

The Medicinal Value of Asteraceae Family Plants in Terms of Wound Healing Activity

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SUMMARY

Plants have been a great resource of medicinal products which are used for the treatment of several ailments. The reports of folk medicine play an initial and important role for the novel drug development from natural sources. The ethnobotanical studies reveal the preparation and usage information of the plants used among the people living in rural areas. From these valuable data, the ethnopharmacological studies are conducted to find a scientific verification for the usage of the plants and with further phytochemical analysis, the compounds responsible from the activities are elucidated. Asteraceae family plants have been found to possess diverse biological effects referring to *in vivo* and *in vitro* researches conducted. This review aims to investigate the traditional usage, *in vitro* and *in vivo* assessments on the plants in Asteraceae family regarding the wound healing effect.

Key Words: Asteraceae, Compositae, ethnobotany, plant, traditional medicine, wound healing,

Asteraceae familyasına ait bitkilerin yara iyileştirici etki yönünden tıbbi değeri

ÖZET

Bitkiler çeşitli hastalıkların tedavisinde kullanılan tıbbi ürünlerin önemli bir kaynağını oluşturmaktadır. Halk tıbbi kayıtları, doğal kaynaklardan yeni ilaçların geliştirilmesinde birincil ve önemli bir rol oynamaktadır. Etnobotanik çalışmalar, kırsal kesimlerde yaşayan halk tarafından kullanılan bitkilerin hazırlanış ve kullanılışlarına dair bilgileri ortaya koyar. Bu değerli bilgilerden, etnofarmakolojik çalışmalar yapılarak kullanılış amacının bilimsel olarak doğrulanması ve ileri fitokimyasal çalışmalarla etkiden sorumlu bileşiklerin aydınlatılması sağlanır. Yapılan *in vivo* ve *in vitro* çalışmalarda, Asteraceae familyası bitkilerinin çeşitli biyolojik etkilere sahip olduğu belirlenmiştir. Bu derleme, Asteraceae familyasına ait bitkilerin geleneksel kullanımını, üzerlerinde yapılan *in vitro* ve *in vivo* araştırmaları yara iyileştirici etki bakımından değerlendirmeyi amaçlamaktadır.

Anahtar kelimeler: Asteraceae, Compositae, etnobotanik, bitki, geleneksel tıp, yara iyileştirici

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INTRODUCTION

There is no doubt that plants used in folk medicine have been a great value for the drug development in today's conventional medical system. Relying on the ethnobotanical information, the potential biological activities of the plants have been investigated in accord with their traditional usage. These ethnopharmacological studies place in the heart of pharmacognosy and both the field researches and experimental part constitute the whole approach.

In traditional medicine all over the world, a wide range of plant preparations are employed as wound healing agents. By the scientific studies, the activities of local plants used for wound healing have been investigated intensively in order to find out scientific confirmation for the reported usage. Because of economic and social factors, especially chronic wounds represent a major burden. Therefore, the search for natural products as new wound healer agents becomes a great target (Alerico et al., 2015).

Wound healing is a complex mechanism for the repairment of tissue integrity, and comprises of four main phases of haemostasis, inflammation, proliferation and tissue remodelling. Any trauma penetrating into the dermis results in bleeding and the blood vessels immediately contracts to reduce the blood loss. Due to platelet aggregation, the clotting process starts to continue the coagulation cascade. A scab occurs by the formation of a fibrin mesh to temporarily close the wounded site and wound continues to produce the blood and serous fluid, in order to cleanse the wound surface from the contaminants (Flanagan, 2000). The healing period can be shortened by application of some medicinal agents having antimicrobial, anti-inflammatory and antioxidant activities. Indeed, the role of antioxidants is very important in cutaneous tissue repair, as oxidants are known to cause cell damage and inhibit the healing process. Therefore, in order to enhance the wound healing process antioxidants were reported to be helpful (Thang et al., 2001).

The medicinal plants contain various secondary metabolites that provide several therapeutic effects. It has been proved in many studies that the wound healing process can be improved with the application of natural products. Sometimes, the activity studies focus on the particular plant families, genus or species. This is probably due to the ethnobotany reports regarding the utilization of the plant species for a specific therapy and the secondary metabolites

they include which provide the therapeutic effects. The family Asteraceae is one of the largest plant families on which the wound healing activity studies have been focused. In the present study, the important role of Asteraceae family plants was investigated in terms of their traditional records for wound healing purposes (Table 1) as well as the preclinical studies conducted to reveal their wound healing activities.

WOUND HEALING ACTIVITY STUDIES ON SOME ASTERACEAE FAMILY PLANTS

As shown in Table 1, several Asteraceae family plants have been utilized as a remedy for wound healing in many countries including India, Turkey, Nigeria, Nepal, South Africa, Britain and Ireland. Especially, *Achillea*, *Ageatum*, *Arctium*, *Artemisia*, *Caesulia*, *Centaurea*, *Chromolaena*, *Cichorium*, *Dendranthema*, *Eclipta*, *Gundelia*, *Helichrysum*, *Saussurea*, *Scorzonera*, *Sonchus*, *Tagetes*, *Tanacetum*, *Tridax* and *Vernonia* were recorded to be used in different ways for the healing of wounds. Therefore, bioactivity of the species belong to these genera have been investigated to reveal possible wound healing potential.

Achillea L. sp.

The wound healing potential of *Achillea biebersteinii* Afan. was assessed. To investigate the activity, 1% ointments prepared from *n*-hexane, chloroform, ethyl acetate and methanol extracts of the roots were applied on the incision and excision wounds created on the rats and mice, for 10 and 12 days, respectively. *n*-Hexane extract provided remarkable increase (40.1%) in tensile strength and noticeable contraction (84.2%) in the wound area. Gas Chromatography-Mass Spectrometry (GC-MS) analysis revealed the presence of β -eudesmol, piperitone, camphor, borneol, α -terpinene, 1,8-cineole as the major constituents of the *n*-hexane extract, suggesting the possible synergistic effect of the compounds (Küpeli Akkol et al., 2011; Küpeli Akkol & Süntar, 2013). In a previous study by Baris et al. (2006), the antimicrobial and antioxidant effects of the essential oil and the methanolic extract obtained from *A. biebersteinii* were demonstrated (Baris et al., 2006). The antimicrobial activity was seen for the oil fractions containing 1,8-cineole, camphor, borneol and piperitone (Sökmen et al., 2004). Moreover, a topical preparation containing *Hypericum perforatum* L. oil and *Achillea millefolium* L. extract was reported to improve wound healing process (Motogna, 1971).

Table 1. Asteraceae family plants traditionally used for wound healing purposes

Species	Parts used	Use and administration	Country	Reference
<i>Achillea biebersteinii</i> Afan.	H	For wound healing; externally, pounded	Turkey	Sezik et al., 1997 Sezik at al., 2001
<i>Ageratum conyzoides</i> L.	Le	For wound healing and burns; leaf juice is applied topically on cuts to stop bleeding	Nigeria India	Okunade, 2002 Sharma et al., 2014
<i>Arctium minus</i> Schkuhr	Le, Rt, St	For burns; applied externally	Britain Ireland Europe	Kenny et al., 2014
<i>Artemisia afra</i> Jacq. ex. Willd.	Le	For wound healing; infusion used as a wash for wounds	South Africa	Grierson & Afolayan, 1999
<i>Artemisia dubia</i> L. ex B.D. Jacks.	Le	Leaves are boiled with water and the warm water is used to take bath to cure scabies and other skin diseases	Nepal	Shrestha et al., 2016
<i>Artemisia indica</i> Willd.	Le	Leaves are grinded and directly applied to cuts and wound	Nepal	Shrestha et al., 2016
<i>Caesulia axillaris</i> Roxb.	Fl	The paste of flowers is applied topically on cuts and wounds	India	Sharma et al., 2014
<i>Centaurea iberica</i> Trev.	Le	For wound healing; externally, pounded	Turkey	Sezik et al., 1997
<i>Centaurea lycopifolia</i> Boiss. Et Kotschy	H	For cuts to stop bleeding; externally, pounded	Turkey	Yeşilada et al., 1995
<i>Centaurea nigra</i> L.	Fl, Rt, Se	For wound healing	Britain Ireland Western Europe	Kenny et al., 2014
<i>Centaurea pterocaula</i> Trautv.	Le	For wound healing; externally, pounded	Turkey	Sezik et al., 1997
<i>Centaurea scabiosa</i> L. Greater	Rt, Se	For wound healing	Britain Ireland Europe	Kenny et al., 2014
<i>Chromolaena odorata</i> (L.) R. King & H. Robinson	Le	For cuts and wounds	India	Bhat et al.,2012
<i>Cichorium intybus</i> L.	Le, H	For cuts and wounds; cooked with the roots of <i>Anchusa</i> sp., butter and pine resin; ashes are mixed with butter and externally applied on wounds as an ointment	Turkey	Sezik et al., 1991 Sezik at al., 2001
<i>Dendranthema indicum</i> (L.) Des Moul.	Le	For cuts	India	Bhat et al.,2012
<i>Eclipta prostrata</i> (L.) L.	Wh	The juice of whole plant is applied topically on cuts and wounds	India	Sharma et al., 2014
<i>Gundelia tournefortii</i> L. var. <i>tournefortii</i>	La	For cuts; external use	Turkey	Sezik at al., 2001
<i>Helichrysum appendiculatum</i> (L.f.) Less.	Le	For wound healing; fresh leaves applied to circumcision wounds; tea from dried leaves applied to circumcision wounds	South Africa	Grierson & Afolayan, 1999
<i>Helichrysum aureonitens</i> Sch.Bip.	Le	For wounds; leaves infusion used as a wash and lotion		
<i>Helichrysum foetidum</i> (L.) Moench	Le	For infected sores; poultice from fresh leaves applied externally		
<i>Helichrysum pedunculare</i> DC.	Le	Fresh leaves applied to circumcision wounds		
<i>Helichrysum plicatum</i> DC. ssp. <i>plicatum</i>	Fl	For wound healing; externally, burned, ash is applied on wounds; decoction is mixed with barley flour to obtain poultice; infusion externally applied on wounds	Turkey	Sezik et al., 1991 Fujita et al., 1995 Sezik at al., 2001
<i>Saussurea gossypiphora</i> D. Don	H Wh	Wooly cotton from the plant is soaked in water and applied on fractured parts and wounds	Nepal	Shrestha et al., 2016
<i>Scorzonera tomentosa</i> L.	La	For wound healing; externally	Turkey	Sezik et al., 1997
<i>Sonchus asper</i> L. (Hill)	Le, St	For wound healing; extracts are applied externally	Britain Ireland Europe	Kenny et al., 2014
<i>Tagetes erecta</i> L.	Le	For wounds with maggots in cattle	India	Bhat et al.,2012
<i>Tanacetum balsamita</i> L.	Le	For wound healing; externally, fresh	Turkey	Sezik et al., 1997
<i>Tridax procumbens</i> (L.) L.	Le	The paste of leaves is topically applied on cuts and wounds to stop bleeding	India	Sharma et al., 2014
<i>Vernonia anthelmintica</i> (L.) Willd.	Se	For cuts and gangrene	India	Bhat et al.,2012

Fl: Flower; H: Herb; La: Latex; Le: Leaf; Rt: Root; Se: Seed; St: Stem; Wh: Whole plant

***Ageratina Spach* sp.**

Ageratina pichinchensis (Kunth) R.M.King & H.Rob. has been used for the wound healing purposes in Mexican folk medicine. In previous studies, *A. pichinchensis* aqueous extract was demonstrated to enhance wound healing by experimental methods (Monroy & Castillo, 2000). Moreover, the extract was shown to be active in the treatment of chronic venous ulcers. The compound responsible from the wound healing effect was identified to be 7-O-(β -D-glucopyranosyl)-galactin (Romero et al., 2013). Therefore, Romero-Cerecero et al. (2014) aimed to investigate the wound healing and possible genotoxic effects of the standardized aqueous and hexane-ethylacetate extracts of *A. pichinchensis* by using a diabetic foot ulcer rat model. A circular lesion was created on the rear of the paw of the streptozotocin-induced diabetic rats and the wound area was topically treated daily until complete healing. 5-methyl-1phenyl-2-(1H) Pyridone was used as a reference material. At the end of the experiment, the skin samples were histopathologically examined. The possible genotoxic properties were examined in a model of spermatozoid viability and morphology. The results revealed that all of the animals treated with *A. pichinchensis* extracts demonstrated wound healing effect between days 4 and 11 of treatment. Regenerative process was recorded for the extract treated group in the histopathological analysis. Furthermore, no genotoxic effect was observed. In conclusion, both standardized aqueous and hexane-ethyl acetate extracts prepared from the aerial parts of *A. pichinchensis* accelerated wound healing in diabetic rats without inducing genotoxicity (Romero-Cerecero et al., 2014).

***Ageratum L.* sp.**

Ageratum conyzoides L. has been applied onto fresh wounds, especially the leaves has been used as a remedy for burns in central Africa (Watt & Breyer-Brandwijk, 1962). Excision, incision and dead space wound models were performed to examine the efficacy of petroleum ether, chloroform, methanol and aqueous extracts of *A. conyzoides*. The methanol and aqueous extracts prepared from the leaves of *A. conyzoides* demonstrated proper wound healing when compared to the other extracts. The chloroform extract was also found to have promising activity, however, less than those of methanol and aqueous extracts (Oladejo et al., 2003).

***Achyrocline* (Less.) DC. sp. and *Matricaria L.* sp.**

The aim of the study by Alerico et al. (2015), was to examine the *in vitro* wound healing activity

of the plants used for healing of skin wounds in Rio Grande do Sul state, Brazil. Ethnobotanical studies from state of Rio Grande do Sul were analyzed and selected species were collected and ethanol and aqueous extracts were prepared for the activity testing. Among 117 plant species from 85 genera, 14 were selected to test the proliferative action by using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay in a keratinocyte cell line (HaCaT). Water extracts of *Achyrocline satureioides* DC Lam. and *Matricaria recutita* L., at concentrations of 25 mg/mL and 50 mg/mL, showed the capacity to stimulate keratinocyte growth up to 120%. The ethanol extract of *A. satureioides* was found to be the most promising species by stimulating the proliferation of keratinocyte and fibroblast at 1 mg/mL concentration (Alerico et al., 2015).

In a study which assessed the wound healing activity of *Matricaria chamomilla* L. extracts, wound healing was completed in nine days, which was found to be a shorter period than those of other treatments (Martins et al., 2009). It was also reported that essential oil and methanol extract of *M. chamomilla* were effective against *Staphylococcus aureus* ATCC 9244 and *Candida albicans* ATCC 10231 (Owlia et al., 2007; Abdoul-Latif et al., 2011; Parsaeimehr et al., 2014).

***Arnica L.* sp.**

A study assessed the wound healing effect of microcurrent application alone or in combination with topical *Arnica montana* L. on the incision wounds created on the dorsal parts of the rats. The animals were randomly divided into the following groups; control group, microcurrent application alone (10 mA/2 min); topical application of gel containing *A. montana*; topical application of *A. montana* gel and microcurrent (10 mA/2 min). For structural and morphometric analysis, the tissue samples were removed on the 2nd, 6th and 10th days after wound induction. Significant wound healing activity was observed in the microcurrent application alone or combined with *A. montana* gel in terms of newly formed tissue, number of blood vessels and percentage of mature collagen fibers. It can be concluded that *A. montana* administration combined with microcurrent application was found to be effective on healing of wounds when compared to the control group (Castro et al., 2012).

***Calendula L.* sp.**

In a previous study, several formulations of lamellar gel phase (LGP) emulsions containing *Calendula officinalis* L. oil were developed and

evaluated for a good amount of anisotropic structure and stability. Furthermore, *in vitro* and *in vivo* wound healing activity evaluation studies were conducted in rats. 15.0% marigold oil; 10.0% of blend surfactants and 75.0% of purified water [w/w/w] LGP emulsion exerted good stability and high viscosity without any cytotoxic activity (50-1000 µg/mL). In the wound healing model, the LGP (15 mg/mL) enhanced the leukocyte migration to the wound on days 2 and 7, but decreased after 14 and 21 days. In addition, LGP emulsion caused a reduction in collagen production on days 2 and 7 and further accelerated the re-epithelialization of process (Okuma et al., 2015).

In a previous study by Chandran and Kuttan (2008), it was reported that flower extracts prepared from *C. officinalis* improved the wound healing process, as evident by the notable increase in hexosamine and collagen-hydroxyproline levels in treated samples (Chandran & Kuttan, 2008). The antioxidant defense mechanism was found to be activated and lipid peroxidation and tissue damage marker enzymes including alkaline phosphatase, alanine and aspartate transaminases were measured to be lower in treated samples when compared to the controls (Parsaeimehr et al., 2014).

Centaurea L. sp.

Centaurea L. species have been used to treat skin wounds in traditional medicine, in Turkey. Especially, the aerial parts of *Centaurea iberica* Trev. ex Spreng. have been utilized for accelerated healing. Therefore, in a previous study by Koca et al. (2009) wound healing properties of *n*-hexane, chloroform, ethyl acetate and aqueous methanol (85%) extracts obtained from the aerial parts of *C. iberica* were investigated by *in vivo* linear incision and circular excision wound models in rats and mice, respectively. 1% methanol extract showed significant wound healing effect by providing 42.2% increase in tensile strength and 81.09% contraction values. Moreover, 200 mg/kg methanol extract showed notable anti-inflammatory activity (31.6%) (Koca et al., 2009; Küpeli Akkol & Süntar, 2013).

In Hungarian folk medicine, the aerial parts of *C. sadleriana* Janka were reported to be used for wound healing in livestock. Therefore, wound healing potential of different solvent extracts of *C. sadleriana* was assessed. Experimental wounds were created on the rats by a branding iron and then the wounds were topically treated with the gel formulation of the extracts and fractions in 2.5% concentration twice a day. The results of the study showed that *n*-hexane fraction of the methanol extract was significantly effective in the wound healing process, confirming

the folk medicinal use of *C. sadleriana* (Csupor et al., 2010).

Chromolaena DC. sp.

Chromolaena odorata (L.) King & H.E. Robins (Devil Weed) is tropical, perennial, scrambling shrub and is distributed in North America and tropical parts of Asia. Traditional information reveals that extracts obtained from *C. odorata* were used to treat malarial fever, headache, toothache, burns, ischuria and skin infections (Parsaeimehr et al., 2014). The leaf extract of *C. odorata* was shown to be beneficial for the treatment of wounds. By using the MTT assay, antioxidant activity of the ethanol and polyphenolic extracts of *C. odorata* leaves was investigated on human dermal fibroblasts and epidermal keratinocytes against hydrogen peroxide and hypoxanthine-xanthine oxidase-induced damage. The ethanol extracts (400 and 800 µg/ml) were found to have high and consistent protective effect on the fibroblasts against hydrogen peroxide and hypoxanthine-xanthine oxidase-induced damage. The antioxidant effects of the phenolic acids (protocatechuic, *p*-hydroxybenzoic, *p*-coumaric, ferulic and vanillic acids) and complex mixtures of lipophilic flavonoid aglycones (flavanones, flavonols, flavones and chalcones) from *C. odorata* were demonstrated on cultured skin cells by using colorimetric and lactate dehydrogenase release assays, indicating the important role of *C. odorata* in treating burns and wounds (Thang et al., 2001). Indeed, eupolin, a product from *C. odorata* leaves was reported to be licensed for the treatment of soft tissue burns and wounds in Vietnam (Phan et al., 1998; Raina et al., 2008). The wound healing effect was attributed to saponins and tannins, essential oils and phenolic compounds present in the plant (Omokhua et al., 2016).

Another research showed that extracts of *C. odorata* (at 10 µg/mL and 100 µg/mL doses) induced the fibroblasts and endothelial cells growth. Anticoagulation effect and antimicrobial activity against *Bacillus thuringiensis*, *B. stearothermophilus* NCTC 10339, *S. aureus* NCTC 6571, *Escherichia coli* (NCTC 11699), *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* TISTR 1843, as well as increase in tissue remodeling effect of *C. odorata* extract were also demonstrated (Irobi, 1997; Lamond & Farnell, 1998; Hanphakphoom et al., 2016).

Panda et al. (2010) studied the wound healing activity of *C. odorata* by the excision wound model measuring the wound contraction and closure time. Petroleum ether, ethyl acetate and methanol extracts in 5, 7.5 and 10% concentrations were applied on rats by comparing the results with Neosporin and

Betadine ointments as reference materials. The methanol extract was found to be significantly active (Panda et al., 2010).

The aqueous and alcoholic (50, 70 and 95% ethanol) extracts of the leaves of *C. odorata* were investigated for haemostatic activity. For the evaluation of the haemostatic activity, the bleeding time was measured in male Wistar rats and *in vitro* platelet aggregation and blood coagulation assays were conducted in sheep plasma. All the extracts noticeably reduced the bleeding time (<2.5 min) but did not induce platelet aggregation or blood clotting (> 0.6 min). 70% ethanol extract demonstrated the highest hemostatic activity with the bleeding time of 1.85 min. The *in vivo* study confirmed the significant ability of the leaf extract of *C. odorata* to stop bleeding (Pandith et al., 2012).

In another study, wound healing effect of the ethanol and aqueous extracts of *C. odorata* was investigated. The shortest clotting and coagulation times were recorded as 0.26 ± 0.012 min 15.18 ± 0.023 min, respectively for the aqueous extract group (Anyasor et al., 2011).

Cichorium L. sp.

Different parts of *Cichorium intybus L.* were reported to be utilized for wound healing purposes in the ethnobotanical studies conducted in Turkey. To assess the wound healing effect of the traditional prescriptions obtained from *C. intybus* aerial parts and roots, *in vivo* linear incision and circular excision wound models were performed by bioassay-guided fractionation techniques. Wound healing effect of the aerial parts, leaves and roots and also ashes of both leaves and roots were examined. The methanol extract of the roots of the plant was subjected to the further biological activity assays including *in vivo* wound healing, anti-inflammatory and *in vitro* antioxidant and enzyme inhibitory tests as well as phytochemical assays including chromatographic techniques. Among *n*-hexane, dichloromethane, ethyl acetate, *n*-butanol and remaining water extracts, dichloromethane subextract was found to possess significant wound healing activity. β -sitosterol was isolated and detected to be the compound responsible for the wound healing effect (Süntar et al., 2012).

Echinacea Moench sp.

Echinacea species, famous for their immunomodulator effect, was previously reported to be used for the healing of wounds. In order to evaluate the claimed effect, *Echinacea pallida* (Nutt.) Nutt. alcohol extract was given orally to mice for 3 days prior to, and 4 days post wounding with a dermal biopsy on the dorsal part of the animals. Meanwhile, mice were exposed restraint stress three

times daily prior to, and 4 times post wounding. *Echinacea* improved wound healing in the stressed mice, but exhibited no significant activity in the non-stressed mice. According to the results of plasma glucocorticoid concentration measurements, the accelerated wound healing efficacy provided by *E. pallida* extract in stressed mice were not mediated through glucocorticoid signaling modulation (Zhai et al., 2009). By the accelerative effect on the fibroblast synthesis and collagen formation, *Echinacea* extracts were shown to have capacity to improve the healing process in arsenic-induced dermal necrosis and minimize the effects of arsenic (Rezaie et al., 2013).

Helichrysum Mill. sp.

In the aim of confirming the traditional use of *Helichrysum graveolens* (Bieb.) Sweet for wound-healing, the activity was evaluated through bioassay-guided fractionation procedures by using *in vivo* wound models and *in vitro* antioxidant and enzyme inhibition assays. The methanolic (85%) flower extract of *H. graveolens* exerted remarkable wound-healing, anti-inflammatory and antioxidant activities. Followingly, the methanol extract was fractionated to give five solvent fractions, among which the ethyl acetate fraction displayed the best wound healing activity. From the ethyl acetate fraction, a flavonoid type compound, apigenin, was isolated by chromatographic methods and determined as one of the active compounds in the ethyl acetate fraction by *in vivo* and *in vitro* assays (Süntar et al., 2013).

Inula L. sp.

Aqueous extract of *Inula viscosa* (L.) Aiton was assessed for its potential wound healing activity. In the dorsal area of the mice, a full thickness wound was created. The wounds were treated during 2 days, for four times daily with the different preparations. The area of the wounds were measured during 16 days. At the end of the experiment, the animals were sacrificed and histopathologically examined. Proper healing was observed in the *I. viscosa* extract-treated group (Khalil et al., 2007).

Scorzonera L. sp.

Scorzonera L. is an important genus in Turkish folk medicine due to its therapeutic potential in a wide range of ailments including wound healing (4, 49). For the evaluation of wound healing activity of some *Scorzonera species* (*Scorzonera acuminata* Boiss. & Balansa, *Scorzonera cana* (C.A.Mey.) Hoffm. var. *alpina* (Boiss.) Chamberlain, *Scorzonera cana* (C.A.Mey.) Hoffm. var. *jacquiniana* (W.Koch) Chamberlain, *Scorzonera cana* (C.A.Mey.) Hoffm. var. *radicosa* (Boiss.) Chamberlain, *Scorzonera eriophora* DC, *Scorzonera laciniata* ssp. *laciniata*

Davis, *Scorzonera* C. Koch subsp. *suberosa* C. Koch and *Scorzonera sublanata* Lipschitz) *in vivo* wound models of incision and excision were performed. Hydroalcoholic aerial part and root extracts were obtained to test the activity in 1% concentration. The aerial part extracts of *S. cana* var. *jacquiniana* and *S. eriophora* displayed 40.5% and 34.3% of increase in tensile strength values and exerted 46.27% and 39.44% of contraction values, respectively. Furthermore, the aerial part extracts of *S. cana* var. *jacquiniana* and *S. eriophora* demonstrated significant increase in the amount of tissue hydroxyproline, remarkable anti-inflammatory activity and *in vitro* anti-hyaluronidase effects. HPLC (High Performance Liquid Chromatography) analyses were employed to reveal the compounds including chlorogenic acid, rutin, hyperoside and luteolin-7-glycoside in *Scorzonera* species (Süntar et al., 2012; Küpeli Akkol & Süntar, 2013).

Potential wound healing effectiveness of the aerial part and root extracts of some *Scorzonera* species including *Scorzonera cericea* DC, *Scorzonera incisa* DC, *Scorzonera latifolia* (Fisch. et Mey.) DC., *Scorzonera mollis* ssp. *szowitsii* (DC) Chamberlain, *Scorzonera parviflora* Jocq., *Scorzonera tomentosa* L. and the dried latex of *S. latifolia* were investigated by *in vivo* linear incision and circular excision experimental wound models. The active components were identified by HPLC. The aerial part extracts of *S. latifolia*, *S. mollis* ssp. *szowitsii* and *S. tomentosa* displayed 30.6%, 25.4% and 23.2% of increase in tensile strength on day 10, respectively on linear incision wound model. The contraction values were calculated as 61.44% for *S. latifolia*, 59.88% for *S. mollis* ssp. *szowitsii*, 37.62% for *S. tomentosa* and 37.62% for dried latex of *S. latifolia* treated group. Hydroxyproline levels were found to be enhanced in the groups treated with the aerial part extracts of *S. latifolia*, *S. mollis* ssp. *szowitsii* and *S. tomentosa*. The aerial part extract of *S. latifolia* (100 mg/kg) inhibited the acetic acid-induced increase in capillary permeability. Chlorogenic acid was detected as the major constituent of the roots and aerial parts *Scorzonera* species. Moreover, hyperoside or rutin was one of the major components of the aerial parts. The wound healing activity was attributed to the combined effect of the constituents present in the extracts (Küpeli Akkol et al., 2012).

Senecio L. sp.

Wound healing activity of *Senecio serratuloides* DC was investigated on a deep partial thickness wound model in pigs for 16 days. Epidermal thickness of the skin was measured to observe the healing process. Plant-treated wounds was found to have thicker

neo-epidermis on day 7 and lower pH on day 2 than those of the control group. Alkaloids were detected in the plant extract by thin layer chromatography. The results of the study demonstrated that *S. serratuloides* accelerated healing of deep partial thickness skin wounds (Gould et al., 2015).

Sphaeranthus L. sp.

Sphaeranthus indicus L. is an essential medicinal plant practiced for the treatment of skin disorders including scabies in folk medicine (Chopra et al., 1956; Kirtikar & Basu, 1999; Nadkarni, 2007). Aerial part extract of *S. indicus* considerably increased the wound contraction rate and the epithelialization period when compared to neomycin in pigs (Sadaf et al., 2006).

Stevia Cav. sp.

A previous *in vivo* study was conducted to investigate the wound healing effect of the aqueous extract of the leaves of *Stevia rebaudiana* (Bertoni) Bertoni. The extract was topically applied for 14 days at 150, 250 and 500 mg/kg doses in excision wound model and orally administered for 10 days in incision wound model, respectively by comparing the effects with 5.0% povidone iodine ointment. *S. rebaudiana* aqueous extract at 500 mg/ kg dose noticeably decreased the wound area (48.2 ± 2.0) and epithelialization time (12.0 ± 0.10) in excision wound model and increased the tissue hydroxylproline content (67.6 ± 0.10). Tensile strength of the treated wounds, weight of the wet and dry granulation tissue and hydroxyproline content remarkably increased in incision wound model, indicating accelerated wound healing ability of *S. rebaudiana* aqueous extract (Das, 2013).

Tridax L. sp.

The aqueous whole plant extract of *Tridax procumbens* L. showed lysyl oxidase activity, increased protein and nucleic acid contents as well as the tensile strength which are relevant to wound healing activity in dead space wound healing model. Whole plant extract was found to have higher activity than those of butanol and petroleum ether fractions (Udupa et al., 1995). Yaduvanshi et al. (2011) reported that, *T. procumbens* extract at 1 mg/g concentration displayed a notable increase (38.81%) in collagen biosynthesis when compared to the vehicle group in excision wound model (Yaduvanshi et al., 2011). Talekar et al. (2012) reported that ethanol and water extracts of *T. procumbens* significantly increased the wound tensile strength and hydroxyproline, collagen and hexosamine content when compared to the control group (Talekar et al., 2012; Agyare et al., 2016).

Vernonia Schreb. sp.

Wound healing activity of the ethanol extract obtained from the leaves of *Vernonia scorpioides* (Lam.) Pers. was evaluated in guinea pigs. 200 mg of a hydrogel containing 50% of extract was administered once a day onto the excised wounds of the animals for 30 days. The histopathological investigation revealed a proper healing for *V. scorpioides* treated group evident by a well organized and regenerated connective tissue (Leite et al., 2002).

Wedelia Jacq. sp.

The leaves of *Wedelia trilobata* (L.) Hitchc have been utilized for wound healing purposes. The study was carried out to obtain scientific data to support its traditional therapeutic application. Ethanol extract from the leaves of *W. trilobata* was subjected to column chromatography to obtain hexane, ethyl acetate and chloroform:methanol (50:50) fractions. *In vitro* wound healing activity models were used to test the activity. Antioxidant effect of the fractions were assessed by the DPPH assay. Antibacterial effect was investigated against *S. aureus* ATCC 25923, *S. epidermidis* TISTR 517, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. The ethyl acetate fraction promoted fibroblast L929 survivability before (more than 90%) and after hydrogen peroxide induced oxidative stress (85%), induced migration in the *in vitro* scratch assay (70%); increased the collagen content (261 µg/mL) and was found to be active against *S. aureus*, *S. epidermidis* with the MIC values of 62.5 and 31.25 µg/mL, respectively. Chloroform:methanol fraction exerted a scavenging activity against DPPH (IC₅₀: 179.5 µg/mL). In conclusion, the results obtained in this study supported the traditional claims for *W. trilobata* leaves (Balekar et al., 2012a).

In another study by the same authors, the extract obtained from the leaves of *W. trilobata* was subjected to bioassay-guided fractionation assay to yield five fractions (WEA1-A, B, C, D, and E) to examine for antimicrobial activity. Among the five fractions, WEA1-B fraction containing ent-kaura-9(11),16-dien-19-oic acid displayed considerable antibacterial activity against *S. aureus* and *S. epidermidis*, with the MIC values of 15.62 µg/ml and 7.81 µg/ml, respectively. This fraction was further investigated for its possible effect on fibroblasts. WEA1-B (2.5-0.08 µg/ml) enhanced the percentage viability of mouse fibroblast L929 cells from 97 to 117% and protected the fibroblast L929 cells against hydrogen peroxide-induced oxidative stress (80-94%). This study demonstrated positive role of *W. trilobata* on tissue repair owing to a combination of antimicrobial, antioxidant and fibroblast growth stimulator effects (Balekar et al., 2012b).

CONCLUSION

Asteraceae is an important plant family for being a valuable and potential source for the natural products possessing wound healing activity. This review, including ethnobotanical researches and biological activity studies, will be useful in providing an ethnopharmacognostical approach for drug discovery and development.

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