.2%, w/v sodium alginate gel), re-epithelialization of the incision wound was

faster with a high rate of wound contraction. The tensile strength of the incision wound was significantly increased in embelin-treated group than the ethanol extract. In dead space wound model also the weight of the granulation was increased indicating increase in collagenation. The histological examination of the granulation tissue of embelin-treated group showed increased cross-linking of collagen fibers and absence of monocytes [151].

### 6.33. Oleaceae

*Jasminum auriculatum* Vahl. is a small, evergreen, climbing shrub widely distributed in Eastern Asia including India, Nepal and Sri Lanka. The leaves are normally used to treat mouth ulcers. Mittal et al. [152] reported that ointment base incorporated with 16% (w/w) of ethanol leaf extract of *J. auriculatum* significantly ( $p < 0.05$ ) decreased the period of re-epithelialization in excision wound model. In the incision wound model, there was significant increase in wound breaking strength and collagen content. Histological examination of wound tissues revealed increased fibroblast proliferation, collagen deposition and neovascularization.

*Jasminum grandiflorum* L. is an evergreen or deciduous shrub found in East tropical Africa countries including Sudan, Eritrea, Ethiopia, Somalia, Uganda, Kenya, Rwanda as well as in Asia. Traditionally it is used as an aphrodisiac, expectorant, painkiller and also to treat skin diseases including mouth ulcers and skin eruptions. Topical application of ointment *J. grandifolium* leaf extract (2% and 4%, w/w) on excision wounds in rats accelerated the healing process. Tissue growth and collagen synthesis were significantly ( $p < 0.05$ ) higher which was determined by total hydroxyproline, hexosamine, protein and DNA content. The rate of wound healing was faster as determined by wound contraction, tensile strength and other histopathological changes. In addition, the 4% extract-treated wounds showed enhanced ( $p < 0.05$ ) the activity of superoxide dismutase (SOD) and catalase (CAT) with high GSH content and low lipid peroxidation products in wound tissue compared to the control [153].

### 6.34. Papaveraceae

*Argemone mexicana* L. is a prickly, glabrous, branching annual herb with yellow juice and showy yellow flowers found in West Indies and Mexico. Traditionally, the plant is used as diuretic, purgative, painkiller, laxative and treatment for skin diseases, wounds and poisons [154]. In excision and incision wound models in rats, methanol, aqueous and chloroform leaf extracts of *A. mexicana* (10%, w/w) ointment significantly ( $p < 0.05$ ) enhanced wound closure, re-epithelialization and breaking strength in wound bed compared to the control group. Histological studies of the extract-treated wound tissues revealed improved collagen deposition and fibroblast proliferation with reduced macrophage infiltration and edema. The methanol extract-treated animals showed significant ( $p < 0.01$ ) increase in dry weight of granulation tissue and hydroxyproline content in dead space wound model. Superoxide dismutase and catalase level in the granulation tissue were significantly increased in methanol extract-treated rats ( $p < 0.01$ ) when compared to the control in dead space wound model. The methanol extract also significantly ( $p < 0.05$ ) improved wound healing in bacterial (*Pseudomonas aeruginosa* and *Staphylococcus aureus*) infected wounds [80].

### 6.35. Pedaliaceae

*Sesamum indicum* L. is used in native medicine in Africa and Asia for a variety of diseases. Mucilaginous leaves or leaf sap are used to treat fever, as a remedy for cough and sore eyes, dysentery and gonorrhoea. In eastern and southern Africa, the leaves are used for the treatment of ulcers. The seeds of *S. indicum* are used traditionally for the treatment of various kinds of wounds. Seeds and oil treatment (2.5% and 5%, w/w) exhibited significant ( $p < 0.05$ ) decrease in the period of epithelialization and wound contraction, and increased the breaking strength of rat wound tissues compared to the control. Also, the seeds and oil treatment (250 and 500 mg/kg; *po*) in dead space wound model produced a significant increase in the breaking strength, dry weight and hydroxyproline content of the granulation tissue which suggest that the extract and its oil possess wound healing property [155].

### 6.36. Piperaceae

*Piper betel* L. is extensively grown in India, Srilanka, Malaysia, Indonesia, Philippines and East African countries [156]. Ointment of white soft paraffin containing 1% of dried residue of aqueous extract of *P. betel* has been reported to possess wound healing activity [157].

### 6.37. Potulacaceae

*Portulaca oleracea* L. is a cosmopolitan weed occurring especially in warm areas; it occurs throughout tropical Africa. It is eaten in many African countries including Côte d'Ivoire, Benin, Cameroon, Kenya, Uganda, Angola, South Africa, Sudan and Egypt. It is used for the treatment of ulcers, eczema and dermatitis [158, 159]. Fresh homogenized crude aerial parts of *P. oleracea* accelerated the wound healing process in mice by decreasing the surface area of the wound and increased the tensile strength. The highest rate of contraction was found at dose of 50 mg, followed by 25 mg [160].

### 6.38. Phyllanthaceae

*Bridelia ferruginea* Benth. is a common savannah species. Ethnomedicines prepared from the bark, leaves and fruits are used for the treatment of bruises, boils, burns, wounds and skin disease [79]. Ethanol stem bark extract of *B. ferruginea* on wound contraction and epithelization in rats significantly enhanced wound contraction and epithelialization [161] (Udegbumam et al., 2011) and the extract (1–30  $\mu\text{g/mL}$ ) has been reported to influence the proliferation of dermal fibroblasts significantly ( $p < 0.05$ ) compared to the untreated cells [162].

### 6.39. Rubiaceae

*Morinda citrifolia* L. is one of the most important traditional Polynesian medicinal plants. The primary indigenous use of this plant appears to be of the leaves, as a topical treatment for wound healing. The ethanol leaf extract (150 mg/kg/day, *p.o*) was used to evaluate the wound healing activity in rats, using excision and dead space wound models. The extract exhibited

71% reduction in the wound area when compared with controls which exhibited 57%. The granulation tissue weight and hydroxyproline content in the dead space wounds were also increased significantly in extract-treated animals compared with controls ( $p < 0.002$ ). Enhanced wound contraction, decreased epithelialization time, increased hydroxyproline content and histological characteristics may indicate that noni leaf extract may be beneficial in wound healing [163].

*Pentas lanceolata* Pentas Benth. originated from East Africa and is commonly called the “Red Egyptian star”. The ethanol flowers extract of *P. lanceolata* given by oral route to rats at a dose of 150 mg/kg per day for 10 days was evaluated on its effect on wound healing, using excision wound model. There was significant ( $p < 0.05$ ) increment in granulation tissue weight, tensile strength, hydroxyproline and glycosaminoglycan content. There was marked increment in the wound contraction in extract treated group as compared to that of controls and these effects may be due to increased collagen deposition as well as better alignment and maturation [164].

*Rubia cordifolia* L. is popular all over the world for its medicinal uses in skin diseases like eczema, dermatitis and skin ulcers. *R. cordifolia* has an extremely large area of distribution, ranging from Africa to tropical Asia, China, Japan and Australia. In Africa, it is found from Sudan and Ethiopia to South Africa. Hydrogel of the alcoholic extract has been found to improve wound contracting ability, wound closure, decrease in surface area of wound, tissue regeneration at the wound site significantly ( $p < 0.01$ ) in treated mice [165].

#### 6.40. Rutaceae

*Aegle marmelos* L., commonly called Bael in Hindu, is a perennial plant indigenous to dry forests on hills and plains of India, Pakistan, Bangladesh, Sri Lanka, Myanmar, Nepal, Vietnam, Laos, Cambodia and Thailand. The fruits and leaves are used to treat pain, fever, inflammation, respiratory disorders, cardiac disorders, dysentery and diarrhea in folk and Ayurvedic medicine. Jaswanth et al. [166] reported the wound healing effect of methanol root extract of *A. marmelos* (5% and 10%, w/w in simple ointment base) using excision and incision wound models in rats. The extract-treated wounds showed significant ( $p < 0.01$ ) increase in wound contracting ability, reduced wound closure time and increase in the tensile strength compared to the control in excision and incision wound models, respectively. Gautam et al. [167] also reported that rats treated with 200 mg/kg *A. marmelos* ethanol leaf extract significantly ( $p < 0.05$ ) increase wound breaking strength and improved ( $p < 0.05$ ) wound contraction rate in *A. marmelos*-treated wounds compared to the control in excision wound model. This was also supported by histological examination of excised wounds which revealed increased granulation tissues formation and reduced inflammatory cell infiltration in 200 mg/kg treated wound tissues compared to the control. Granulation tissues showed increased ( $p < 0.001$ ) collagen content compared to the control group. Catalase, superoxide dismutase and glutathionine levels were markedly elevated, whereas lipid peroxidation, myeloperoxidation and nitric oxide levels were markedly ( $p < 0.05$ ) lower in *A. marmelos*-treated wounds compared to the control group.

#### 6.41. Sapotaceae

*Mimusops elengi* L. is native to India, Sri Lanka, the Andaman Islands, Myanmar and Indo-China, but is commonly planted as an ornamental tree throughout tropical countries including Ghana, Tanzania, Mozambique, Réunion Island and Mauritius. In Asia, the leaves are used medicinally to treat headache, toothache, wounds and sore eyes, and are smoked to cure infections of the nose and mouth. A decoction of the bark mixed with the flowers has been used for treatment of fever, diarrhea, inflammation of the gums, toothache, gonorrhoea and wounds. The flowers have been used for the management of diarrhea [161, 168, 169]. Methanol bark extract of *M. elengi* (5%, w/w) exhibited significant ( $p < 0.05$ ) influence on the rate of wound closure, tensile strength and dry granuloma weight. Histological investigation of the wound tissues revealed similar effects consistent with its *in vivo* wound healing properties [170].

#### 6.42. Solanaceae

*Datura metel* L. is found growing in most tropical countries in Africa and it is used for the treatment of haemorrhoids, boils, sores and skin diseases [171, 172]. The ethanol leaf extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in synthesis of DNA, total protein and total collagen content of granulation tissues. The extract-treated wounds were found to heal much faster with improved rates of epithelialization and wound contraction and these observations were confirmed by histological examinations of the wound tissues. The leaf extract of *D. metel* significantly ( $p < 0.001$ ) increased the wound breaking strength compared to the controls. Wet and dry granulation tissue weights increased significantly ( $p < 0.001$ ). There was a significant increase in wound closure rate, tensile strength, dry granuloma weight, wet granuloma weight and a decrease in epithelialization period in *D. metel* extract treated group when compared to control and commercial drug treated groups [173].

*Solanum xanthocarpum* Schrad and Wendl is known as Indian night shade or yellow berried night shade plant. It is more commonly used for the management of diseases like bronchial asthma, cough, worms etc. The fruits facilitate the seminal ejaculation, alleviate worms, itching, and fever and reduce fats [86]. Ethanol leaf extract of *S. xanthocarpum* significantly ( $p < 0.01$ ) improved wound healing via increased re-epithelialization, tensile strength and hydroxyproline content which may be due to the presence of secondary metabolites such as alkaloids, glycosides, saponins, carbohydrates, tannins, phenolic compounds, proteins and fats [174].

#### 6.43. Vitaceae

*Cissus quadrangularis* L. is a perennial climber popularly known as “Hadjod” in India and is widely distributed in the tropics. Traditionally, it is used to treat gastritis, bone fractures, skin infections, constipations, eye diseases, piles, anemia, asthma, irregular menstruation, burns and wounds. Treatment of wounds with ointment containing 2% (w/w) methanol extract and 2% w/w aqueous extract of *C. quadrangularis* significantly ( $p < 0.001$ ) enhanced wound closure and breaking strength compared to the control group in excision and incision wound models, respectively in rats [175].



#### 6.44. Verbenaceae

*Clerodendron splendens* G. Don is a climbing shrub, mostly found growing on cultivated lands between food crops in Ghana and other West African countries. The plant is used in ethno-medicine in Ghana for the treatment of vaginal thrush, bruises, wounds and various skin infections [72]. The methanol aerial parts extract of *C. splendens* improved wound closure and hydroxyproline biosynthesis compared to the control group in the excision wound model in rats. The extract also increased the tensile strength of wounds compared to the control group [176].

*Lantana camara* L. occurs widely in the Asia-Pacific region, Australia, New Zealand, Central and South America, West Indies and Africa. It is used in herbal medicine for the treatment of skin itches, wounds, leprosy and scabies [177]. Treatment of the wounds in animals with leaf extract of *L. camara* enhanced the rate of wound contraction, synthesis of collagen and decreased mean wound healing time [138].

#### 6.45. Zingiberaceae

*Curcuma aromatica* Salisb. is a medicinal plant cultivated most extensively in India, Bangladesh, China, Thailand, Cambodia, Malaysia, Indonesia, and Philippines. It has been grown in most tropical regions in Africa, America, and Pacific Ocean Islands. Rhizomes of *C. aromatica* are used as a stomachic, carminative and emmenagogue remedies for skin diseases [178] and also for snakebites [179] (Chopra et al., 1941). Report by Santhanam and Nagarajan [157] has shown that ointment of white soft paraffin containing 1% of powdered *C. aromatic* rhizome promotes wound contraction and epithelialization. Kumar et al. [137] also reported that ethanol dried rhizome of *C. aromatica* extract significantly ( $p < 0.001$ ) improved wound contraction in rat excision wound model.

*Curcuma longa* L., commonly known as tumeric, is a rhizomatous perennial herb native to India. In traditional medicine, it is used to treat skin ailments, wound, worm infestation and as blood purifier. *C. longa* contains three major curcuminoids, namely, curcumin, demethoxycurcumin, and bis-demethoxycurcumin [180]. *C. longa* possesses antibacterial, anti-inflammatory, anti-arthritic, anti-hepatotoxic (liver protective) and anti-allergic properties. Topical application (5% and 10%, w/w simple ointment) of ethanol rhizome extract of *C. longa* promotes significantly ( $p < 0.01$ ) enhanced wound contraction, increased hydroxyproline and tensile strength of wounds in excision and incision wound models in rats and rabbits. Histological studies also showed increased collagen, fibroblasts and blood vessels formation [181, 182]. Sidhu et al. [183] reported via immunohistochemical investigations that *C. longa*-treated wounds show highly localized transforming growth factor- $\beta$ 1 in wound bed compared with untreated wounds. There was an increment in the mRNA transcripts of transforming growth factor- $\beta$ 1 and fibronectin in curcumin-treated wounds.

*Curcuma purpurascens* Blume. is commonly known as "Temu tis" and "Koneng tinggang" in Indonesia. The rhizome of this plant has been reported to have extensive traditional uses in rural communities against different skin ailments and dermatological disorders, especially wounds and burns. Macroscopic evaluation of wounds showed conspicuous elevation in

wound contraction ( $p < 0.05$ ) after topical administration of hexane extract of the rhizome of *C. purpurascens* (100 and 200 mg/kg body weight) to wounded rats. Histological analysis revealed enhanced collagen content and fibroblast proliferation and scanty inflammatory cells in the granulation tissues of *C. purpurascens*-treated wounds compared to the control. At the molecular level, *C. purpurascens* facilitated wound-healing process by down-regulating Bax and up-regulating Hsp70 protein at the wound site. In addition, the plant enhanced catalase, glutathione peroxidase, superoxide dismutase activity and reduced malondialdehyde levels in wound tissues compared to the control group [184].

#### 6.46. Zygophyllaceae

*Balanites aegyptiaca* (L.) Diel is widely distributed in tropical regions of Africa. The plant is used in folk medicine for treatment of circumcision wounds, worm infestation, abdominal and chest pains, and as an abortifacient and contraceptive [177, 185]. Methanol extract of *B. aegyptiaca* at concentration of 33.3% (w/w) significantly ( $p < 0.001$ ) improved wound closure, tensile strength and hydroxyproline production compared to the control in the excision wound model in rats [112].

### 7. Phenolic compounds with wound healing properties

Though many crude plant extracts have been scientifically demonstrated to have wound healing activities, enriched fractions and isolated compounds from some of these plants have also been shown to possess specific promising wound healing properties. The commonly known effects of the active constituents of plant extracts towards wound healing are known to be through blood clotting, antimicrobial, antioxidant, mitogenic activities and also enhancing the expression of vascular endothelial growth factor thereby improving angiogenesis and blood flow as the tissue repair process advances [179, 186–188]. In chronic wounds, agents inducing differentiation of keratinocytes play an important role.

Plant polyphenols are among the most abundant phytochemicals present in the human diet, and they range from simple molecules such as phenolic acids to highly polymerized compounds, such as condensed tannins [189]. Several plants extracts used in wound healing contain phenolics in the form of procyanidins, flavonoids and phenolic acids [187] as their active ingredients. Tannins and procyanidins are known to actively facilitate wound healing [190].

Resveratrol is a natural polyphenol found predominantly in the skin of red grapes that has been studied extensively for its potential health benefits [191]. Resveratrol is a popular nutritional supplement and ingredient in over-the-counter skin care products. In humans, resveratrol was shown to protect against sun damage to the skin, enhance moisture and elasticity, reduce wrinkle depth and intensity of age spots, and protected keratinocytes from nitrous oxide-induced death [191, 192]. Its positive effect on keratinocytes has beneficial effect on wound healing. Resveratrol administration significantly increased the tensile strength of the abdominal fascia, and increased the hydroxyproline 1 levels *in vivo*. The acute inflammation

scores, collagen deposition scores and the neovascularization scores on postoperative days 7 and 14 were found to be significantly higher in the resveratrol treatment group. The amount of granulation tissue and the fibroblast maturation scores were found to be significantly higher on postoperative day 14 in the treatment group when compared to the control group [193].

### 7.1. Tannins

Tannins are natural polyphenols and in many cases the active constituents in plants in which they are found. Tannins have a wide range of pharmacological activities including antimicrobial, wound healing, antioxidant and anti-inflammatory activities. The physical and chemical properties of tannins suggest that they may act by virtue of their complexation, astringent, antioxidant and radical scavenging activities, and their ability to form complex with proteins [194].

### 7.2. Ellagitannins

Ellagitannins, namely geraniin and furosin isolated from *Phyllanthus muellerianus*, were demonstrated to stimulate cellular activity, differentiation and collagen synthesis of human skin keratinocytes and dermal fibroblasts. Geraniin and furosin increased the cellular energy status of human skin cells (dermal fibroblasts NHDF, HaCaT keratinocytes) and triggered the cells towards higher proliferation rates. Furosin and geraniin stimulated the biosynthesis of collagen from normal human dermal fibroblasts. Geraniin also significantly stimulated the differentiation in normal human epidermal keratinocytes while furosin had a minor influence on the expression of involucrin and cytokeratins K1 and K10. The study proved that geraniin exhibit stimulating activity on dermal fibroblasts and keratinocytes, leading to increased cell proliferation, barrier formation and formation of extracellular matrix proteins [98].

### 7.3. Flavanols and proanthocyanidins

Flavanols are a sub-family of flavonoids which are present in plants as aglycones, as oligomers, or esterified with gallic acid and the most common oligomers of procyanidins present in edible plants are derived from epicatechin [189].

Flavanols and procyanidins are chemically able to prevent oxidation, and their administration has been associated with a decrease in oxidative stress markers in humans with improve blood supply to the wounded area to accelerate wound healing. They have been shown to exert a wide range of biological activities including wound healing property. The known biological activities of proanthocyanidins include antioxidant activity, anti-inflammatory activity, antimicrobial activities and wound healing activities [92, 189, 195].

A redox-active grape seed proanthocyanidin extract has been shown to up regulate oxidant and tumor necrosis factor- $\alpha$  inducible VEGF expression in human keratinocytes. Furthermore this grape seed proanthocyanidin extract was shown to accelerate wound contraction and closure *in vivo*, to enhance deposition of connective tissue and to improve histological architecture [186].

Wound healing property of *Camellia sinensis*, also known as green tea, has been linked to the presence of proanthocyanidins which are mainly made up of epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate and these induce differentiation of epidermal keratinocytes and also accelerate epithelial neoformation during wound healing [196].

Similarly, a fraction of the methanol extract of *Persea americana* Mill. seeds, containing high amounts of procyanidins B1 and B2 as well as an A-type trimer, was shown to stimulate proliferation of normal primary keratinocytes and fibroblasts cells but on another hand inhibited the proliferation of HaCaT-keratinocytes [197].

A study conducted on a proanthocyanidins rich fraction from *Hamamelis virginiana* showed that this fraction strongly increased the proliferation of skin cells. This effect was attributed to the tannin fraction, consisting of hydrolysable and condensed tannins, which account to 12% of *Hamamelis* bark [198].

A study of the wound healing activities of the hydrolyzable tannins from the hydro-alcoholic stem bark extract of *Poincianella pluviosa* enhanced the proliferation of human keratinocytes and dermal fibroblasts, which suggests that epidermal barrier formation can be accelerated by the use of *P. pluviosa* [199]. Treatment of keratinocytes with apple procyanidins has been shown to inhibit apoptosis and promote cell proliferation, migration and survival, necessary for revascularization and re-epithelialization of the wound. *In vivo* studies have shown that apple procyanidins (also known as procyanidins B1, B2 and C1) not only stimulate angiogenesis but also cause epithelial cells to grow mimicking keratinocyte re-epithelialization [200].

Epicatechin also blocks radiation-induced apoptosis via down-regulation Jun N-terminal kinase and p-38 in the HaCaT cells [201]. Epicatechin and procyanidins dimers are known to inhibit NADPH-oxidase and the subsequent superoxide production by directly binding to the enzyme or regulating calcium influx, or potentially inhibiting the binding of ligands that trigger NADPH-oxidase activation to their receptors (e.g. TNF- $\alpha$ ). These functions are means by which epicatechin may provide cytoprotection to the cell. Both epicatechin and the respective procyanidin dimers can interact with the DNA-binding site of the nuclear factor kappa B (NF- $\kappa$ B) proteins, preventing the interaction of NF- $\kappa$ B with  $\kappa$ B sites in gene promoters, thus inhibiting gene transcription [189]. The reduced NF- $\kappa$ B activation results in the suppression of inflammatory cytokines [200].

Procyanidins are known to induce the differentiation of keratinocytes. It has been reported that epigallocatechin-3-gallate induces differentiation of human epidermal keratinocytes [202]. In comparison to epigallocatechin-3-gallate, procyanidin B2 is more inductive to differentiation at lower concentrations [92].

Procyanidin B2 is also known to have beneficial effects in pathologies with pro-inflammatory components by inhibiting NF- $\kappa$ B-driven gene expression, including various cytokines and anti-apoptotic prote [203, 204]. It has been reported that several selective protein kinase C inhibitors, including procyanidin B-2, promote hair epithelial cell growth [205]. This presupposes that procyanidin B2 could be useful for aesthetic purposes during wound healing by stimulating the regrowth of skin appendages in the wounded area.

Procyanidin C1 inhibits nitric oxide production and the release of pro-inflammatory cytokines (IL-6 and TNF- $\alpha$ ). Additionally, the potent anti-inflammatory effect of procyanidin C1 occurs through inhibition of mitogen-activated protein kinase and NF- $\kappa$ B signaling pathways. These two factors play a major role in controlling inflammation in the wounds [206]. In wound healing, procyanidin C1 activity presents a novel and effective means of inflammation control. Procyanidin dimers and trimers extracted from grape seeds are also known to exhibit higher growth-promoting activity than the monomer on hair epithelial cells *in vivo* [207].

#### 7.4. Flavonoids

Flavonoids are a chemically defined group of polyphenols that have a basic structure of two aromatic rings (A and B) linked through three carbons that usually form an oxygenated heterocycle (C ring). The chemical characteristics of the C ring define the various subgroups of flavonoids by providing different arrangements of hydroxy, methoxy, and glycosidic groups, and the bonding with other monomers [208].

An important effect of flavonoids is the scavenging of oxygen-derived free radicals, reduction of lipid peroxidation, anti-inflammatory and wound healing activities. A drug that inhibits lipid peroxidation is believed to increase the viability and strength of collagen fibers and prevents cell damage by promoting DNA synthesis. Flavonoids prevent or delay the onset of cell necrosis and also improve vascularity to the wounded area [179].

Several flavonoids, including quercetin, result in a reduction in ischemia-reperfusion injury through the activity of constitutive nitric-oxide synthase which is important in maintaining the dilation of blood vessels [209]. Quercetin, in particular, inhibits both cyclooxygenase and lipoxygenase activities, thus diminishing the formation of their inflammatory metabolites [210, 211].

Certain flavonoids, notably diosmin and hesperidin, have been used routinely in Europe for many years to treat varicose veins, hemorrhoids, and the edema that accompanies chronic venous insufficiency. These flavonoids have now been employed in the treatment of wounds. Purified micronized flavonoid fraction, comprising 90% diosmin and 10% hesperidin, is basically used as a phlebotonic and vasculoprotector agent. It also has anti-inflammatory and anti-edematous actions. In a clinical study, groups with infected wounds that were orally and topically treated, accelerated wound healing when compared to the untreated control group. This was confirmed with surface area measurements and histopathological evaluation. This study showed that oral or topical administration of micronized flavonoid fraction in infected wounds is beneficial [212].

A flavonoid rich fraction of *Martynia annua* L. has also been shown to induce mature collagen fibers and promote fibroblasts with improved angiogenesis in an *in vivo* model [213]. Isovitexin and vitexin are the major flavonoid constituents of *Jatropha multifida* L. which is used commonly for the treatment of infected wounds and skin [214].

Flavonoids from *Vernonia arborea* and *Pentas lanceolata* have been reported to promote wound healing by their astringent and antimicrobial properties, which seems to be responsible for wound contraction and increased rate of epithelialization [215].

*Martynia annua* L. is a plant that has tannins, phenols, flavonoids, carbohydrates and anthocyanins as its constituents [216]. A flavonoid rich fraction and luteolin isolated from *M. annua* was shown to improve wound healing in streptozotocin induced diabetic rats. The results showed that, percent wound contraction were significantly greater for the flavonoid rich fraction and luteolin-treated groups. Presence of matured collagen fibers and fibroblast with better angiogenesis were observed histopathologically in these groups [213].

## 8. Fats and oils with wound healing properties

Several unsaturated fatty acids such as oleic, linoleic, eicosapentanoic and arachidonic acids are among the natural ligands for peroxisome proliferative activator receptors (PPAR) which are involved in wound healing. These PPAR are nuclear hormone receptors and are up regulated in keratinocytes after injury and have been found to be important regulators of re-epithelialization [217, 218]. Also  $\omega$ -3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) affect the synthesis and activity of proinflammatory cytokines which to a large extent initiate the inflammatory stage of wound healing [219, 220]. It can therefore be said that the presence of these fatty acids in plant extracts and other compounds could contribute to the survival and differentiation of keratinocytes through the activation of PPAR. Also they may promote the recovery of the epidermal barrier, skin homeostasis and anti-inflammatory activity to the skin during the wound healing process.

### 8.1. Eucalyptus oil (Dinkum oil)

This oil is obtained by steam distillation of fresh leaves of *Eucalyptus globules* which belongs to the family Myrtaceae. It is indigenous to Australia and Tasmania. It is cultivated in United States, Spain, Portugal and India. It contains eucalyptol, pinene, camphene, phellandrene, citronellal and geranyl acetates. In skin care, it is used to treat burns, blisters, herpes, cuts, wounds, skin infections and insect bites [221].

### 8.2. Aroeira (*Schinus terebinthifolius*) oil

The aroeira tree (*Schinus terebinthifolius* Raddi.) belongs to the family Anacardiaceae and it is popularly known as Brazilian pepper, Florida Holly, rose pepper and Christmas berry. It is used to treat wounds and ulcers of skin and mucous membranes, against infections of the respiratory system, digestive system, genito-urinary tract, hemoptysis and metrorrhagia [222]. The essential oil of *S. terebinthifolius* is obtained by hydro-distillation of crushed fresh leaves. Aroeira oil is reported to accelerate the healing process of wounds by significantly ( $p < 0.01$ ) increasing contraction of oil-treated wounds in rats [223].

### 8.3. Virgin coconut oil

*Cocos nucifera* L. (Arecaceae), commonly known as coconut, is a palm, which thrives within the tropical zone. Its fresh kernel is consumed by people all over the world. Oil of *C. nucifera* which

is extracted from the dried inner flesh of coconut [224] predominantly contains medium chain triglycerides, with 86.5% saturated fatty acids, 5.8% monounsaturated fatty acids, and 1.8% polyunsaturated fatty acids. Virgin coconut oil is also known to have antibacterial and antifungal properties [225, 226]. Excised wounds treated with virgin coconut oil healed much faster, as indicated by a decreased time of complete epithelization and increased in pepsin-soluble collagen, as well as an increase in fibroblast proliferation and neovascularization [227]. Also in burn wounds, there was improvement in wound contraction and decreased period of epithelialization when treated with coconut oil [224].

#### 8.4. *Vitis vinifera* (grape) oil

Oil extracted from the seeds of grapes *Vitis vinifera* (Family Vitaceae) has been found to exhibit wound healing activity. In the excision wound model, grape oil-treated animals had increased wound area contraction and hydroxyproline content. Also histological analysis of the grape oil-treated wound tissue showed increased well organized collagen band [228].

#### 8.5. *Vaccinium macrocarpon* (cranberry) oil

*Vaccinium macrocarpon* (family Ericaceae) is an evergreen creeping shrub native to North America [229]. Excision wounds on animals treated with cranberry oil showed faster rates of wound area contraction with higher hydroxyproline content. The cranberry oil-treated wound tissue had well organized bands of collagen [228].

#### 8.6. *Melaleuca alternifolia* (Tea tree) oil

The essential oil derived from steam distillation of the leaves and terminal branches of *Melaleuca alternifolia* (family Myrtaceae) commonly known as tea tree [230], is composed of a mixture of monoterpenes, 1-terpinen-4-ol, cineole and other hydrocarbons. Tea tree oil possesses antimicrobial, anti-inflammatory and analgesic properties [231]. Tea tree oil has been reported to aid in healing of bacterial infected wounds, including diabetic wounds, characterized by reduced healing time, rapid reduction in inflammation, pain and wound odor [232, 233].

#### 8.7. *Vitellaria paradoxa* (Shea tree) oil

*Vitellaria paradoxa* (family Sapotaceae) commonly known as shea butter is an indigenous species of Sub-Saharan African [234]. The nuts and seeds are a very rich source of fats and oils, from which shea butter is derived. Shea butter is known to accelerate healing after circumcision [235]. The healing effect of shea butter may be attributed to the presence of allantoin, since it is a substance known to stimulate the growth of healthy tissues in ulcerous wounds [236].

#### 8.8. Virgin fatty oil of *Pistacia lentiscus*

*Pistacia lentiscus* L. (Anacardiaceae) is a dioecious sclerophyllous evergreen species widely distributed along the Mediterranean basin. The essential oil of *P. lentiscus* obtained by hydro-

distillation of leaves, fruits or trunk exudates called mastic gum [229] contains 73% unsaturated fatty acids (oleic and linoleic) and 25.8% saturated fatty acids (palmitic and stearic) and has been proven to exhibit antimicrobial, antioxidant, anti-inflammatory and antiatherogenic activities [237, 238]. The virgin fatty oil of *P. lentiscus* exhibited wound healing property in burn wound model in rabbits. *P. lentiscus* oil treated wounds showed higher wound contraction and faster time of healing as compared to the untreated wounds. *P. lentiscus* virgin fatty oil promoted significantly ( $p < 0.05$ ) wound contraction and reduces epithelization period in rabbit model [239].

## 9. Miscellaneous substances

### 9.1. Wound healing properties of honey

Honey is a collection of nectar processed by honey bees [240]. It is rich in nutrients and defined substances such as glucose, fructose, sucrose, minerals, vitamins, antioxidants, amino acids and many other products, which may be responsible for its numerous therapeutic roles and potency [241]. Its therapeutic properties include antimicrobial activity which may be attributed to its osmotic effect, a naturally low pH, and the production of hydrogen peroxide [242, 243]. Honey attacks antibiotic-resistant strains of bacteria and prevents bacterial growth even when wounds are heavily infected [244]. Again, honey has been reported to exhibit antioxidant activity [245, 246]. In wound care, honey has been used extensively as wound healing agent for almost all kinds of wounds. It has been assessed for the treatment of venous leg ulcers, burns, chronic leg ulcers, pressure ulcers, as well as diabetic wound [247], with scarless healing in cavity wounds, less edema, fewer polymorphonuclear and mononuclear cell infiltrations, less necrosis, better wound contraction, improved epithelialization, lower glycosaminoglycan and proteoglycan concentrations, increased granulation tissue formation and tissue growth, collagen synthesis and development of new blood vessels in the bed of wounds [241].

## 10. Conclusion

Most of these medicinal plants and natural products traditionally used for the treatment and management of these various types of wounds had their wound healing properties, including wound contraction, tensile strength, antioxidant and antimicrobial activities, hydroxyproline content assay and histological investigations namely re-epithelization, collagen synthesis, granulation, proliferation and differentiation of fibroblasts and keratinocytes, assessed and evaluated through *in vitro* and *in vivo* model studies. Hence there is a need to subject these products to both primary and advanced clinical studies with specific types of wounds to ascertain or confirm the reported wound healing properties. These trials must be done after safety profiles of these products have been determined.



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