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REVIEW

Medicinal plants and their natural components as future drugs for the treatment of burn wounds: an integrative review

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Abstract Burn wound healing is a complicated process including inflammation, re-epithelialization, granulation, neovascularization and wound contraction. Several biochemicals are involved in burn healing process including antioxidants, cytokines and liver and kidney damage biomarkers. Although several preparations are available for the management of burn wound, there is still a necessity of researching for efficacious medicine. The aim of the present study was to evaluate herbal preparations and their phytochemical constituents for burn wound management. For this purpose, electronic databases including Pubmed, Scirus, Scopus and Cochrane library were searched from 1966 to July 2013 for in vitro, in vivo or clinical studies which examined the effect of any herbal preparation on different types of burn wound. Only 3 human studies were found to include in this review. In contrast, there were 62 in vivo and in vitro studies that show the need for more clinical trials to prove the plant's potential to cure burn wound. Among single herbal preparations, *Allium sativum*, *Aloe vera*, *Centella asiatica* and *Hippophae rhamnoides* showed the best burn wound healing activity. Flavonoids, alkaloids, saponins and phenolic compounds were active constituents present in different herbs facilitating wound closure. Glycosides including madecassoside and asiaticoside and proteolytic enzymes were among the main active components. Phytochemicals represented positive activity at different stages of burn wound healing process by various mechanisms including antimicrobial, anti-inflammatory, antioxidant, collagen synthesis stimulation, cell proliferative and angiogenic effect. Overall, several herbal medicaments have shown marked activity in the management of wounds—especially burn wounds—and therefore can be considered as an alternative source of treatment. Furthermore, various natural compounds with verified burn-induced wound healing potential can be assumed as future natural drugs.

Keywords Medicinal plant · Burn wound · Integrative review · In vitro · In vivo · Human study

Introduction

Burn is defined as tissue injury caused by heat, chemicals, electricity, radiation etc. According to the depth, burn wounds are classified as first degree (superficial), second degree (partial thickness) and third degree (full-thickness) [15]. Burn wound healing is a complicated process including inflammation due to disruption of blood vessels and extravasation of blood constituents, re-epithelialization that begins hours after injury, formation of granulation tissue mainly by macrophages and fibroblasts that are responsible for recovery of the extracellular matrix, neovascularization that pertains to extracellular matrix in the wound bed, as well as migration and mitogenic stimulation of endothelial cells and wound contraction as a result of interaction between cells, extracellular matrix and

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cytokines [63]. Several biochemicals are involved in burn healing process including matrix metalloproteinases (MMPs), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO), vascular endothelial growth factor (VEGF), hydroxyproline, hexosamine, ascorbic acid (vitamin C) and protein content in damaged and surrounding tissue, serum levels of aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine as indicators of liver and kidney damage and tumor necrosis factor (TNF) for evaluation of generalized tissue damage [53, 63, 71]. Moreover, various cytokines are involved in the healing process of burn wound including interleukin-6 (IL-6) and TNF-α, which are the most important cytokines in the inflammation phase of burn-induced damage [12].

Severe burn wounds need to be treated as soon as possible since any delay can postpone the healing process or result in infection. Although several topical preparations are present in market for management of burn wound, there is still an obvious lack of suitable drug since most of the available products have antimicrobial activity rather than wound healing effect, as well as their probable negative performance and toxicity as in the case of silver sulfadiazine on fibroblasts [27]. About 1–3 % of drugs in modern medicaments are being suggested to be effective on normal and damaged skin; in comparison, near one-third of herbal medicines are for such use [38]. Poultices and ointments are different topical forms of herbal preparations that have been used since ancient times. Medicinal plants can act as wound healing agents because of their vast variety of different constituents like alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, fatty acids and phenolic compounds, which are potentially able to improve healing process of burn wound. Low cost, availability and fewer side effects are other advantages of herbal remedies. A lot of researches are under process all over the world to identify and isolate the active components of medicinal plants responsible for their wound healing properties [18, 51, 68]. The aim of the present study is to evaluate single and combined herbal preparations and their phytochemical constituents for burn wound management.

Method

For this purpose, electronic databases including Pubmed, Scirus, Scopus and Cochrane library were screened for in vitro, in vivo or clinical studies that examined the effect of any herbal preparation on the first-, second- and third-degree burn wounds. Data were collected for the years 1966–2013 (up to July). Only published articles were included in this review, and unpublished works were not considered. Language restriction was performed, and English language articles were included. The search terms were "burn wound" in title and abstract and "plant," "extract" or "herb" in the whole text. Results from primary search were screened by two independent investigators. References of final included articles were reviewed for relevant studies. Included articles were reviewed to extract plant scientific names, complete ingredients of the product (in combined preparations), part and extract of the plants, active components (if mentioned), degree of induced burn wound, animal model for in vivo and type of cell line for in vitro studies. Results were looked for differences between test group and control group in wound contraction, period of epithelialization, neovascularization, collagenation, keratinization, inflammatory reactions, number of inflammatory cells, local and systemic biomarkers of tissue damage and total microbial count. Results were abstracted in Tables 1, 2 and 3. ↑ and ↓ show increase and decrease in mentioned variables, respectively. In human studies, study design, number of patients, interventions, duration of treatment, Jadad score and efficacy and tolerability of the herbal treatment were also collected. Jadad score, which indicates the quality of the studies based on their description of randomization, blinding and dropouts (withdrawals), was used to assess the methodological quality of trials [15]. The quality scale ranges from 0 to 5 points with a low-quality report of score 2 or less and a high-quality report of score at least 3.

Findings and results

From total 480 results, 199 reports were excluded because of duplication. 40 reports were excluded since they were reviews. 149 (including 26 human and 123 in vivo or in vitro studies) were excluded according to their title and abstract: 78 (including 3 human and 75 other studies) because they were evaluations of plant materials on other models of wound rather than burn (incision wound, excision wound, dead space wound), 13 (including 9 human studies) because they used other complementary and alternative medicament rather than plants (honey, crocodile oil, fly larva, egg, yeast, mushroom, lichen), 19 because it was combination of plants with a chemical or non-herbal material (allantoin, amino acids, honey, synthetic vitamins), 8 because they were mechanical and biocompatible characterization of wound dressing materials without a pharmacological test, 7 (including 1 human study) because they did not have English full text, 5 because they were tested antibacterial activity without evaluation of wound healing effect, 4 because they were anti-inflammatory studies without any wound induction, 13 because they were human studies rather than clinical trial, e.g., case report,

Table 1 Single herbal preparations used for treatment of burn wound

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Achillea millefolium	Aerial part/ aqueous extract	–	Thermal burn wound	Male white rabbit	In vivo	↑Wound contraction, ↓microbial count	[67]
Achillea millefolium	Aerial part/ ethanolic extract	–	Thermal burn wound	Male New Zealand white rabbit	In vivo	↑Wound contraction, ↓microbial count	[61]
Actinidia deliciosa	Fruit paste	Enzymes	Full-thickness burn wound	Male Sprague–Dawley rat	In vivo	↑Wound contraction, ↑scar separation, ↑debridement	[25]
Actinidia sp.	Fruit	–	Deep second-degree burn wound	Male albino Wistar rat	In vivo	↑Wound contraction, ↑granulation, ↓inflammation, ↑vascularization, antibacterial and debridement activity were also observed	[46]
Achyranthes aspera	Leaf/methanolic extract	–	Thermal burn wound	Rat	In vivo	↑Wound contraction, ↑SOD,↑CAT, ↑protein content, ↑hydroxyproline, ↑MMP-2 and 9, ↑vit C in wound tissue	[8]
Allium sativum	Bulb/aqueous extract	–	Partial-thickness burn wound	Wistar albino rats of both sexes	In vivo	Intraperitoneal administration: ↑GSH, ↓MDA, ↓protein oxidation, ↓MPO in liver, intestine and lung tissue samples	[56]
Allium sativum	Bulb/aqueous extract	–	Thermal burn wound	Mongrel dogs of both sexes	In vivo	↑Wound contraction, ↓total number of microorganism	[60]
Allium sativum	Bulb/ethanolic extract	–	Thermal burn wound	Male white rabbit	In vivo	↑Wound contraction, ↓microbial count	[62]
Alkanna tinctoria	Root olive oil topical preparation	–	Partial-thickness, severe and hot olive oil burn wound	Male New Zealand white rabbit	In vivo	↓Wound healing time, ↑well formed dermal–epidermal junctions in partial-thickness and olive oil burn but not in severe burn.	[48]
Aloe barbadensis	Gel and raw polysaccharides	Polysaccharides	Deep Partial-thickness burn wound	Male Wistar rats	In vivo	↓NO release of wound tissue, ↓vascular inflammatory reaction, ↓permeability and edema, optimization in NO/endothelin ratio	[42]
Aloe littoralis	Gel/topical preparation	–	Thermal burn wound	Male Wistar rat	In vivo	↑Wound contraction	[26]
Aloe vera	Gel/topical preparation	–	Second-degree burn wound	Male Wistar rat	In vivo	↑Wound contraction, ↑microcirculation	[65]
Aloe vera	Gel/topical preparation	–	Second-degree burn wound	Male Wistar rat	In vivo	↑Wound contraction, ↑re-epithelialization of the epidermis and ↑fibrosis of the dermis	[28]
Aloe vera	Gel/topical preparation	–	Full-thickness burn wound infected with *Klebsiella pneumoniae* B5055	Balb/c mice	In vivo	↑Survival rate, antibacterial activity in unautoclaved *A. vera* gel but not in autoclaved one	[39]
Aloe vera	Gel/topical preparation	–	Thermal burn wound	Male Wistar Furth rat	In vivo	↓Inflammation in burn tissue, ↓leukocyte adhesion, ↓TNF-α, ↓IL-6	[14]

Table 1 continued

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Aloe vera	Gel/topical preparation	–	Thermal burn wound	Hartley guinea pigs	In vivo	↓Wound healing time, ↓microbial count	[52]
Alternanthera brasiliana	Leaf/methanolic extract	–	Full-thickness burn wound	Sprague–Dawley rat of either sex	In vivo	↑Wound contraction, ↑hydroxyproline content, ↑protein content, ↑GSH, ↑SOD, ↑CAT, ↑vit C, ↓epidermis formation time	[7]
Amygdalus communis	leaf/ethanolic extract	–	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]
Arnebia euchroma	Leaf and root/gel	–	Second-degree burn wound	Female Wistar rat	In vivo	↑wound contraction, ↑neovascularization, ↑re-epithelialization, ↑fibroblasts proliferation, ↑collagen synthesis as well as anti-inflammatory activity	[4]
Arnebia euchroma	Root/ethanolic extract	–	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]
Astilbe thunbergii	Rhizome/ different fractions of ethanolic extract	Eucryphin, bergenin, astilbin	Thermal burn wound	Male Balb/c mice	In vivo	↑Wound contraction, eucryphin showed the highest action	[35]
Bauhinia purpurea	Leaf/methanol and chloroform extract	–	Partial-thickness burn wound	Sprague–Dawley rat	In vivo	↑Wound contraction, ↓re-epithelialization time (better effect in higher doses)	[3]
Brassica oleracea	Leaf/aqueous extract	–	Deep second-degree burn wound	Female Sprague–Dawley rat	In vivo	↑wound contraction, ↑re-epithelialization, ↑vascularization	[27]
Calendula officinalis	Flower/ethanolic extract	Flavonoids, alkaloids and triterpinoids	Thermal burn wound	Female Wistar rat	In vivo	Oral administration of the extract: ↓haptoglobin, ↓orosomucoid, ↑hydroxyproline, ↑hexosamine, ↑GSH and ↓lipid peroxidation in liver tissue, ↑SOD, ↑CAT; also ↓serum levels of GPT, ALP, GOT and bilirubin	[10]
Camellia sinensis	Leaf/ethanolic extract	–	Type II burn wound	Male Wistar rat	In vivo	↑Wound contraction, no significant difference in re-epithelialization and angiogenesis	[31]
Carica candamarcensis	Fruit/latex	P1G10 fraction	Thermal burn wound	Mouse	In vivo	↑Re-epithelialization, no significant difference in wound contraction	[22]
Carica papaya	Fruit/latex	–	Thermal burn wound	Male swiss albino mice	In vivo	↑Wound contraction, ↑re-epithelialization, ↑hydroxyproline content of damaged tissue	[24]

Table 1 continued

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Carissa spinarum	Root/methanolic extract	–	Partial- thickness burn wound	Adult swiss albino mice	In vivo	↑Wound contraction, ↑re-epithelialization, ↑stratification and polarity of epithelial cells, ↑hydroxyproline of damaged tissue, as well as antimicrobial activity	[54]
Celosia argentea	Leaf/ethanolic extract	–	Thermal burn wound	Primary human dermal fibroblasts and human epidermal keratinocytes (1), Male albino Wistar rat (2)	In vitro(1) and In vivo(2)	↑Cell motility and proliferation in primary fibroblasts but not in primary keratinocytes, no effect on cell responses to the wound repair-associated EGFR ligands (1) ↑wound contraction, ↑hydroxyproline, ↑collagen, ↑hexosamine (2)	[49]
Centaurea sadleriana	Aerial parts/ different extracts and fractions	–	Thermal burn wound	Female Sprague–Dawley rat	In vivo	↓Wound healing time, n-hexane fraction of the methanolic extract was the most potent one	[11]
Centella asiatica	Madecassoside, asiaticoside, madecassic acid and asiatic acid	Madecassoside, asiaticoside, madecassic acid and asiatic acid	Thermal burn wound	Human skin fibroblast cells (1), male ICR mice (2)	In vitro (1) In vivo(2)	Not enhance cell proliferation in human fibroblast cells, ↑synthesis of collagen type-I and type-III by asiaticoside and madecassoside through activating fibroblasts via TGF-β, and madecassoside showed higher action than asiaticoside(1), oral administration resulted in: ↑wound contraction (2)	[74]
Centella asiatica	Aerial parts/ ethanolic extract	Asiaticoside	Full-thickness burn wound	Human monocyte cell line and human keratinocyte cell line (1), Male Balb/c mice (2)	In vitro (1) In vivo (2)	↑IL-1β production in THP-1 macrophages with MCP-1 but not without MCP-1 or with LPS, ↑MCP-1 in HaCaT cells but no direct effect on VEGF (1), ↑wound contraction, ↑MCP-1 production from the burn wound area, ↑VEGF, ↑IL-1β, ↑macrophage accumulation and VEGF-positive cells in the tissue surrounding the burn wound area (2)	[36]
Centella asiatica	Aerial parts/ND	Madecassoside	Thermal burn wound and rat aortic ring test	Male Sprague-Dawley rats for rat aortic ring test (1), Male ICR mice (2)	In vitro (1) In vivo(2)	↑Endothelial cell growth in rat aortic ring test(1) oral administration: ↓NO, ↓MDA, ↑GSH ↑epithelization induced by proliferation of fibroblasts and granulation tissue, ↑ hydroxyproline content, ↑collagen synthesis, ↑angiogenesis(2)	[40]
Centella asiatica	Aerial parts/ different extracts	–	Partial-thickness burn wound	Male Sprague–Dawley rat	In vivo	↓Wound healing time, ↑re-epithelialization, ↑keratinization	[64]
Cocos nucifera	Fruit inner flesh oil	–	Partial-thickness burn wound	Wistar rats of both sexes	In vivo	↑Wound contraction, ↓period of re-epithelialization	[66]

Table 1 continued

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Crocus sativus	Pollen/ hydroethanolic extract	–	Second-degree burn wound	Male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization	[33]
Datura alba	Leaf/different fractions of ethanolic extract	–	Thermal burn wound	Male albino Wistar rat	In vivo	Antibacterial effect on burn wound pathogens with crude extract and chloroform fraction, ↑wound contraction, ↑infiltration of inflammatory cells, ↑angiogenesis, ↑collagen and hexosamine content of granulation tissue, ↑MMP2 and MMP9	[50]
Euphorbia hirta	Whole plant/ ethanolic extract	–	Thermal burn wound	Male albino Wistar rat	In vivo	↑Wound contraction	[29]
Ginkgo biloba	Leaf/ND	–	Partial-thickness second-degree burn wound	Wistar albino rats of both sexes	In vivo	Intraperitoneal administration: ↓serum level of ALT, AST, BUN, creatinine, TNF-α and LDH. In renal and hepatic samples :↑GSH, ↓MDA, ↓reactive oxygen species, ↓MPO, ↓collagen content of hepatic and renal tissues	[53]
Hippophae rhamnoides	Seed oil	Omega-3 and omega-6 fatty acids, tocopherols and carotenoids	Full-thickness burn wound	Male Sprague–Dawley rat	In vivo	Oral plus topical administration: ↓edema, ↑DNA, ↑total protein, ↑hydroxyproline, ↑hexosamine content in the granulation tissues, ↑tissue regeneration, ↑GSH, ↓reactive oxygen species, ↑granulation tissue density, ↑MMP-2 and 9, ↑VEGF, ↑collagen type-III	[70]
Hippophae rhamnoides	Leaf/aqueous extract	–	Full-thickness burn wound	Chick chorioallantoic membrane (1), Male Sprague–Dawley rat (2)	In vitro (1) and In vivo (2)	↑Angiogenesis (1), ↓edema, ↑re-epithelialization, ↓lipid peroxidation, ↑MMP-2 and 9, ↑VEGF expression, ↑hydroxyproline, ↑hexosamine, ↑collagen type-III expression, ↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑glutathione-S-transferase, ↑vit C (2)	[71]
Lantana camara	Leaf/ethanolic extract	–	Thermal burn wound	Male sprague-dawley rat	In vivo	No significant difference in wound contraction and re-epithelialization period in comparison with negative control, antimicrobial activity against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli*	[47]
Malva sylvestris	flower/ethanolic extract	–	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]
Matricaria chamomilla	Aerial part/ hydroalcoholic extract	–	Second-degree burn wound	Male albino rat	In vivo	↓Wound healing time	[30]

Table 1 continued

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Michelia champaca	Flower/ethanolic extract	–	Partial- thickness burn wound and dexamethasone-suppressed burn wound models	Male albino Wistar rat	In vivo	Oral and topical administration : ↑wound contraction, ↓period of re-epithelialization, in both models	[59]
Nigella sativa	Seed oil	–	Full-thickness burn wound	Male albino Wistar rat	In vivo	↓Wound healing time, ↑thickness of granulation tissue, ↓period of re-epithelialization	[75]
Olea sp.	Purified oil	–	Partial-thickness burn wound	Domestic female pig	In vivo	Did not promote wound healing	[23]
Onosma dichroanthum	Root/acetonic extract	–	Second-degree burn wound	Female Wistar rat	In vivo	↑Wound area, negative effect on wound healing process	[45]
Otostegia persica	Aerial parts/ methanolic extract	–	Thermal burn wound	Male Wistar rat	In vivo	↑re-epithelialization, ↑angiogenesis, ↓inflammation, ↑collagen accumulation	[20]
Panax ginseng	Root/crude saponin fractions	Six ginsenosides	Thermal burn wound	Human keratinocyte cell line (1), Male Balb/c mice (2)	In vitro (1) and In vivo(2)	Rb1 resulted in :no cytotoxicity, no effect on proliferation, ↑HIF-1α, ↑VEGF in presence of IL-1β (1) ↑Wound contraction, ↑angiogenesis, ↑VEGF expression in keratinocytes, ↑IL-1β (2)	[34]
Panax ginseng	Root/crude saponin fractions	Ginsenoside Rb1	Thermal burn wound	Male Balb/c mice	In vivo	↑Wound contraction, ↑neovascularization, ↑VEGF, ↓substance P, ↑IL-1β, ↑HIF-1α expression in keratinocytes	[32]
Phyllanthus niruri	Fruit/ethanolic extract	–	Thermal burn wound and dexamethasone-suppressed burn wound models	Rat	In vivo	Topical and oral administration :No significant effects in wound contraction and period of re-epithelialization in burn wound, ↑wound contraction and re-epithelialization in dexamethasone-suppressed burn wound model	[58]
Pistacia lentiscus	Fruit/virgin fatty oil	–	Deep third degree burn wound	Male New Zealand rabbit	In vivo	↑Wound contraction, ↓period of re-epithelialization	[13]
Plantago major	Seed/aqueous extract	–	Third degree burn wound	Male Sprague-Dawley rat	In vivo	↑Wound contraction, ↑re-epithelialization, ↑granulation, ↑tissue organization	[2]
Punica granatum	flower/ethanolic extract	–	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	No effect on wound contraction, no significant effect on re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]
Pterocarpus santalinus	Wood powder preparation	–	Thermal burn wound	Normal and diabetic rats	In vivo	↑Wound contraction, ↑collagenesis	[9]
Scrophularia deserti	Stem/ethanolic extract	–	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]

Table 1 continued

Scientific name	Part/extract	Active component	Model	Animal	Study design	Results	References
Sesamum indicum	Seed and seed oil/topical preparation	Sesamol, sesaminol, sesamolinol and sesamolin	Partial-thickness burn wound	Male albino Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization (seed oil had better effect than the seed and low doses were more potent)	[37]
Silybum marianum	Fruit/ND	Silymarin	Partial-thickness burn wound	Wistar albino rats of both sexes	In vivo	Topical and topical + oral administration : serum levels of ↓TNF-α and ↓LDH, ↓MDA, ↑GSH, ↓MPO, ↓thromboplastic activity, ↓reactive oxygen species, ↓burn-induced dermal degeneration	[69]
Tectona grandis	Frontal leaf/ hydroalcoholic extract	–	Thermal burn wound	Rat	In vivo	↑wound contraction, ↓period of re-epithelialization	[43]
Tephrosia purpurea	Aerial part/ flavonoid-rich fraction	Flavonoids	Partial-thickness and Full-thickness burn wound	Rat	In vivo	Partial-thickness: ↑wound contraction, ↑tensile strength Full-thickness: ↑hydroxyproline, ↑collagen fiber, ↑fibroblasts, ↑angiogenesis of wound tissue	[41]
Thymus sp.	Essential oil(diluted in olive oil)	–	Thermal burn wound	Male Sprague–Dawley rat	In vivo	↓Healing time, ↑formation of new tissue, ↓NO level	[16]
Tribulus terestris	Leaf/aqueous extract	–	Thermal burn wound	Rat	In vivo	↑Wound contraction, ↓period of re-epithelialization	[73]
Tridax procumbens	Leaf/ND	–	Partial-thickness burn wound and dexamethasone-suppressed burn wound models	Rat	In vivo	Oral and topical administration: ↑wound contraction, ↓period of re-epithelialization in both models	[6]

CAT catalase, *SOD* superoxide dismutase, *GSH* reduced glutathione, *MMP* matrix methaloproteinase, *MDA* malondialdehyde, *MPO* myeloperoxidase, *VEGF* vascular endothelial growth factor, *GPT* glutamate pyruvate transaminase, *GOT* glutamic oxaloacetic transaminase, *ALP* alkaline phosphatase, *EGFR* epidermal growth factor receptor, *MCP-1* Monocyte Chemoattractant Protein-1, *LPS* lipopolysaccharide, *AST* Aspartate transaminase, *ALT* Alanine transaminase, *BUN* blood urea nitrogen, *TNF-α* tumor necrosis factor, *HIF* hypoxia-inducible factor, *TGF-β* transforming growth factor β, *ND* not determined, *LDH* Lactate dehydrogenase, *ICR mouse* Imprinting Control Region mouse, *NO* nitric oxide; ↑, significant increase in mentioned variable; ↓, significant decrease in mentioned variable

Table 2 Multi-herbal preparations used for treatment of burn wound

Preparation name	Ingredients	Model	Animal	Study design	Results	References
Ampucare	*Azadirachta indica, Berberis aristata, Curcuma longa, Glycyrrhiza glabra, Jasminum officinale, Pongamia Pinnata, Rubia cordifolia, Terminalia chebula, Trichosanthes dioica, Symplocos racemosa, Ichnocarpus frutescens, Capsicum abbreviata, Nymphaea lotus*	Second-degree burn wound	Male Wistar rat	In vivo	↑Wound contraction, ↓NO, ↓xanthine oxidase activity, ↑protein level, ↑vit C, ↑reduced glutathione, ↓MDA in blood samples	[17]
Ampucare	*Azadirachta indica, Berberis aristata, Curcuma longa, Glycyrrhiza glabra, Jasminum officinale, Pongamia Pinnata, Rubia cordifolia, Terminalia chebula, Trichosanthes dioica, Symplocos racemosa, Ichnocarpus frutescens, Capsicum abbreviata, Nymphaea lotus*	Partial-thickness burn wound	Male Sprague-Dawley rat	In vivo	↑Wound contraction	[55]
–	*Malva sylvestris, Punica granatum, Amygdalus communis, Arnebia euchroma, Scrophularia deserti*	Thermal burn wound	Alloxan-induced diabetic male Wistar rat	In vivo	↑Wound contraction, ↓period of re-epithelialization, ↑collagenation, ↑fibroblasts, ↑angiogenesis, ↑extracellular matrix	[21]
–	*Achillea millefolium* honey	Thermal burn wound	Male white rabbit	In vivo	↑Wound contraction, ↓microbial count, no significant difference between single or combined form	[67]

MDA malondialdehyde, *NO* nitric oxide, ↑ significant increase in mentioned variable, ↓ significant decrease in mentioned variable

and 2 because they were cases of electrical burns. From 92 retrieved reports, 27 were excluded based on full text: 14 because they were plants in combination with non-herbal materials (fish scale, fish oil, honey), 7 because they evaluated the effect of plants on other types of wounds rather than burn wounds, 6 because the whole ingredients of the combination medicaments were not mentioned. Final results consist of 62 in vitro and in vivo reports, as well as 3 human studies. Among the 3 human studies, one gained Jadad score of 3 [44] and the other two obtained Jadad score of 0 [72] and 2 [57]. Figure 1 shows a diagram of study selection process.

Single herbal preparations

Achillea millefolium

A. millefolium aerial part possesses burn-induced wound healing function with reduction of microbial agent [61, 67].

Actinidia deliciosa

A. deliciosa fruit paste showed burn wound healing effect by keeping the wound moist, allowing enzymes to digest the scar and increasing debridement in a rat model [25]. It also decreased the inflammation and showed angiogenic, debridement, granulation and antimicrobial functions [46].

Table 3 Human studies on medicinal plants used for the treatment of burn wound

Scientific name	Part/extract	Model	Study design	Intervention	Jadad score	Control group treatment	Results	References
Aloe vera	Gel/topical preparation	Second-degree burn wound	Randomized controlled clinical trial	25 treated with *Aloe vera* gel twice daily and 25 with 1 % silver sulphadiazine cream twice daily until healing was complete. Final results were evaluated after 2 months of follow-up. *P* value <0.05 used to indicate statistical significance.	2	Silver sulphadiazine 1 %	↓Wound healing time, ↓re-epithelialization time, ↓rendering pain time in both groups; no difference in infection between two groups	[57]
Aloe vera	Gel/topical preparation	Partial-thickness burn wound	Placebo controlled clinical trial	27 treated with *Aloe vera* gel and 27 with vaseline gauze. The treatment was continued until complete healing was achieved. *P* value <0.002 used to indicate statistical significance.	0	vaseline gauze	↓Wound healing time and ↑re-epithelialization in Aloe group compared with that of vaseline gauze	[72]
Avena sp.	Oat meal	Wide range of burns with different depth	Assessor blind clinical trial	17 treated with Product A contained liquid paraffin with colloidal oatmeal 5 % and 17 with Product B contained only liquid paraffin for 30 days. *P* value <0.001 used to indicate statistical significance.	3	liquid paraffin	↓ itch and ↓antihistamine intake in Product A group compared with those in Product B	[44]

↑ Significant increase in mentioned variable, ↓ significant decrease in mentioned variable

Achyranthes aspera

A. aspera leaves exhibited wound healing activity by elevating antioxidant enzymes including SOD and CAT and pro-healing factors like protein and hydroxyproline content. Elevation of MMP-2 and 9 was also observed by gelatin zymography [8].

Allium sativum

In a study on Wistar rats, intraperitoneal administration of *A. sativum* bulb extract could reverse the oxidative responses to burn injury after 24 h in liver, intestine and lung tissue [56]. It also reduced microbial count in a dog model [60]. Ethanolic extract of the plant showed burn healing activity by decrease in microbial count in rabbit [62].

Alkanna tinctoria

Root topical preparation in olive oil showed healing potential in second-degree burn, but not in severe cases in rabbit model [48].

Aloe species

Burn healing and anti-inflammatory activity was observed in topical treatment with *A. barbadensis* and *A. littoralis* gel preparations [26, 42]. Although the most studied species of this genus is *Aloe vera* which the gel demonstrated burn wound healing potential by anti-inflammatory effect and increasing re-epithelialization and microcirculation [65, 28, 52, 72]. TNF-α, IL-6 and leukocyte adhesion were found to be decreased in a rat model of burn wound treated with *A. vera* gel [14]. A human study proved the efficacy of *A. vera* on second-degree burn wound patients [57]. It also showed antibacterial effect against *Klebsiella pneumoniae*, a nosocomial pathogen [39].

Alternanthera brasiliana

The leaf extract of the plant could enhance healing process of burn wound by increase in SOD, GSH, CAT, vit C, protein and hydroxyproline content of the damaged tissue [7].

Amygdalus communis

A. communis leaf extract could improve re-epithelialization, collagenation and angiogenesis in a diabetic rat model of burn injury [21].

Arnebia euchroma

Root and leaf extract of the plant showed wound healing activity by neovascularization, collagenation, anti-inflammatory effect and induction of fibroblast proliferation [4]. The root extract has also been proved to increase re-epithelialization, collagen synthesis, fibroblasts and extracellular matrix [21].

Astilbe thunbergii

A. thunbergii rhizome demonstrated burn healing properties. Phenolic compounds of ethyl acetate-soluble fraction including eucryphin, bergenin and astilbin were isolated as active components responsible for the pharmacological activity [35].

Avena sp.

Use of shower and bath oil containing 5 % colloidal oat meal in patients with partial-thickness burn showed significant reduction in itch in comparison with control group [44].

Bauhinia purpurea

Ethanolic extract of the plant has been proved to have dose-dependent wound healing activity in a rat model [3].

Brassica oleracea

B. oleraceae leaf extract showed burn healing function with increase in re-epithelialization and vascularization [27].

Calendula officinalis

Oral administration of flower extract of the plant exhibited burn-induced wound healing by elevating antioxidant defense mechanisms, as well as decrease in serum levels of liver biomarkers in rat. Hexosamine, hydroxyproline and protein content of the damaged tissue were also elevated [10].

Camellia sinensis

Leaf extract of *C. sinensis* was able to improve burn wound contraction by angiogenesis in rat model [31].

Carica species

C. cardamarcensis fruit latex proteolytic fraction (containing cysteine proteinases) could increase re-epithelialization in burn wound [22]. *C. papaya* fruit latex had burn healing effect by increasing re-epithelialization and hydroxyproline content of the damaged tissue [24].

Carissa spinarum

Root extract of the plant demonstrated burn healing potential via increase in re-epithelialization, stratification and polarity of epithelial cells and hydroxyproline content of the damaged tissue in two rodent species models. It also showed antimicrobial activity [54].

Celosia argentea

In vitro studies of *C. argentea* resulted in increase in cell motility and proliferation in primary human dermal fibroblasts, but not in human epidermal cells. The extract was also showed in vivo burn healing effect by elevation of collagen, hexosamine and hydroxyproline content of the burned tissue [49].

Centaurea sadleriana

Burn healing effects of different extracts and fractions of *C. sadleriana* were evaluated, and the most potent one was the *n*-hexane fraction of the methanolic extract [11].

Centella asiatica

Different extracts of *C. asiatica* aerial parts were investigated for burn healing activity, and all types of the extracts had positive effect on wound healing by increasing re-epithelialization and keratinization, also the most potent one was the ethylacetate extract [64]. Two glycosides (madecassoside and asiaticoside) and their corresponding aglycones (madecassic acid and asiatic acid) isolated from *C. asiatica* were tested for their in vitro and in vivo burn healing properties, which exhibited its stimulatory action on synthesis of collagen type I and III through activating fibroblasts via TGF-β in human skin fibroblast cells and also wound contraction in mice by madecassoside and asiaticoside [74]. Moreover, asiaticoside demonstrated in vitro burn healing activity by increasing VEGF and IL-1β production in macrophages. It also induced monocyte chemoattractant protein-1 (MCP-1) from the burn wound area, macrophage accumulation and VEGF-positive cells in the tissue surrounding the burn wound area in Balb/c mice [36]. Oral administration of madecassoside increased proliferation of fibroblasts and granulation tissue, hydroxyproline content, collagen synthesis and angiogenesis in burn wounds of ICR mice [40].

Cocos nucifera

Fruit inner flesh oil of *C. nucifera* could improve wound contraction and re-epithelialization in burn wound [66].

Crocus sativus

C. sativus pollen exhibited burn healing effect by decreasing inflammatory cells in rat model [33].

Datura alba

D. alba leaf demonstrated wound healing effect via increase in infiltration of inflammatory cells, angiogenesis, MMPs, collagen and hexosamine content of the granulation tissue and also showed antimicrobial activity against common burn wound pathogens [50].

Euphorbia hirta

Whole plant had burn healing potential in a rat model [29].

Ginkgo biloba

Intraperitoneal administration of the plant leaf extract reduced serum level of liver biomarkers and also improved antioxidant functions. Furthermore, it enhanced collagen content and reactive oxygen species levels of renal and hepatic tissue samples in a period of 24 h in second-degree burn wound rats [53].

Hippophae rhamnoides

Oral and topical administration of *H. rhamnoides* seed oil resulted in increase in tissue regeneration, GSH, MMP-2 and 9, VEGF, collagen type-III, DNA, total protein, hydroxyproline and hexosamine content in the granulation tissues, as well as decrease in reactive oxygen species and edema. Omega 3 and omega 6 fatty acids, tocopherols and carotenoids are probable active components of the oil [70]. The leaves were also showed in vivo burn healing effect by increasing re-epithelialization, MMP-2 and 9, VEGF, hydroxyproline, hexosamine, collagen type-III and antioxidant function. In vitro study in chick chorioallantoic membrane also demonstrated the angiogenic effect of the plant extract [71].

Lantana camara

Burn healing effect of *L. camara* leaf extract was investigated in a rat model. Although antimicrobial activity against *S. aureus*, *K. pneumoniae* and *E. coli* was observed, there was no significant difference in wound contraction between test and negative control group [47].

Malva sylvestris

Flower extract of *M. silvestris* showed burn healing activity in diabetic rat by increasing re-epithelialization, collagenation, fibroblasts and angiogenesis [21].

Matricaria chamomilla

Aerial parts of *M. chamomilla* could improve wound healing process in a rat model of burn wound [30].

Michelia champaca

Oral and topical administration of *M. champaca* flower extract resulted in increase in wound contraction and re-epithelialization in a rat model of burn wound and dexamethasone-suppressed burn wound [59].

Musa sp.

In an open controlled study with 30 patients, banana leaf dressing could improve feeling comfort and handling dressing with less pain [23].

Nigella sativa

N. sativa seed oil was effective on burn wound with increase in thickness of granulation tissue and re-epithelialization [75].

Olea sp.

Purified olive oil was investigated for treatment of partial-thickness porcine burns, but there was no significant difference between treatment and negative control groups [23].

Onosma dichroanthum

Root of *O. dichroanthum* showed negative effect on healing process of burn wound in rats [45].

Otostegia persica

O. persica aerial parts exhibited burn healing effect by increasing re-epithelialization, angiogenesis, and collagen accumulation and suppressing inflammation [20].

Panax ginseng

In vitro and in vivo burn healing activities of six ginsenosides isolated from root of *P. ginseng* were investigated in human keratinocyte cell line and mice, respectively. The strongest wound healing effect was observed with Rb1 by increasing angiogenesis, VEGF and hypoxia-inducible factor-1α (HIF-1α) expression in keratinocytes [32, 34].

Phyllanthus niruri

Topical and oral administration of *P. niruri* ethanolic extract could increase re-epithelialization in a rat model of dexamethasone-suppressed burn wound, but not in normal burn wound model [58].

Pistacia lentiscus

Fruit virgin fatty oil of *P. lentiscus* demonstrated burn healing effect with increase in re-epithelialization in rabbit [13].

Plantago major

P. major seed had healing potential of burn wound by improving tissue organization, re-epithelialization and granulation [2].

Punica granatum

P. granatum flower extract was investigated for burn healing properties in diabetic rat, but it had no effect on wound contraction and period of re-epithelialization although it was effective on collagenation, fibroblasts, angiogenesis, neutrophils and extracellular matrix [21].

Pterocarpus santalinus

Wood powder preparation of *P. santalinus* exhibited burn healing effect in normal and diabetic rats by increasing collagenesis [9].

Scrophularia deserti

S. deserti stem showed burn healing effect in a model of diabetic rat with increase in re-epithelialization, collagenation, fibroblasts, angiogenesis and extracellular matrix [21].

Sesamum indicum

S. indicum seed, seed oil and a mixture of them were effective for healing process of burn wound. The burn healing effects were reversely dose dependent, and better results were obtained by the oil [37].

Silybum marianum

Topical and oral plus topical administration of silymarin (active component of *S. marianum*) showed stimulatory function on antioxidant responses, thromboplastic activity and also dermal regeneration on damaged tissue [69].

Tectona grandis

T. grandis frontal leaves showed burn healing effect by increasing re-epithelialization [43].

Tephrosia purpurea

Flavonoid-rich fraction of *T. purpurea* aerial parts demonstrated wound healing effect in full-thickness and partial-thickness burns by increasing hydroxyproline, collagen fiber, fibroblasts and angiogenesis and improving tensile strength, respectively [41].

Thymus sp.

Thymus essential oil could help burn healing process with reduction of nitric oxide (NO) level and induction of new tissue formation [16].

Tribulus terestris

T. terestris leaves were able to improve re-epithelialization on burn wound in rat model [73].

Tridax procumbens

Oral and topical administration of *T. procumbens* extract resulted in increase in re-epithelialization both in partial-thickness and dexamethasone-suppressed burn wounds [6].

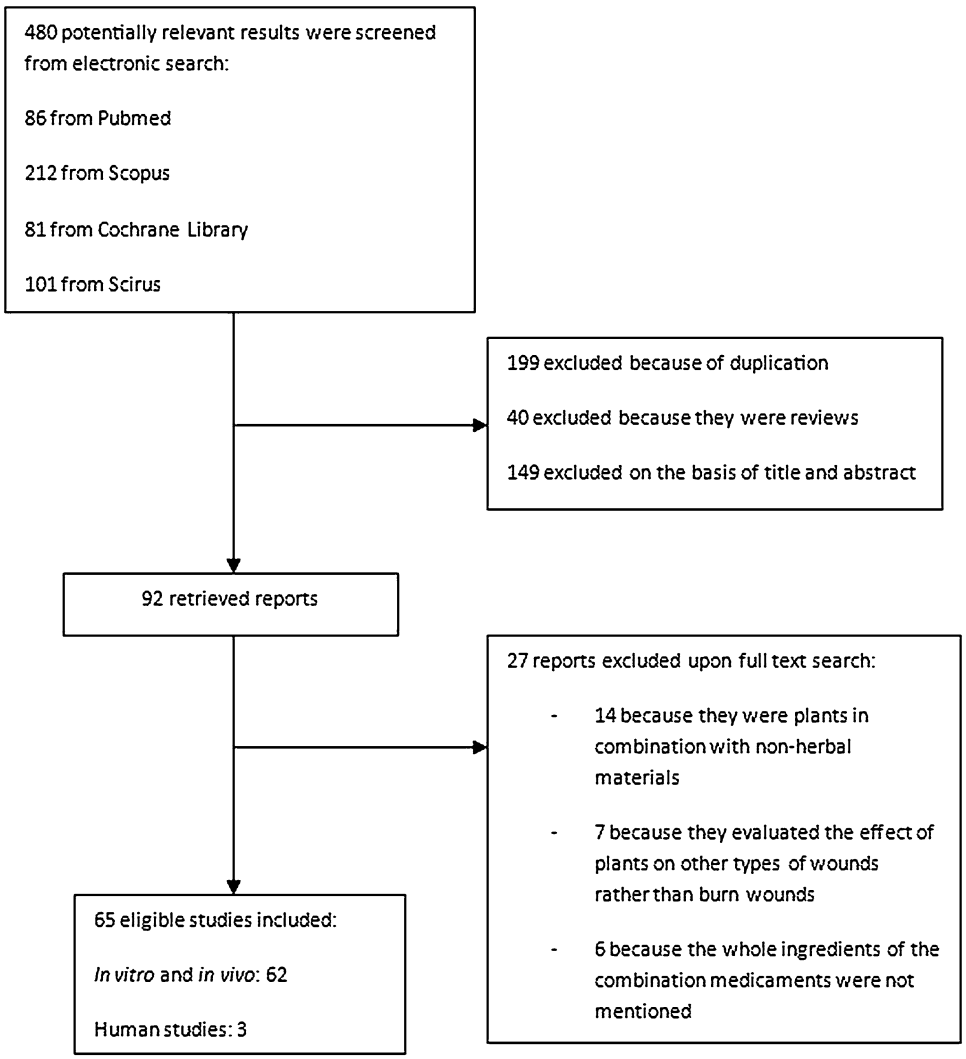

Fig. 1 Flow diagram of study design

Multi-component herbal preparations

Ampucare

Ampucare is a topical oil-based preparation containing *Azadirachta indica, Berberis aristata, Curcuma longa, Glycyrrhiza glabra, Jasminum officinale, Pongamia pinnata, Rubia cordifolia, Terminalia chebula, Trichosanthes dioica, Symplocos racemosa, Ichnocarpus frutescens, Capsicum abbreviata, Nymphaea lotus* etc. Application of ampucare in second-degree burn showed burn healing effect with enhancement of antioxidant function, NO level, as well as increase in protein level and vitamin C in rats [17, 55].

Combination of five Iranian medicinal plants

A combination of *M. sylvestris*, *P. granatum, A. communis, A. euchroma* and *S. deserti* was topically effective in burn wounds of diabetic rats by increasing re-epithelialization, collagenation, fibroblasts, angiogenesis and extracellular matrix. Although the best results were obtained by *A. communis* extract [21].

Conclusion

The aim of the present study was to evaluate different single and multi-component herbal preparations investigated for burn wound healing properties. Following are the most recommended plants to treat burn wound according to the results represented in Tables 1, 2 and 3.

Among single herbal preparations, *A. sativum*, *A. vera*, *C. asiatica* and *H. rhamnoides* had best evidences for their wound healing effect via different mechanisms. Moreover, in combined herbal preparations, ampucare was the most potent one by stimulating wound contraction and antioxidant defense mechanisms.

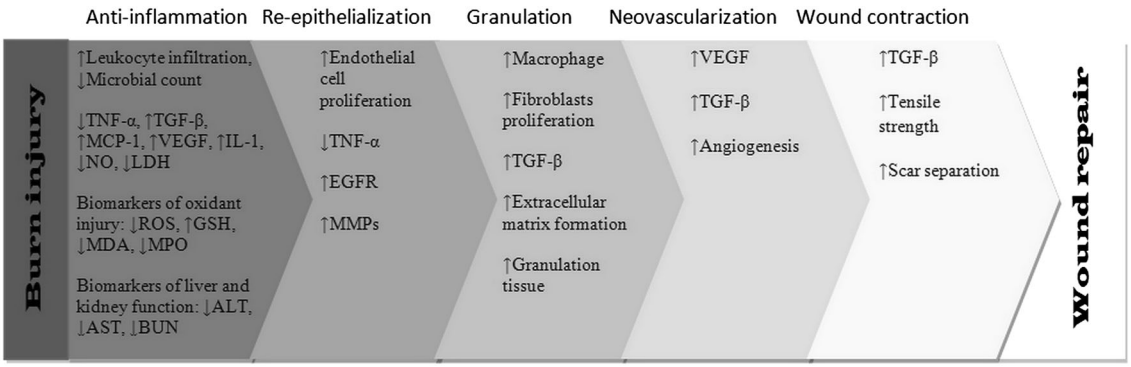

Fig. 2 Role of phytochemicals in different stages of burn wound healing process

In human studies, only clinical trials were included since they provide reliable evidences in comparison with other types of clinical studies like case reports or case studies. One of the limitations of present study was the small number of clinical trials included, and most of included studies were in vitro or in vivo. Furthermore, small sample size of clinical studies is another limitation. So the first recommendation is to complete efficacy and safety profile of these plants and then go through clinical trials to prove their efficacy. Since the included studies involved different plants with different phytochemical profiles, heterogeneity could be considered as another limitation of this study.

Only three human studies were found to include in this review that shows the necessity of more clinical trials to prove the plant's potential for burn wound healing. A 2-month randomized controlled clinical trial on 50 second-degree burned patients showed beneficial effects of *A. vera* gel preparation in comparison with silver sulphadiazine cream by reducing wound contraction and re-epithelialization time, although there were no differences in infection [57]. Another placebo controlled clinical trial on 27 partial-thickness burned patients confirmed *A. vera* gel potential for burn wound [72]. An assessor blind clinical trial on 35 patients showed itch reduction effect of shower and bath oil containing 5 % oat meal in comparison with liquid paraffin [44]. Among these three studies, only one had high methodological quality according to Jadad score [44] and the other two did not possess high methodological quality [57, 72]. Because of low number of human studies and their various limitations such as small number of patients, low methodological quality, and being single-center, the levels of evidence for this review are low. More clinical trials with greater number of patients and high methodological quality are needed to obtain more conclusive results from the efficacy of medicinal plants in burn wounds.

Studies on electrical burns were not included since they have different pathology from thermal skin damages. Fish oil, fish scale, honey, crocodile oil, fly larva, fungi and other non-herbal preparations were excluded because the goal of this study was limited to evaluate the effect of herbal materials. Some studies on herbal combinations were excluded because the exact ingredients of the preparation were not described in the article or one of the ingredients had non-herbal source.

A. sativum could decrease infection and biomarkers of organ damage. Several studies supported anti-inflammatory and antibacterial effects of *A. vera* gel. Glycosides of *C. asiatica* including madecassoside and asiaticoside showed in vitro and in vivo improvement in biochemical and histological markers of burn wound. Preparations of different parts of *H. rhamnoides* increased collagen synthesis and angiogenesis. In some plants including *Actinida* and *Papaya* species, proteolytic enzymes were active components with debridement effect.

Eucryphin, bergenin, astilbin, madecassoside, asiaticoside, omega-3 and omega-6 fatty acids, tocopherols, carotenoids, ginsenoside Rb1, sesamol, sesaminol, sesamolinol, sesamolin, silymarin and debridement enzymes were identified active phytochemicals with potential wound healing function and could be considered as novel natural agents. Table 1 shows the phytochemicals and related medicinal plants in detail.

In contrast, *Lantana camara* extract and *Olea* sp. oil could not increase wound contraction significantly in comparison with negative control group. *Onosma dichroanthum* had a negative performance on healing process of burn wound.

Wound healing process consists of inflammation, re-epithelialization, granulation and neovascularization, which result in wound contraction. Phytochemicals can affect various stages of this process via different mechanisms including elevation of TGF-β, MCP-1, VEGF, IL-1 and reduction of NO, LDH and ROS, as well as improving antioxidant poverty of tissues and organs in inflammatory phase, increase in EGFR, MMPs and endothelial cells proliferation during re-epithelialization, improve in proliferation of damaged tissue cells in granulation, improve angiogenesis by elevating mediators like VEGF and TGF-β

that finally results in reduction of wound contraction time. Figure 2 shows various mechanisms by which phytochemical constituents exhibit their beneficial effects in burn wound healing.

Safety of plants with wound healing properties should be assessed based on international safety guidelines because of their vast variety of phytochemicals potentially able to be toxic or allergic for damaged dermal cells; however, most of the mentioned plants were prepared in a topical form that reduces the risk of toxicity. On the other hand, according to mentioned in vitro studies, some of these preparations were not only harmful, but also beneficial for dermal cells proliferation and repair.

According to traditional medicine of different countries, including Iranian traditional medicine, there are lots of medicinal plants which potentially possess burn wound healing effect. *Malva* spp., *Althaea officinalis, Sambucus ebulus, Olea europaea, Cupressus sempervirence, Pinus* sp., *Tragopogon graminifolius, Hypericum perforatum, Iris* spp., *Cucurbita maxima, Cucurbita pepo, Plantago major* and *Arnebia euchroma* are examples of the plants mentioned in text books of Iranian traditional medicine [1, 5]. Previously, anti-ulcer function of these herbs have been verified in various experimental studies, and it is exhibited that their healing activity on gastrointestinal ulcer is via several mechanisms of action including antioxidant, wound healing, antimicrobial, anti-secretory, immunomodulatory, cytoprotective and angiogenic effect [18, 19]. Further modern studies in order to exploring their wound healing mechanisms of action and responsible active components are suggested to be done.

In conclusion, several herbal medicaments possess efficacious action for the management of wounds—particularly burn wounds—and can be considered as an alternative source of treatment. Furthermore, various phytochemical agents exhibited wound healing function. Phytochemicals showed their positive activity at different stages of burn wound healing process by various mechanisms including antimicrobial, anti-inflammatory, antioxidant, collagen synthesis stimulation, cell proliferative and angiogenic effects. Advanced clinical and pharmaceutical studies are recommended in order to the production of novel natural drugs for burn wound treatment.

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