



# An Evidence-Based Review on Wound Healing Herbal Remedies From Reports of Traditional Persian Medicine

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## Abstract

Research on wound healing agents is a developing area in biomedical sciences. Traditional Persian medicine is one of holistic systems of medicine providing valuable information on natural remedies. To collect the evidences for wound-healing medicaments from traditional Persian medicine sources, 5 main pharmaceutical manuscripts in addition to related contemporary reports from Scopus, PubMed, and ScienceDirect were studied. The underlying mechanisms were also saved and discussed. Totally, 65 herbs used in traditional Persian medicine for their wound healing properties was identified. Related anti-inflammatory, antioxidant, antimicrobial, and wound-healing activities of those remedies were studied. Forty remedies had at least one of those properties and 10 of the filtered plants possessed all effects. The medicinal plants used in wound healing treatment in traditional Persian medicine could be a good topic for further in vivo and clinical research. This might lead to development of effective products for wound treatment.

## Keywords

medicinal plants, Persian medicine, wound healing

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Research on wound healing agents is a developing area in biomedical sciences. Skin wounds affect the quality of life of the patients significantly<sup>1</sup> and are considered as one of major causes of physical disabilities. At the moment the available treatments are suboptimal. Skin wounds are defined as any interruption of the continuity of body surface.<sup>2</sup> They can be result of many conditions such as burns, surgeries, trauma, and arterial disease. It can either be a chronic or acute condition. A wound is called chronic when it requires a prolonged time to heal or does not heal. Given the wide range of their causes, their accurate incidence and impact are difficult to be calculated. Chronic wounds are often progressive and resistant to treatments.<sup>2</sup>

Wound healing is a complex process, which includes coordination between diverse immunological and biological systems.<sup>3</sup> In the past 20 years, our knowledge on wound healing process has improved.<sup>4</sup> Normally in an acute wound the process of healing is predictable. It includes the initial inflammation, deposition of collagen and fibroblast, formation of new blood vessels or angiogenesis, contraction of the wound area, and scar remodeling.<sup>3</sup> The inflammatory process has direct effects on wound healing. Lipid mediators of inflammation involving wound healing are transforming growth factor- $\beta$  and prostaglandin E2.<sup>5</sup> Collagen is the major component that supports the extracellular tissue in wound healing process.<sup>6</sup> Research has shown that NO (nitric oxide) has a positive effect on wound healing by accelerating fibroblast migration and

collagen deposition in wound tissue.<sup>7</sup> Promotion of antioxidant defense proteins such as heme oxygenase-I and keratinocyte growth factor could have a positive effect on wound healing by protecting the regenerating tissue against oxidant damage.<sup>8</sup>

In chronic wounds, the repair process has been disrupted by conditions such as infection or low immunity.<sup>3</sup> Such wounds enter a state of inflammation if the microbial clearance is incomplete. Bacteria and endotoxins can lead to pro-inflammatory cytokines elevation (interleukin-1 and tumor necrosis factor- $\alpha$ ) if this process continues, the wound may fail to heal.<sup>9</sup>

This chronic state is a challenging clinical condition which affects 6 million patients annually. Today there are a variety of treatment options for chronic wounds and many of them are ineffective. There is increasing number of products in this area

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at considerably high costs.<sup>2</sup> Various herbal constituents have proven wound-healing properties. As an example, tannins could promote wound healing through free radical removal, increasing the contraction of the affected area and increasing the formation of blood vessels and fibroblasts. Other active principles such as triterpenes, alkaloids, and flavonoids have proven to be effective in this process.<sup>10</sup>

Traditional systems of medicine provide valuable information on natural remedies. They have played a significant role in discovering novel drug leads.<sup>11</sup> Today, traditional and alternative remedies are used to treat many chronic conditions in developed countries. This could be due to the lack of effective modern remedies for chronic conditions. Traditional systems of medicine usually have a holistic approach and provide us with many remedies for various chronic medical conditions. These systems of medicine provide remedies for treating wounds as well. Over the past few decades, we have observed increasing interest in researches based on traditional medicines of the world.<sup>12</sup> Researchers are hoping to find new drug leads hidden in the formulations of traditional systems of medicine. Traditional Persian medicine has a rich background of practice from the ancient Persia until today.<sup>13</sup> The ingredients used in this system of medicine as wound remedies could be an interesting subject for further research.

## Materials and Methods

To collect the data from medicinal medieval texts, 5 main pharmaceutical manuscripts of Persian medicine were studied for plants used in wound healing. The studied books include: *Kitāb al-hāwī fī al-tibb* (*The Comprehensive Book on Medicine*) by Rhazes (9th-10th centuries), *Canon of Medicine* by Avicenna (10th-11th century), *Ikhtiyārāt-i Badī'ī* (*Selections for Badī'ī*) by Hājji Zayn al-'Attār (14th century), *Tuhfat al-mu'minīn* (*Present for the Faithful*) by Daylamī Tunakābunī (17th century), and *Makhzan al-adviyah* (*The Storehouse of Medicaments*) by Alavī Shīrāzī (18th century).<sup>14-18</sup> The plants used in wound healing according to Persian manuscripts are listed in Table 1. Authentications of the plants were confirmed according to botanical textbooks such as *Dictionary of Medicinal Plants*, *Matching the Old Medicinal Plant Names With Scientific Terminology*, *Indian Medicinal Plants*, and *Dictionary of Iranian Plant Names*.<sup>19-21</sup>

Databases such as PubMed and ScienceDirect were searched for mechanisms or pharmacological activities of reported medicinal plants in the field of wounds healing and discussed. Thus, each herb was searched along with keywords, “wound healing,” “antimicrobial,” “antioxidant or radical scavenging,” and “anti-inflammatory.” From numerous articles, the current work tried to cite latest publications with regard to each reported plant.

## Results

In the 5 traditional books that we searched, a total number of 65 herbs that were used in traditional Persian medicine for their wound-healing properties could be identified (Table 1). From this number, 40 herbs had at least 1 of the searched mechanisms of action or pharmacological functions. These 40 herbs belong to 34 families (Table 2). Although the familial distribution is sporadic but Apiaceae and Lamiaceae have the highest share of

3 herbs each among the plant families found. We introduced 10 herbs derived from traditional Persian medicine whose wound-healing properties have been proven by modern medicine. In the next step, we highlighted the herbs that had the 3 searched mechanisms of action related to the wound-healing process. In this regard, we found 9 herbs whose wound-healing properties have been shown by modern research, with their antioxidant, antimicrobial, and anti-inflammatory properties could be attributed to the underlying mechanism of action. There were also 9 herbs that were studied for the 3 mechanisms of action related to wound healing and showed positive effect but their wound-healing properties have not been studied yet.

## Discussion and Conclusion

Despite of the new advances in the field of medicine there are conditions such as chronic wounds, which have high incidence and economic burden but their management is far from effective. As a result, there is urgent need of novel therapies for these conditions.<sup>22</sup> Today, researchers are interested to study traditional systems of medicine to find remedies for the current medical issues. One of these systems is traditional Persian medicine, which is still being practiced in Iran. To investigate the herbs that have the potential of further clinical research, we reviewed traditional Persian texts and compared them with the modern published work in this area.

The 9 plants that were considered as wound remedies by traditional Persian medicine and had positive effect on wound healing in the modern research were *Cocos nucifera* L, *Commiphora mukul* (Hook ex Stocks) Engl, *Gentiana lutea* L, *Teucrium polium* L, *Punica granatum* L *Plantago major* L, *Adiantum capillus-veneris* L, *Aloe vera* (L) Burm f and *Potentilla reptans* L. These 9 herbs also have been studied for the 3 mechanisms of actions related to wound healing, which we searched. All these herbs showed antioxidant properties in the modern research. Antioxidants have a positive effect on wound healing by protecting the regenerating tissue.<sup>8</sup> *Aristolochia rotunda* L was another plant used in traditional Persian medicine for its wound-healing properties. It did not have proven antioxidant, antimicrobial, and anti-inflammatory properties but is studied for its positive effect on wound-healing process. Its collagenase activity was demonstrated by collagen zymography and atomic force microscopy studies.<sup>23</sup>

The fruit of *Cocos nucifera* L has been shown to have positive effect on wound-healing process when its effect on epithelium cell thickening was observed by Zakaria et al<sup>24</sup> in an animal study. In this study, fresh juice and aqueous extract of the plant were used and the length, color, and inflammatory aspects of the area around the wound were also examined. In another study, methanol extract of the fruit had antibacterial effect against *Staphylococcus* spp.<sup>25</sup> Today, we know the implication of these microorganisms in delayed wound healing.<sup>26</sup>

The exudate of *Commiphora mukul* (Hook ex Stocks) Engl was mentioned in traditional Persian medicine books as an effective treatment for different types of wounds. In a clinical study, a mouthwash prepared from the exudate of this plant was

**Table 1.** Topical Remedies for Different Wounds From Reports of Traditional Persian Medicine.

Family	Scientific Name	Traditional Name	Part Used
Amaranthaceae	<i>Beta vulgaris</i> L	Selgh	Root
Amaryllidaceae	<i>Allium porrum</i> L	Koras	Leaf
Anacardiaceae	<i>Rhus coriaria</i> L	Somagh	Fruit
Apiaceae	<i>Opopanax chironium</i> WDJ Koch	Javsheir	Aerial part
	<i>Prangos ferulacea</i> (L) Lindl	Jaavosheir	Aerial part
	<i>Coriandrum sativum</i> L	Kozbore	Leaf, Seed
Araceae	<i>Arisarum vulgare</i> O Targ Tozz	Loaf	Leaf, Seed
Arecaceae	<i>Phoenix dactylifera</i> L	Tamr	Fruit
	<i>Cocos nucifera</i> L	Nargil	Fruit
Aristolochiaceae	<i>Aristolochia rotunda</i> L	Zaravand	Root
Asparagaceae	<i>Ornithogalum narbonense</i> L	Ashraas	Seed
Asteraceae	<i>Carlina gummifera</i> (L) Less	Eshkheis	Leaf
	<i>Arctium tomentosum</i> Mill	Argheitoun	Leaf
	<i>Tanacetum parthenium</i> (L) Sch Bip	Oghhovan	Aerial part
	<i>Heracleum persicum</i> Desf ex Fischer	Safeidoulion	Flower
Boraginaceae	<i>Arnebia afghanica</i> (Kitam) Rech f and Riedl	Abokhalsa	Flower
Brassicaceae	<i>Raphanus sativus</i> L	Fojl	Leaf, Seed
Burseraceae	<i>Boswellia sacra</i> Flueck	Kondor	Exudate
	<i>Commiphora mukul</i> (Hook ex Stocks) Engl	Maghal	Exudate
Convolvulaceae	<i>Ipomoea nil</i> (L) Roth	Habb-ol-nil	Seed
Crassulaceae	<i>Sempervivum tectorum</i> L	Abroan	Flower
Cupressaceae	<i>Juniperus sabina</i> L	Abhol	Fruit, Leaf
Fabaceae	<i>Lupinus aberrans</i> C P Sm	Termes	Seed
	<i>Calicotome spinosa</i> (L) Link	Darshishaan	Fruit
	<i>Senna alexandrina</i> Mill	Sana maki	Leaf
	<i>Vicia ervilia</i> (L) Willd	Karasne	Leaf, Seed
	<i>Lablab purpureus</i> (L) Sweet	Lablab	Leaf
	<i>Baptisia tinctoria</i> (L) Vent	Neil	Leaf
	<i>Lathyrus aphaca</i> L	Banghe	Seed
Fagaceae	<i>Quercus ilex</i> L	Baloot	Fruit, Leaf
	<i>Quercus lusitanica</i> Lam	Afs	Fruit
Gentianaceae	<i>Gentiana lutea</i> L	Jentiana	Leaf, Root
Iridaceae	<i>Crocus sativus</i> L	Zaferan	Flower
Juglandaceae	<i>Juglans regia</i> L	Jowz	Seed (Juice)
Lamiaceae	<i>Teucrium polium</i> L	Joode	Aerial part
	<i>Teucrium chamaedrys</i> L	Komazairoos	Aerial part
	<i>Ajuga chamaepitys</i> (L) Schreb	Komafeytoos	Flower, Leaf
Lauraceae	<i>Cinnamomum camphora</i> (L) J Presl	Kafour	Leaf
Liliaceae	<i>Lilium candidum</i> L	Soosan	Root
Loranthaceae	<i>Loranthus europaeus</i> Jacq	Debgh	Seed
Lythraceae	<i>Punica granatum</i> L	Romman	Fruit
Moraceae	<i>Morus alba</i> L	Toot	Fruit
Oxalidaceae	<i>Oxalis acetosella</i> L	Hammaz	Leaf, Root
Pinaceae	<i>Pinus albicaulis</i> Engelm	Sanoubar	Leaf
Plantaginaceae	<i>Plantago major</i> L	Lesan-ol-hamal	Leaf, Flower
Polygonaceae	<i>Polygonum aviculare</i> L	Asioraie	Leaf
Potamogetonaceae	<i>Potamogeton natans</i> L	Jaronahr	Leaf
Primulaceae	<i>Anagallis arvensis</i> L	Anaghalls	Leaf
Pteridaceae	<i>Adiantum capillus-veneris</i> L	Barsiavashan	Aerial part
Ranunculaceae	<i>Thalictrum acutifolium</i> (Hand-Mazz) B Boivin	Piaranga	Root
	<i>Aconitum ferox</i> Wall ex Ser	Beesh	Root
	<i>Ranunculus arvensis</i> L	Kafolhar	Leaf, Flower
Rhamnaceae	<i>Ziziphus jujuba</i> Mill	Onnab	Leaf
Rosaceae	<i>Potentilla reptans</i> L	Bentaafalon	Leaf
Salicaceae	<i>Salix babylonica</i> L	Gharab	Leaf, Flower
Smilacaceae	<i>Smilax china</i> L	Choob-e-chini	Leaf, Root
	<i>Smilax glauca</i> Walter	Oshbe maghrebie	Leaf, Flower
Solanaceae	<i>Lycium afrum</i> L	Osaj	Root

(continued)

**Table 1.** (continued)

Family	Scientific Name	Traditional Name	Part Used
Verbenaceae	<i>Nicotiana tabacum</i> L	Tanbako	Leaf
	<i>Physalis alkekengi</i> L	Kakanj	Fruit
	<i>Solanum americanum</i> Mill	Enab-ol-saalab	Leaf, Fruit
	<i>Verbena supina</i> L	Ayaranootani	Leaf
	<i>Verbena officinalis</i> L	Alhamam	Leaf
Xanthorrhoeaceae	<i>Asphodelus ramosus</i> L	Khonsa	Root
	<i>Aloe vera</i> (L.) Burm f	Sebr	Leaf exudate

**Table 2.** Related Pharmacological Activities of Remedies Filtered From Traditional Persian Medicine Manuscripts.

Scientific Name	Assay(s) and Outcomes (Fraction or Extract)
<i>Adiantum capillus-veneris</i>	– AO: DPPH (crude flavonoids extract) <sup>48</sup> – AM: <i>Candida</i> , <i>Trichoderma</i> , <i>Aspergillus</i> spp (methanol and ethanol extract) <sup>42</sup> – AI: Inhibiting the NF-κB activation (ethanol extract) <sup>49</sup> – WH: Angiogenic effects (aqueous fraction of methanol extract) <sup>41</sup>
<i>Ajuga chamaepitys</i>	– AO: DPPH, NBT, OH, and chelating (chloroform and methanol extracts) <sup>50</sup> – AM: <i>Pseudomonas</i> spp. (methanol extract) <sup>50</sup>
<i>Allium porrum</i>	– AO: DPPH (ultrasonic and ethanol extracts) <sup>51</sup> – AM (weak activity): multiresistant <i>Staphylococcus</i> spp. (leaf ether extract) <sup>52</sup>
<i>Aloe vera</i>	– AO: DPPH, ABTS (lyophilized powder) <sup>53</sup> – AM: <i>Trichophyton</i> , <i>Aspergillus</i> spp. (ethanol, acetone extracts) <sup>45,54</sup> – AI: Downregulation of MMP-9 in blood cells (aqueous extract) <sup>55</sup> – WH: Accelerating the burn healing time and epithelialization (gel topical application) <sup>44</sup>
<i>Arisarum vulgare</i>	– AO: ABTS and DPPH (methanol water and subfractions) <sup>56</sup>
<i>Aristolochia rotunda</i>	– WH: gelatinolytic, collagenase and protease inhibitory potencies (aristolochic acid, protein fraction) <sup>23</sup>
<i>Beta vulgaris</i>	– AO: Thiocyanate and DPPH (methanol extract) <sup>57</sup> – AI: carrageenan-induced rat paw edema method (ethanol extract) <sup>58</sup>
<i>Boswellia sacra</i>	– AO: DPPH (methanol apolar subfractions) <sup>59</sup> – AM: <i>Staphylococcus</i> spp. (essential oil and methanol extracts) <sup>60</sup> – AI: Lipoxygenase inhibitor (terpenoids of resin, acetyl-11-keto-β-boswellic acid) <sup>61</sup>
<i>Cinnamomum camphora</i>	– AO: NO and LP (methanol water extract) <sup>62</sup> – AM: <i>Staphylococcus</i> spp. (essential oil) <sup>63</sup> – AI: Modulation of cytokines, NO and PG-E <sub>2</sub> production (ethyl acetate fraction of 80% methanol extract) <sup>62</sup>
<i>Cocos nucifera</i>	– AO: DPPH, FRAP, and deoxyribose (methanol extract) <sup>25</sup> – AM: <i>Staphylococcus</i> spp (methanol extract) <sup>25</sup> – AI: Formalin-caused paw thickness edema (fresh juice and aqueous extract) <sup>24</sup> – WH: The epithelium cell thickening observed (fresh juice and aqueous extract) <sup>24</sup>
<i>Commiphora mukul</i>	– AO: Thiocyanate (ethyl acetate extract) <sup>64</sup> – AM: Gram-positive and -negative (essential oil, chloroform extract, and 7 sesquiterpenes) <sup>65</sup> – AI: (steroidal fraction: guggulsterone Z) <sup>66</sup> – WH: Promote healing in less than 2 weeks (myrrh suspension) <sup>27</sup>
<i>Coriandrum sativum</i>	– AO: DPPH, OH, and LP inhibition (essential oil) <sup>67</sup> – AM: <i>Streptococcus</i> spp. (essential oil) <sup>68</sup>
<i>Crocus sativus</i>	– AO: DPPH, ABTS (crocin and kaempferol) <sup>69</sup> – AM: <i>Streptococcus</i> spp. (methanol stigma extract) <sup>70</sup>
<i>Gentiana lutea</i>	– AO: DPPH, MPO inhibition (water and ethanol aqueous) <sup>71</sup> – AM: Gram-positive and -negative (methanol extract, mangiferin, isogentisin and gentiopicrin) <sup>31</sup> – AI: inflammation-induced rats and mice (ethanol and petrol-ether extract) <sup>30</sup> – WH: 300 and 500 mg/kg (ethanol and petrol-ether extract) <sup>30</sup>
<i>Heracleum persicum</i>	– AO: LP (ethyl acetate extract, furanocoumarins) <sup>72</sup> – AM: <i>Bacillus anthracis</i> (essential oil) <sup>73</sup> – AI: carrageenan-induced rat paw edema (essential oil and hydroalcoholic extract) <sup>74</sup>
<i>Juniperus sabina</i>	– AO: TBARS and ABAP (essential oils) <sup>75</sup> – AM: weak activity on <i>Staphylococcus</i> spp., <i>Candida</i> and <i>Bacillus subtilis</i> (essential oil) <sup>76</sup>
<i>Lathyrus aphaca</i>	– AO: DPPH, ABTS (methanol and buffer extracts) <sup>77</sup>
<i>Lilium candidum</i>	– AO: DPPH (methanol extract) <sup>78</sup>
<i>Loranthus europaeus</i>	– AO: DPPH, FRAP (ethyl acetate and methanol extracts) <sup>79</sup>

(continued)

Table 2. (continued)

Scientific Name	Assay(s) and Outcomes (Fraction or Extract)
<i>Morus alba</i>	– AO: reduction in lipid peroxidation product in animal model (freeze-dried powder) <sup>80</sup> – AI: carrageenan-induced model of inflammation (mulberroside A and oxyresveratrol) <sup>81</sup>
<i>Ornithogalum narbonense</i>	– AO: DPPH, ABTS, FRAP, and CUPRAC (ethyl acetate, methanol, and water) <sup>82</sup>
<i>Oxalis acetosella</i>	– AO: DPPH (methanol extract) <sup>83</sup>
<i>Phoenix dactylifera</i>	– AO: TEAC, ABTS, FRAP (methanol water extract) <sup>84</sup> – AM: <i>Bacillus subtilis</i> , <i>Staphylococcus</i> (water and ethanol extracts) <sup>85</sup>
<i>Physalis alkekengi</i>	– AO: DPPH, OH, NBT (polysaccharides from hot water extract) <sup>86</sup> – AM: Gram-positive (methanol extract and physalin D) <sup>87</sup> – AI: inhibition of MMP-9 and AP-1 activation (methanol extract) <sup>88</sup>
<i>Plantago major</i>	– AO: DPPH (methanol extract) <sup>48</sup> – AM: <i>Staphylococcus aureus</i> (aqueous extract) <sup>39</sup> – AI: COX-2 mRNA expression inhibitor (acteoside and geniposidic acid) <sup>40</sup> – WH: ex vivo porcine wound-healing model (freeze-dried ethanol-based extracts) <sup>38</sup>
<i>Polygonum aviculare</i>	– AO: DPPH, LP, NBT (lyophilized ethanol extract) <sup>89</sup> – AM: <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> (chloroform extract) <sup>90</sup> – AI: inhibition of elastase release, in vitro (flavonol and isorhamnetin glucuronides) <sup>91</sup>
<i>Potentilla reptans</i>	– AO: DPPH (aqueous extract) <sup>46</sup> – AM: <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i> (ethanol root extract) <sup>53</sup> – AI: phenol-in-acetone induced mice ear edema (rhizome aqueous extract) <sup>46</sup> – WH: Indirect by inhibition of wound pathogens growth (75% ethanol extract) <sup>47</sup>
<i>Prangos ferulacea</i>	– AO: DPPH and LP inhibition (methanol extract) <sup>92</sup> – AM: <i>Staphylococcus</i> spp, <i>Pseudomonas</i> spp (essential oil) <sup>93</sup>
<i>Punica granatum</i>	– AO: DPPH, ABTS (polysaccharide fraction) <sup>94</sup> – AM: <i>Staphylococcus</i> spp (tannin-rich fractions, ellagitannins, phenolic acids) <sup>37</sup> – AI: carrageenan-induced mice paw edema, NO inhibition (peel and fruit extracts) <sup>36</sup> – WH: In alloxan-induced diabetic rats by collagen regeneration (peel polyphenol gel) <sup>35</sup>
<i>Quercus ilex</i>	– AI: topical effect (isolated flavonoids) <sup>95</sup>
<i>Ranunculus arvensis</i>	– AO: DPPH, OH, phosphomolybdenum (methanol extract: Rutin) <sup>96</sup> – AM: Moderate effect on <i>Staphylococcus</i> spp, <i>Candida</i> (essential oil) <sup>97</sup>
<i>Raphanus sativus</i>	– AO: OH, NO, DPPH (methanol extract) <sup>98</sup> – AM: Gram-positive and -negative (seed methanol extract) and <i>Staphylococcus</i> spp, <i>Bacillus subtilis</i> ( <i>n</i> -hexane and ethyl acetate fractions of ethanol extract) <sup>99</sup> – AI: lipopolysaccharide-stimulated murine microglia cells (phenylpropanoid sucrosides) <sup>100</sup>
<i>Rhus coriaria</i>	– AO: DPPH and DMPD (water and ethanol extracts) <sup>101</sup> – AM: <i>Staphylococcus epidermidis</i> (hydroalcoholic extract) <sup>102</sup>
<i>Sempervivum tectorum</i>	– AO: ultraviolet-irradiated liposomal system (kaempferol, kaempferol-3-glucoside) <sup>103</sup> – AM: <i>Staphylococcus aureus</i> (polyphenols) <sup>104</sup>
<i>Smilax china</i>	– AO: DPPH, ABTS, RP (methanol, ethanol, acetone, and water) <sup>105</sup> – AM: <i>Staphylococcus aureus</i> (ethanol extract) <sup>105</sup> – AI: egg albumin-induced edema in mice (aqueous extract) <sup>106</sup>
<i>Tanacetum parthenium</i>	– AO: DPPH, Fe <sup>2+</sup> -chelating ability (ethanol: phenolic compounds) <sup>107</sup> – AM: (antifungal), (essential oil: camphor, chrysanthemyl acetate, and camphene) <sup>108</sup> – AI: cyclo-oxygenase and 5-lipoxygenase inhibitors (flavonoids) <sup>109</sup>
<i>Teucrium chamaedrys</i>	– AO: DPPH (water, methanol, and acetone extracts) <sup>110</sup> – AM: <i>Staphylococcus aureus</i> , <i>Candida albicans</i> (ethanol extract) <sup>111</sup>
<i>Teucrium polium</i>	– AO: $\beta$ -carotene/linoleic acid, thiocyanate, DPPH (methanol extract: flavonoids) <sup>112</sup> – AM: <i>Bacillus anthracis</i> (ethanol extract), <i>Bordetella bronchiseptica</i> (methanol extract) <sup>35</sup> – AI: Carrageenan-induced inflammation and cotton-pellet granuloma (ethanol extract) <sup>33</sup> – WH: Accelerating the burn wound healing ( <i>Teucrium</i> 2% topical application) <sup>32</sup>
<i>Verbena officinalis</i>	– AO: DPPH (methanol extract, caffeoyl derivatives) <sup>113</sup> – AM: antifungal (50% methanol extract, caffeoyl derivatives) <sup>113</sup>
<i>Ziziphus jujuba</i>	– AO: DPPH, FRAP (methanol extract) <sup>114</sup> – AM: <i>Streptococcus pyogenes</i> (ethanol extract) <sup>115</sup> – AI: Attenuation of nitric oxide expression, in vivo (hydroalcoholic extract) <sup>116</sup>

Abbreviations: ABTS, 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulfonic acid; AO, antioxidant; AI, anti-inflammatory; AM, antimicrobial; CUPRAC, cupric ions reduction capacity; DMPD, *N,N*-dimethyl-*p*-phenylenediamine; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRAP, ferric-reducing antioxidant power; LP, lipid peroxidation; NBT, nitroblue tetrazolium chloride; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NO, nitric oxide; TEAC, Trolox equivalent antioxidant capacity; WH, wound healing.

found to be effective in the treatment of intra-oral mucosal wounds.<sup>27</sup> Its anti-inflammatory properties have been related to COX<sub>1</sub> inhibition.<sup>28</sup> Essential oil of this oleo-gum-resin has antimicrobial effect against a range of Gram-positive and -negative bacteria.<sup>29</sup>

*Gentiana lutea* L was studied for its anti-inflammatory and wound healing properties by Mathew et al.<sup>30</sup> This was an animal study on ethanol and petrol-ether extract of the rhizomes. They were effective on reducing the inflammation and excision, resutured incision, and dead space wound models when animals were fed 500 and 1000 mg/kg doses and 300 and 500 mg/kg, respectively.<sup>30</sup> Its Methanol extract of flowers and leaves, as well as separated mangiferin, isogentisin, and gentiopicrin show antimicrobial activity against Gram-positive and -negative bacteria as well as the yeast *Candida albicans*.<sup>31</sup>

In one study, the topical application of *Teucrium polium* L extract accelerated healing of burn wounds.<sup>32</sup> Inhibition of carrageenan-induced inflammation in an animal study showed the anti-inflammatory effect of this plant.<sup>33</sup> Its ethanol and ethanol extracts have been shown to be effective on veterinary pathogens.<sup>34</sup>

The polyphenols from peels of *Punica granatum* L were shown to increase fibroblast infiltration, collagen regeneration, vascularization, and epithelialization in the wound area of diabetic rats. This has been related to increasing hydroxyproline, nitric oxide production, and activity as well as elevation of transformin growth factor- $\beta$ 1, vascular endothelial growth factor, and epidermal growth factor in wound tissues.<sup>35</sup> Its peel and fruit extract have shown anti-inflammatory effect by inhibiting the expression of pro-inflammatory proteins.<sup>36</sup> The tannin-rich fractions, ellagitannins, phenolic acids are effective against *Staphylococcus* spp.<sup>37</sup>

In an ex vivo porcine wound-healing model, wound-healing property of leaf extract of *Plantago major* L was confirmed.<sup>38</sup> Its aqueous extract was also shown to have antimicrobial property against *Staphylococcus aureus*.<sup>39</sup> Its methanol extract has inhibitory effects on lipopolysaccharide-induced interleukin-1 $\beta$ , interleukin-6, and COX-2 mRNA expression in mouse macrophage cells.<sup>40</sup>

Ethanol extract of *Adiantum capillus-veneris* L was tested in vitro and it showed capillary-like tubular formations and proliferation of endothelial cells in vitro.<sup>41</sup> Its aqueous extract has angiogenic effects.<sup>41</sup> Aqueous, methanol, and ethanol extracts of this plant showed significant antibacterial and antifungal activities against most of the multidrug-resistant bacterial and fungal strains.<sup>42</sup>

Hydro-alcoholic extract of *Aloe vera* (L) Burm f leaves decrease burn healing time.<sup>43</sup> The gel increases wound contraction, epithelialization, alignment, and organization of the regenerated scar tissue. It also decreases scar tissue size when compared with a control group.<sup>44</sup> It also exerts antimicrobial and antifungal properties.<sup>45</sup>

Rhizome aqueous extract of *Potentilla reptans* L showed anti-inflammatory effects in an animal study.<sup>46</sup> Its antibacterial effect on *Pseudomonas aeruginosa* and *Escherichia coli*, which have been proven in modern research, suggests that it may be effective for treating wound infections.<sup>47</sup>

We found 9 other plants that had wound-healing properties according to traditional Persian medicine and have been studied for their antimicrobial, antioxidant or radical scavenging, and anti-inflammatory effects but have not been studied for their wound-healing property by modern research. They include *Boswellia sacra* Flueck, *Cinnamomum camphora* (L) J Presl, *Heracleum persicum* Desf ex Fischer, *Physalis alkekengi* L, *Polygonum aviculare* L, *Raphanus sativus* L, *Smilax china* L, *Tanacetum parthenium* (L) Sch Bip, and *Ziziphus jujuba* Mill.

The use of traditional medicinal information has contributed to drug discovery worldwide. Currently, the available wound-healing remedies are suboptimal, but using traditional medical knowledge in this area might provide a good direction for future medical and pharmaceutical research. It is best to work on the remedies that have a traditional base and modern studies have revealed their underlying mechanisms of action. In this work, we revealed the herbal remedies for wound healing in traditional Persian medicine and reviewed their possible mechanisms of action.

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## Author Contributions

AH and MMZ defined the study theme and designed the issues. ER and MF studied the medieval manuscripts and collected the data. MMZ and AH analyzed the data and interpreted the results. AH wrote the draft of the article. All authors have reviewed and confirmed the final draft.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Since this work was a review article, no ethical approval was needed.

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