

Mini Review Article

A review on botanicals with wound healing activity for pemphigus vulgaris: perspective of traditional Persian medicine and conventional medicine

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Abstract

Objective: As a rare autoimmune disease, pemphigus vulgaris has a poor prognosis especially in lack of proper medical support. This blistering disease involves both the skin and mucus membranes. The challenge is improving the healing process of skin lesions of which, superimposed infections are among the main causes of the disease mortality. Accordingly, we aimed to assess the treatment options suggested by traditional Persian medicine (TPM) and compare them with current findings.

Materials and Methods: We studied the main clinical and pharmaceutical textbooks of TPM (Kitāb al-hāwīfī al-tibb, the Canon of Medicine, Eksir-e-Aazam, Tuhfat al-mu'minīn, Makhzan al-adviyah (focusing on the skin chapter and respective herbal remedies for the inflamed skin and ulcers. Additionally, scientific databases such as PubMed, Science direct, Scopus, and Google Scholar were searched for the current pharmacological evidence. In the studied books, the term "hot ulcers" was found close to what is known as "Pemphigus vulgaris".

Results: Reported medicinal herbs possess anti-inflammatory, antioxidant, wound healing, and antibacterial activities reported by recent studies. Therefore, they could be introduced as novel natural remedies for pemphigoid wounds.

Conclusion: Taken as a whole, the review of traditional remedies for hot ulcers in Persian medical and pharmaceutical literature may open a new window toward developing new topical treatments for this disease.

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Introduction

Pemphigus vulgaris (PV) is a rare blistering autoimmune disease of the skin and mucous membranes. It is caused by auto-antibodies produced against antigens on the surface of keratinocytes (Kershenovich et al., 2014). There is no general agreement about the related treatment strategies. Treatment approaches mostly include establishment of disease remission in addition to effective control of it (Martin et al., 2011). These strategies are essentially conducted by systemic administration of corticosteroids. However, the undesirable side effects of these medicaments are often mentioned as the most frequent causes of morbidity and mortality (Poulin et al., 1984). Most important causes of death are: opportunistic superimposed infections, complications of long-term and high-dose usage of corticosteroids, and prolonged consumption of immune suppressant medicines (Ahmed, 2001).

Several investigations have been conducted on supplementary and natural medicaments to reduce the dose and consequently complications of the applied steroids (Ahmed, 2001; Mutasim et al., 2005; Poulin et al., 1984). Of course, it should be noticed that even such medicines may cause life-threatening infections as well as increased risk of infertility and cancer (Mutasim et al., 2005). Topical treatment approaches to PV are considered as supplementary therapy to systemic treatment. These strategies are believed to be effective via prevention of infection and promotion of re-epithelialization of the eroded skin (Ruocco et al., 2013).

In PV, skin lesions are among the most important sources of infection. In this regard, any topical treatment shortening the healing time of lesions and reducing the total drug dosage could be clinically reasonable (Tabrizi et al., 2007).

Herbal pharmacotherapy has a long history in traditional Persian medicine (TPM) (Golshani SA et al., 2015). With

reference to the remaining documents of TPM which has been attributed to Unani medicine in Harrison's Principles of Internal Medicine (Kasper et al., 2015) and in line with our previous investigations (Atarzadeh et al., 2016 (a) and (b)), the present study aimed at compiling a framework encompassing pharmacological and medical aspects of PV management in the light of TPM insights.

Methodology

Initially, recent etiopathogenesis findings on PV emerged in PubMed, Scopus and Science direct databases were studied. The traditional term of "hot ulcer" was found very close to PV with regard to the clinical manifestations. Accordingly, description and etiological aspects of this disorder as well as pharmaceutical managements were derived from main medical and pharmaceutical manuscripts of TPM from the 10th to 18th centuries AD. The pharmaceutical literature included *Tuhfat al-mu'minīn* (MS P 21, 22- NLM, NLM Microfilm Reel: FILM 48-136 no. 2; *The Present for the Faithful*, written by Hakim Momen Tonekaboni in 1670) and *Makhzan al-advīyah* (MS P 12- NLM, NLM Microfilm Reel: FILM 48-133 no. 2; *The Storehouse of Medicaments*, written by Aghili Shirazi 1670-1749 AD) (Shīrāzī, 2009; Tunakābunī, 2007). Medical literature was the *Canon of Medicine* by Avicenna (MS A 53, NLM, NLM Microfilm Reel: FILM 48-122 no. 5; 2nd volume, 980-1037 AD) (4th volume) and *Eksir-e-Aazam* (The Great Elixir written by Mohammad Azam Khan 1814-1902 AD) (Azam Khan, 2008; Ibn Sina, 1988).

Finally, to make a conclusion on collected medicaments, the results were compared and confirmed with the recent evidence on the herbs' related pharmacological activities and therapeutic mechanisms of action.

Etiologic factors involved in the pathogenesis of PV

The main pathologic process in PV is “acantholysis” which is the result of cells detachment due to the destruction of their adhering glue, desmoglein by autoantibodies (Shah and Parmar, 2016). Although the cause of this autoimmune disease is originally unknown, some factors have been recognized to be involved in pathogenesis of the disease. For instance, there are circulating IgG autoantibodies directed against the normal desmogleins (Dsg) (a cell-to-cell adhesion molecule) (Kershenovich et al., 2014). T helper (Th) cells are also involved in the pathogenesis of PV. The role of auto-reactive T cells in induction and regulation of antibody production has been suggested in a recent study (Veldman et al., 2004). Moreover, contribution of interleukin-4 (IL-4), IL-5, IL-6 and IL-10 to the pathogenesis of PV suggests Th2 involvement (Okon and Werth, 2014). Oxidative stress is another issue which is considered to be involved in the etiology and pathogenesis of PV. In addition, there is a significant correlation between serum oxidative stress marker level and serum anti-desmoglein antibody level in PV (Abida et al., 2012).

Traditional approach to ulcer

“Wound” and “ulcer” are comprehensively outlined in the Canon of medicine with the special term of “jerahat” and “gharhe”. Ulcers may be hard or soft, hot or cold, septic or aseptic. Some have discharge but some do not, and finally they may be easily healed or may be difficult to treat. According to the TPM, “gharhe” is divided into hot and cold types. Cold ones have a broad base and white color, with minimal itching; in contrast, hot types are sharp with red base, itching, burning sensation, and irritation (Azam Khan, 2008; Ibn Sina, 1988).

Pemphigus wounds are irritating with burning sensation, sometimes are itching, with prolonged healing time, and probably

have superimposed infection (Mutasim et al., 2005). Although there may not be a distinct entity in TPM that could be fully attributed to PV, the aforesaid description seems to be relevant with hot ulcers in TPM sources. In other words, PV could be generally considered as a hot inflamed ulcer in TPM categorization of ulcers. Various natural topical remedies have been used in TPM for hot ulcer (Atarzadeh et al., 2016 (b)). These remedies which have been used for many years by Iranian physicians are summarized in Table 1 (Azam Khan, 2008; Ibn Sina, 1988; Shīrāzī, 2009; Tunakābunī, 2007). In addition, *in vitro* and *in vivo* studies on plants used for hot ulcer healing in the studied ancient books are cited in Table 2.

Discussion

Prolonged wound healing process of pemphigus erosions in addition to the associated pain, discomfort, and cosmetic problems are important determining factors in the duration of hospitalization and risk of secondary infections (Ali et al., 2006). Skin lesion is one of the most important sources of infection. For that reason, using local treatment, decreasing healing time of lesions, and reducing the total dosage of drugs are reasonable strategies (Tabrizi et al., 2007).

Clinical evidence about proper interventions for PV is scant and additional research is needed (Kasperkiewicz et al., 2012). Nowadays, Complementary and Alternative Medicine (CAM) has become more popular in different societies (Danish et al., 2011) and there is an increasing trend in its integration with healthcare systems. In this regard, our primogenitor has made a lot of discoveries about the healing effects of plants through trial and error (Jaladat et al., 2015) that could be helpful even in modern-day applications.

Botanicals with wound healing activity in *Pemphigus vulgaris*

Table1. Medicaments used for wound healing in hot ulcer and their underlying mechanisms of action.

Scientific name	Traditional name	Part used	Application in Traditional medicine	Activities*					Ref.
				AO	AI	AB	WH	CT	
<i>Portulacaoleracea</i> L.	<i>Baghlat-al-hamgha</i>	Aerial parts, Seed	Topical	+	+	+	+	-	(Alam et al., 2014; Kumar et al., 2008; Lee et al., 2012; Lim and Quah, 2007; Rashed et al., 2003)
<i>Plantago ovata</i> L.	<i>Bazr-e-ghatouna</i>	Seed mucilage	Topical	+	+	+	+	-	(Masood and Mirafab, 2004; Motamedi et al., 2010; Rodriguez-Cabezas et al., 2003; Singh et al., 2011; Souri et al., 2008)
<i>Rosa damascena</i> Mill	<i>Vard-e-ahmar</i>	Flower	Topical	+	+	+	+	-	(Boskabady et al., 2011; Hajhashemi et al., 2010; Kalim et al., 2010; Nikbakht and Kafi, 2004; Talib and Mahasneh, 2010)
<i>Curcuma longa</i> L.	<i>Orogh-alsofr</i>	Root	Topical	+	+	+	+	-	(Chattopadhyay et al., 2004; Julie and Jurenka, 2009; Kim et al., 2001; Singh et al., 2002)
<i>Plantago major</i> L.	<i>Lesan al-hamal</i>	Seed mucilage	Topical	+	+	+	+	-	(Amini et al., 2010; Mahmood and Phipps, 2006; Reina et al., 2013; Sharifa et al., 2008)

*AO: Antioxidant; AI: Anti-inflammatory; AB/AF: Antibacterial/Antifungal; WH: Wound healing; CT: Cytotoxicity

Table2. *In vitro* and *in vivo* studies on plants used in TPM for wound healing in hot ulcers.

Scientific name	Part used/Species	Results*	Ref.
<i>Portulaca oleracea</i>	Fresh crude extract (Mice)	Wound healing	(Rashed et al., 2003)
	Polysaccharide Ethanol, aqueous extract	Antioxidant activity- ↓NO Anti-inflammatory, ↓TNF- α - ↓ROS- ↓MCP	(Alam et al., 2014) (Lee et al., 2012)
	Ethanol extract	Antioxidant activity- Anti-inflammatory, ↓MPO, Il6, TNF- α	(Yang et al. 2016; Agyare et al. 2015)
<i>Plantago ovata</i>	Methanol, ethanol extract	Antimicrobial activity against Gram-positive and Gram-negative human pathogens	(Motamedi et al., 2010)
	Seed extract	Antioxidant activity	(Souri et al., 2008)
	Psyllium seeds (Rats)	Anti-inflammatory	(Rodríguez-Cabezas et al., 2003)
<i>Rosa damascena</i>	Butanol, aqueous extract	Antibacterial activity against <i>Salmonella typhimurium</i> , <i>Bacillus cereus</i> , <i>Candida albicans</i> and Methicillin resistant <i>Staphylococcus aureus</i>	(Talib and Mahasneh, 2010)
	Flower extract Hydroalcoholic extract (Rats)	Antioxidant activity Anti-inflammatory, wound healing activity	(Boskabady et al., 2011) (Hajhashemi et al., 2010)
	Oily extract of petals (Rats)	wound healing activity	(Fahimi et al., 2015)
<i>Curcuma longa</i>	Curcumin	Anti- inflammatory-down regulation of cyclooxygenase-2. Significantly inhibit the generation ROS like superoxide anions, H2O2 and nitrite radical generation by activated macrophages, which play an important role in inflammation.	(Chattopadhyay et al., 2004)
	Turmeric powder (Rats, Rabbits)	significantly inhibit the generation ROS Healing effect on both aseptic and septic wound	(Chattopadhyay et al., 2004) (Chattopadhyay et al., 2004)
	Curcumin	modulates the inflammatory response via inhibiting inflammatory cytokines production (TNF-α, IL-1,2,6,8, and 12, MCP)	(Julie and Jurenka, 2009)
	Rhizome extracts	Antibacterial activity against pathogenic strains of Gram-positive and Gram-negative bacteria, Wound healing effect	(Singh et al., 2002)
	Curcumin (Bovine)	Reduce the TNF- α	(Chattopadhyay et al., 2004)

	Ethanol extract of rhizome, Curcumin, Sodium curcuminatate (Rats)	Anti-inflammatory	(Chattopadhyay et al., 2004)
<i>Plantago major</i>	Aqueous extract Hexane extract Methanol extract	Wound healing effect, Antioxidant activity Anti-inflammatory activity Antibacterial effects against Gram-positive and Gram-negative bacteria such as <i>Staphylococcus aureus</i> and <i>Escherichia coli</i>	(Mahmood and Phipps, 2006) (Reina et al., 2013) (Sharifa et al., 2008)
	Baicalein and aucubin	↓ROS production	(Reina et al., 2013)
<i>Myrtus communis</i>	Essential oil	Wound healing effect, Antioxidant activity, Anti-inflammatory activity Antibacterial activity on some Gram-positive and Gram-negative bacteria	(Ameri et al., 2015) (Akin et al., 2012)
	Essential oil methanol extract, leaf, stem and flower	Antioxidant activity	(Aidi et al., 2010)
	Myrtucommuacetalone, myrtucommulone M, Myricetin	Ability to modulate the immune response-↓NO - ↓T cell proliferation -↓ROS	(Choudhary et al., 2013)
	Ethanol extract, Myrtucommulone (Rats, Mice)	Anti-inflammatory	(Aleksic and Knezevic, 2014)
	Essential oil (Rats)	Anti-inflammatory activity, ↓MPO activity- ↓TNF- α ↓IL6- ↓Leukocyte migration Wound healing activity	(Maxia et al., 2011) (Asgarpanah and Ariamanesh, 2015)
<i>Solanm nigrum</i>	Methanol extract	Anti-inflammatory	(Ravi et al., 2009)
	Chloroform fraction	↓NO-↓TNF- α - ↓IL6	(Kang et al., 2011)
	Ethanol, methanol, ethyl acetate, diethyl ether, leaves, seed and roots hexane and chloroform extract	Antibacterial activity against pathogenic bacteria such as <i>Bacillus subtilis</i> , <i>S. aureus</i> , <i>Klebsiella pneumonia</i> , <i>E. coli</i>	(Sridhar et al., 2011)
	Aqueous extract of leaves(Rats)	Wound healing activity	(Fahimi et al., 2015)
	Water extract (Mice)	Anti-inflammatory	(Kibichiy et al., 2013)
	Aqueous extract (Mice)	Antioxidant activity	(Liu et al., 2016)
<i>Santalum album</i>	Methanol extract	Antibacterial activity against <i>Staphylococcus aureus</i> , <i>B. cereus</i>	(Parekh et al., 2005)
	HESP (Hydrolyzed Exhausted Sandal Wood Powder) oil (Rats)	Anti-inflammatory	(Ahmed et al., 2013)
	Bark hydroalcoholic extract (Rats)	Antiulcer	(Ahmed et al., 2013)

*ROS: reactive oxygen species; IL: interleukin; MCP: monocyte chemoattractant protein; TNF- α : Tumor necrosis factor alpha; NO: Nitric oxide; MPO: myeloperoxidase

Botanicals with wound healing activity in *Pemphigus vulgaris*

The therapeutic approach of Persian medicine for the treatment of ulcers is related to its specific classification for ulcers based on hotness and coldness, having discharge, extent, and rate of healing (Ibn Sina, 1988). Clinical features such as irritation, itching, red base, and burning sensation are somehow relevant with hot ulcers in TPM sources. Avicenna believed that these ulcers are sharp red-based ones which are accompanied by itching and irritation (Ibn Sina, 1988).

In TPM sources, many medicinal herbs have been mentioned for wound healing. Some of these herbs such as *Portulacaoleracea* L., *Plantago ovata* Forssk. and *Plantago major* L. have mucilaginous characteristics and tissue regenerating ability and have been used for hot swelling and hot ulcer topically. *Plantago major* L., for instance, could be applied for removing the pus out of the infected wound; thus, it is useful for burns and skin diseases. *Portulaca oleracea* L. and *Plantago ovata* Forssk. with rose oil are also beneficial for burns and hot ulcers (Shīrāzī, 2009).

Plantago major L. is a very effective remedy for superficial wounds. Its aqueous extract has shown wound healing effects in rats. Mechanism of action of its wound healing activity is related to its antioxidant properties (Mahmood and Phipps, 2006).

It has been suggested that treatment of white Swiss mice skin wounds with fresh homogenized crude extract of *Portulaca oleracea* has accelerated the wound healing process (Rashed et al., 2003).

Plantago ovata Forssk. Mucopolysaccharide also has beneficial properties for wound cleansing and wound healing (Masood and Miraftab, 2004).

It is to be mentioned that almost every herb proposed in TPM sources for hot ulcer treatment, has anti-inflammatory, antioxidant and wound-healing activities which have been shown to be beneficial in treatment of Pemphigus lesions, in recent studies. Moreover, they have antibacterial

activity which could accelerate the wound healing process in infected wounds (Tables 1 and 2).

As the main limitation of our study, we only considered those herbal remedies with good levels of evidence reported by *in vivo* and/or *in vitro* wound healing investigations.

Conclusion

In this review, we aimed at summarizing the approach of Persian medicine toward wound healing and particular herbs that can be used for Pemphigus ulcers re-epithelialization as a complementary treatment.

In general terms, reviews on Persian medicinal herbs could pave the way for development of new herbal-based formulations for better management of Pemphigus lesions. While basic research provides data about wound-healing and the favorable effects of some herbs or herbal compounds, well-designed clinical trials should also be considered in the future.

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Conflict of Interests

There is no conflict of interest in this study.

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