

Skin Wound Healing: From Mediterranean Ethnobotany to Evidence based Phytotherapy

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Phytotherapy plays an important role in wound healing. Medicinal plants have represented for thousands of years the only remedy for wound care, and still maintain an important therapeutic role thanks to peculiar and desirable features of plant phytocomplexes. The use of herbal preparations exploiting synergistic and multitasking activities is distinctive of phytotherapy as a branch of pharmacology and could be alternative, more often complementary, to the use of monomolecular synthetic drugs. The European Medicines Agency (EMA), as well as World Health Organization (WHO) and European Scientific Cooperative on Phytotherapy (ESCOP), confirm that one of the most frequent indication for which many medicinal plants are used in the European Community and in the rest of the world, is the treatment of skin disorders and minor wounds. The study of medicinal plants used in wound healing has its origins in the ethnobotanical knowledge and in folk medicine. Ethnobotany encompasses both wild and domestic species, and is rooted in observation, relationship, needs and traditional ways of knowing. Various ethnobotanical investigations that took place in Italy and in Greece confirmed the use of many species enlisted by EMA, ESCOP and WHO for use in wound healing. The interviewed subjects provided important practical details about the use of medicinal plants for the treatment of tissue lesions and they also described how every single plant, as well as every preparation, is destined to a specific type of wound. This work summarizes the medicinal plants used in Mediterranean countries, particularly Italy and Greece, for wound healing, reporting mechanisms of action, clinical efficacy and peculiar characteristics. These data provide the rationale for using different natural remedies on different types of wounds, showing that local health seeking strategies can help in resolving wound healing problems.

Keywords: Ethnobotany, Medicinal plants, Phytotherapy, Wound healing.

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Introduction

Ethnobotany is the science that studies the uses of herbal species in a human society. Consequently, there is a straight relation between those kind of uses and the geopolitical and cultural characteristics of every population. The indications of skin inflammation, minor wounds and small burns are frequently treated with medicinal plants, the use of which is spread since from ancient times. The modern pharmacological investigations have shown that many medicinal plants used in the ethnobotanical tradition worldwide, are being currently used in a very rational way (S.I.Fit; EMA; Agyare et al., 2016; Seebaluck et al., 2015; Kumar et al., 2007). In fact, the mixture of phytoconstituents of some species is able to speed up and improve the wound healing, by acting simultaneously on different phases of the reparative process.

Phytotherapy is a branch of pharmacology that uses medicinal substances derived from the extraction or from other chemical or physical processes applied to medicinal plants (Giachetti and Monti, 2005) and includes the use of medicines whose active ingredients are represented by a herbal substance. Phytotherapy plays an important role in wound healing. Medicinal plants have represented for thousands of years the only resource of remedies for wound care, and until nowadays maintain a very important role thanks to the multitasking features possessed by the plant phytocomplex.

After a tissue damage, the ability of the skin to regenerate and restore the barrier function towards the external environment is vital for the survival. The wound healing process is crucial after surgical incisions, burns and chronic ulcers.

Bearing in mind that the wound healing process and the scar outcome, such as the cutaneous healing after a burn, are influenced by various factors including oxygenation, hydration, bacterial infections, nutrition, diseases and the assumption of drugs, is evident that the problematic of wound healing is typically multifactorial, and that is why it is necessary to act on several targets contemporarily (Pazyar et al., 2014). In this context, phytotherapy plays a key role both in traditional medicine and in modern pharmacology.

The Mediterranean montane and coastal zones are very privileged from the floristic point of view, and their botanical biodiversity reflects a richness in herbal principles. Given the natural heritage of these areas, we have tried to evaluate the present status of the medicinal flora and the viability of folk medicine tradition regarding the treatment of minor wounds, small burns and tissue lesions.

Bibliographic data have been considered, and semi-structured interviews have been carried out in different study areas, both in Italy and in Greece, in order to collect information on the traditional use of plants for the treatment of skin disorders. Similarities and differences in the use of plants have been noticed and the peculiarity of every single zone has been highlighted.

Materials and Methods

Information relating to the ethnobotany of the various geographical areas regarding the treatment of skin disorders and minor wounds, was collected from the relevant literature and enriched by the observations and data (Table 1), derived from visits and interviews made with subjects (mostly old people) who had personal experience in self-medication using herbs. Data were obtained mainly through open informal or semi-structured interviews, with the informants' consent for the participation in the interview. In these kind of interviews, informants give extensive responses to a series of questions, some of which have been prepared in advance and some of which arise naturally during the course of the conversation (Martin, 2004).

Quite often, the interviews took place in the squares of villages, in the fields or in the houses of informants. The informants were requested to indicate vernacular names of plants, folk uses, parts used, preparation procedures, and possible species associations (Table 2). In several cases, the information collected included the description of recipes and their sources (for example old manuscripts, grandparents, etc.). The identification of the most common taxa was carried out in the field but some specimens were collected and identified in the laboratory according to more recent taxonomic revisions. The study areas in Italy include the coastal area Riviera di Levante, in Liguria region, and the montane area of the North-Western Ligurian Alps. The Greek study areas are represented by various regions such as Thessaly, Epirus, Cyclades, Crete and Macedonia.

Additionally, we completed our data consulting two studies made in Zagori, which is a group of villages in and around the National Park of Vikos-Aoos, in Epirus, north-west Greece (Vokou et al., 1993, Malamas and Marselos, 1992) and a study made in the herbal market of Thessaloniki, Greece (Hanlidou et al., 2004).

Moreover, the aim of the present study was to explore the traditional plant knowledge related to the herbal species used for the treatment of skin disorders such as burns, insect bites and picks and more importantly minor wounds.

Table 1. *Sources of Information for Ethnobotanical Taxa*

Sources	Data from bibliographic sources	Data from original interviews
Coastal Italy	Cornara et al., 2009	29
Montane Italy	Cornara et al., 2014	---
Coastal Greece	Hanlidou et al., 2004	30
Montane Greece	Malamas and Marselos, 1992 Vokou et al., 1993	---

Table 2. *Questionnaire for Collecting Ethnomedicinal Data*

Informants' details	Data about medicinal plant	Data about medicinal use of the plant
Name	Plant (local name)	Name of disease(s) treated
Gender	Habit (tree/herb/shrub....)	Method of preparation
Age	Cultivated/wild	Mode of administration
Occupation/ Education	Plant part used	Dosage
Location/Residence	Method of collection/ storage	Association with other plants

Results and Discussion

Only a few recent studies have examined the Mediterranean ethnobotany (González-Tejero et al., 2008; Hadjichambis et al., 2008; Pieroni et al., 2006; Heinrich et al., 2005) trying to compare the similarities and differences that characterize the uses of plants as wild and semi-domesticated food, for traditional animal healthcare, and as medicine. However, the specific medicinal subcategory of skin disorders and minor wounds has never been deeply investigated.

The ethnobotanical data that came out from this study revealed that 105 species belonging to 51 different plant families are used in the study areas, for the indication of skin disorders and minor wounds (Table 3). The survey areas are representative of the Mediterranean region and the information collected is mainly referred to wild species, whereas semi-cultivated or cultivated species are less frequently used. Two plant families were reported in all four survey areas and were the most represented in terms of number of species. These are Asteraceae (13 species) and Lamiaceae (11 species). The majority of both species and plant families are reported in single areas (for example 29% of taxa in the montane Greece). Only a few taxa were cited in common in the coastal and montane zones of both countries. On the contrary, more than 20% of the plant families are used at least in 3 out of 4 considered zones (Figure 1).

Figure 1. *Percentages of Sharing for Taxa (Families and Species) Used for Treating Skin Diseases in Greece and Italy*

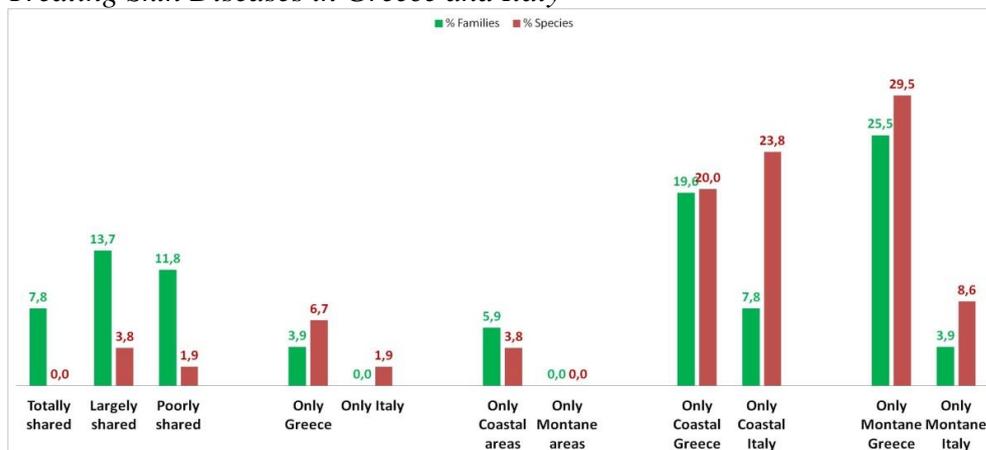


Table 3. Number of Taxa for Each Family Reported as Dermatologic Remedies in the Four Survey Areas. Families Cited in All Survey Areas Are in Bold

Family	Coastal Italy	Montane Italy	Coastal Greece	Montane Greece	All areas
Acanthaceae				1	1
Agavaceae	1				1
Aizoaceae			1		1
Alliaceae	2	2	1	1	3
Anacardiaceae	1		1		2
Apiaceae	2		2	1	3
Araliaceae			1		1
Aristolochiaceae				1	1
Asphodelaceae			1		1
Aspleniaceae				1	1
Asteraceae	4	3	4	4	13
Brassicaceae	1			1	2
Capparaceae	1				1
Caprifoliaceae			1	1	1
Caryophyllaceae			1		1
Cistaceae			1		1
Crassulaceae	1			1	2
Cucurbitaceae			1	1	2
Cupressaceae				1	1
Equisetaceae			1		1
Fabaceae				1	1
Fagaceae	1			1	2
Gentianaceae				2	2
Hamamelidaceae			1		1
Hypericaceae	1		1	1	1
Juglandaceae	1		1		1
Lamiaceae	3	2	2	5	11
Lauraceae				1	1
Lentibulariaceae		1			1
Liliaceae	1			1	2
Malvaceae	1		2	2	3
Oleaceae	1			1	2
Ophioglossaceae	1				1
Papaveraceae				1	1
Pinaceae		3			3
Plantaginaceae	2	2	1	1	2
Platanaceae			1		1
Polygonaceae	3		1		4
Primulaceae			1		1
Ranunculaceae				2	2
Rosaceae	1		2	1	3
Ruscaceae			1		1
Rutaceae	3			1	3
Sapindaceae				1	1
Scrophulariaceae		1	1	1	2
Solanaceae	1	1	3		4
Thymelaeaceae				1	1
Tiliaceae				1	1
Ulmaceae	1				1
Urticaceae	2		2	1	4
Violaceae				1	1
Total no. species	36	15	36	41	105

Species Used in Traditional Medicine

The three more important species that are used in common in all four areas are *Hypericum perforatum* L., *Juglans regia* L., and *Plantago lanceolata* L.

Hyperici herba, consists in the dried flowering tops of *Hypericum perforatum* L., that was known since ancient times and it is used nowadays by modern phytotherapy. The herb of *H. perforatum* is used for the treatment of wounds in the whole Europe (Weiss et al., 2000) being also the most referred taxon for treating skin disorders in Spain (González-Tejero et al., 2008). However, specific studies on wound healing and burns treatment are rarely reported (Sanna et al., 2006; Quave et al., 2008). A well-known use related to *H. perforatum* L. is the one of St. John's wort oil, which is obtained by maceration of fresh flowering tops in vegetable oil (1-4:20) for 30-40 days until the oil's color becomes intensively red (European Medicines Agency, EMA). When this process is completed the oil is ready to be applied on tissue lesions or skin burns. In Italy, the collection of the inflorescences is related to the San Giovanni's day which is dated on 24th June. St. John's oil is effective and well tolerated by the majority of people, and has been studied enough to prove a rational traditional use according to the 2004/24/EC (Samadi et al., 2010; Clewell et al., 2012; Najafizadeh et al., 2012). St. John's wort extract presents a wound healing activity through an increase of collagen granule number in fibroblasts, which plays a fundamental role in the wound healing process (Dikmen et al., 2011). Flavonoids, hypericins and phloroglucinols, with their anti-inflammatory (Wolfe et al., 2014) and antibacterial activity (Saddiqe et al., 2010), are involved in this process.

Juglans regia L. is a species mentioned and described for being used in wound healing in both coastal zones. The leaves are contemporarily used to target skin ailments as an anti-inflammatory, astringent and depurative. The leaves are also used to treat skin disorders: acne (Magin et al., 2006; Reuter et al., 2010), eczema, herpes, scrofulous disease, in excessive perspiration of the hands and feet and slow healing wounds as a wash, compress or poultices. Its astringent activity is assigned to the tannin content (Blumenthal, 2000; Weiss and Fintelman, 2000; Wichtl, 2004; Wyk and Wink, 2004; Frohne, 2006).

Plantago major L. (*Plantago major* ssp. *major* L.) and *Plantago lanceolata* L. are perennial plants that belong to the Plantaginaceae family. Brøndegaard has extensively described the use of *P. lanceolata* L. and *P. major* L. for the treatment of wounds in folk medicine. *P. major* L. leaves have been used as a wound healing remedy for centuries in almost all parts of the world (Samuelsen, 2000). *P. major* was also described in 'Flora Danica' by Simon Paulli in 1648 as a very efficient wound healing remedy. The nerves were pulled out of the leaves, and then the leaves were applied on the wounds morning and evening. For superficial wounds to heal, it was sufficient to apply the juice of the plant (Brøndegaard, 1963).

Among the taxa that are reported only in single areas, it is noteworthy to report the traditional use of some ointments.

In Northern Italy aerial parts of the fern *Ophioglossum vulgatum* L. (Ophioglossaceae) are reported to be soaked in olive oil to give an ointment that is used mainly as wound poultice, particularly as haemostatic (Uncini et al., 1996). This species occurs all over the northern hemisphere, and in Italy it is prevalently found in the northern and central regions (Pignatti, 1982). Similar use of this fern was described in the European folk medicine: leaves' extracts were known in Great Britain as "Green oil of charity" (Leyel, 1937). The traditional use of *O. vulgatum* L. ointments on wounds and burns suggests the occurrence of lipophilic compounds in this species with tissue repair properties.

Phytochemical and pharmacological studies of *Ophioglossum* species were rather scattered to date. The triglycoside 3-O-methylquercetin-7-O-diglycoside-4-O-glycoside was isolated from *O. vulgatum* (Markham et al., 1969). More recently, the aqueous extract of *O. vulgatum* was found to be active at a low concentration against the bovine viral diarrhea virus (BVDV) (Herrmann et al., 2011).

Clericuzio isolated from the aerial parts of *O. vulgatum* two new glycosylated and acylated flavonols: quercetin-3-O-[(6-caffeoyl)- β -glucopyranosyl (1 \rightarrow 3) α -rhamnopyranoside]-7-O- α -rhamnopyranoside), and kaempferol-3-O-[(6-caffeoyl)- β -glucopyranosyl (1 \rightarrow 3) α -rhamnopyranoside]-7-O- α -rhamnopyranoside. These compounds, along with the yet known quercetin-3-O-methyl ether were all found to be active in scratch-wound healing assays on keratinocytes, with quercetin-3-O-methyl ether being the most active one showing maximum activity at 20 μ M. (Clericuzio et al., 2012).

The same research group isolated and characterized a galactosyldiacylglycerol mixture, composed mainly of 1,2-di-O-linolenoyl- 3-O- β -D-galactopyranosylglycerol, from the fern frond dichloromethane extract. The wound healing properties of this mixture were assessed *in vitro* on human keratinocytes. Scratch wound assays showed increased wound closure rates in keratinocyte monolayers treated with the galactosyldiacylglycerol mixture at 5 μ g/ml, with results comparable to that recorded by platelet lysate used in clinical settings. The use of inhibitors of the main cellular pathways involved in wound repair, revealed that the fern compounds significantly modulated intracellular calcium levels and the ERK1/2 MAP kinase activation. Conversely, a PCR array of genes involved in wound healing showed an almost total absence of gene modulation. Taken together, the data suggest that the fern galactosyldiacylglycerol mixture acts through a Ca^{2+} -dependent, non-genomic mechanism involving the activation of ERK1/2 MAP kinase (Clericuzio et al., 2014). Hence, galactosyldiacylglycerol mixture is a main candidate to explain the wound healing virtues of *O. vulgatum* ointment, and is proposed as a possible new drug in tissue repair and regenerative medicine.

Other ointments used in the past in Italy, were based on the sugary liquid present in the galls of some plants, such as *Pistacia terebinthus* L. (Anacardiaceae) and *Ulmus minor* Mill. (Ulmaceae). Small amount of this slightly oily liquid was collected at the dawn of the day of Saint John the Baptist, June 24, and quoted as a valuable remedy to use against the bite of poisonous animals (e.g.

wasp bites) or on wounds. Analogous uses were also reported in other Italian regions, such as Latium and Tuscany (Guarrera, 2006).

In Greece an interesting information that has been reported by the informants of the Macedonian region is the topical application of *Momordica charantia* L. ointment which is prepared with the same method used for *H. perforatum* L. ointment. *M. charantia* is a tropical spreading plant that belongs to Cucurbitaceae. The species has a geographical distribution throughout various parts of the world. It bears a fruit that is emerald-green in colour and has a bitter taste, since it is called bitter melon (Gürbüz et al., 2000). *M. charantia* is used both as a food and as a traditional herb for treating various diseases, such as common cold, fever, helminths, rheumatism and wounds (Piskin et al., 2014). It is also used as an antioxidant, antispasmodic, anticholinergic and antiulcerogenic agent to treat gastric and malignant ulcers (Wu et al., 2007; Ozbakis Dengiz et al., 2005). Today, the antidiabetic properties of *M. charantia* are being largely studied and confirmed (Habicht et al., 2014).

The popularity of its use in traditional medicine has led to a great interest arisen from scientific community (Prarthna et al., 2014).

A study conducted recently (Teoh et al., 2009) observed the topical effect of bitter melon extract on the wound-healing process in rats with diabetes induced by streptozotocin. The diabetic group exhibited delayed wound healing as compared to the normal group. Interestingly, the diabetic group treated with topical *M. charantia* extract showed better results than the non-treated group. The results of this study show that administration of *M. charantia* extract improves and accelerates the process of wound healing. *M. charantia* fruit powder, in the form of an ointment (10% w/w dried powder in simple ointment base), was evaluated for wound healing potential in an excision, incision and dead space wound model in rats. Powder ointment showed a statistically significant response, in terms of wound-contracting ability, wound closure time, period of epithelization, tensile strength of the wound and regeneration of tissues at wound site when compared with the control group (Prasad et al., 2006).

In the region of Macedonia, bitter melon is widely used for its healing properties. In the local dialect it is called "Kantouri" and replaces almost completely the use of conventional drugs such as silver sulfadiazine. The small red fruits are collected and fragmented into small pieces; subsequently they are immersed in olive oil and placed under the sun to macerate for 30-40 days. After preparation, the oil containing the fruits is preserved and is ready to apply on the wound. In addition, apart from the use of this ointment in the treatment of minor wounds the shepherds of this region used it to treat animals' wounds. The bitter melon oil has beneficial properties for peptic ulcers, for the treatment of which was assumed a spoon daily, usually in the morning.

From Mediterranean Ethnobotany to Evidence-based Phytotherapy

The European Medicines Agency (EMA), in the revision of the literature about the species used for medicinal purposes in Europe, confirms that skin

disorders and minor wounds are among the most frequent indications for which many medicinal plants are used. Surprisingly, only 12% (13 of the 105) of the species cited at least once by the informants are catalogued in the EMA list that contains the species registered for the treatment of skin disorders and minor wounds (Table 4).

Table 4. Taxa Cited by Informants and Included in the EMA List

Largely shared (used in 3 out of 4 areas)

Hypericum perforatum L.

Only in coastal areas of both countries

Juglans regia L.

Only in Greece

Agrimonia eupatoria L.

Urtica dioica L.

Only in coastal Greece

Achillea millefolium L.

Hamamelis virginiana L.

Origanum dictamnus L.

Urtica urens L.

Only in coastal Italy

Arctium lappa L.

Quercus pubescens Willd.

Only in montane Greece

Matricaria chamomilla L.

Salvia officinalis L.

Only in montane Italy

Calendula officinalis L.

Conclusions

The extensive review of medicinal plants that have an official therapeutic role in wound healing shows that their study is based on the ethnobotanical knowledge and the medical tradition, and is developed through the contemporary clinical and experimental investigations aimed at understanding their mechanisms of action. The use of conventional products for the treatment of skin wounds presents some important limits that are confirmed, indirectly and frequently, by the use of alternative products such as blood products (Fontana et al., 2016). Recently there has been noticed a reversion towards the ethnobotanical knowledge and folk medicine. The enhancement of medicinal plants' traditional use could represent nowadays, in a seriously difficult moment for the pharmaceutical synthetic chemistry, one of the most effective approaches to new pharmaceutical research in several fields. Finally, it could also represent the deepening of a frequent and important issue as that of tissue lesions.

The ethnobotanical data show that in the Mediterranean basin self-medication practices are still present mainly in rural areas or in zones that are linked to agriculture. This research indicates a significant use of a large number of wild and/or semi-cultivated Mediterranean plants, for therapeutic applications related to the treatment of skin disorders, such as burns, ulcers and small wounds. The fact that only 12% of these species are catalogued by EMA for this type of indication opens up many opportunities for scientific studies on the use of new principles derivable from such species. This study represents the first step of a larger project aimed to examine more sample areas and to create a list of Mediterranean species potentially useful in wound healing and in the treatment of other skin problems.

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